UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN

COUNTY OF WAYNE and COUNTY OF OAKLAND, Plaintiffs, vs. PURDUE PHARMA L.P., CEPHALON, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA PHARMACEUTICALS USA, INC., ENDO INTERNATIONAL PLC, JANSSEN PHARMACEUTICALS, INC., INSYS THERAPEUTICS, INC., MALLINCKRODT PLC, MALLINCKRODT PHARMACEUTICALS, AMERISOURCEBERGEN CORPORATION, CARDINAL HEALTH, INC. and McKESSON CORPORATION, Defendants.	Civ. No. COMPLAINT FOR (1) VIOLATION OF MICHIGAN CONSUMER PROTECTION ACT; (2) PUBLIC NUISANCE; (3) NEGLIGENCE; (4) UNJUST ENRICHMENT; AND (5) VIOLATION OF THE RACKETEER INFLUENCED AND CORRUPT ORGANIZATION ACT DEMAND FOR JURY TRIAL

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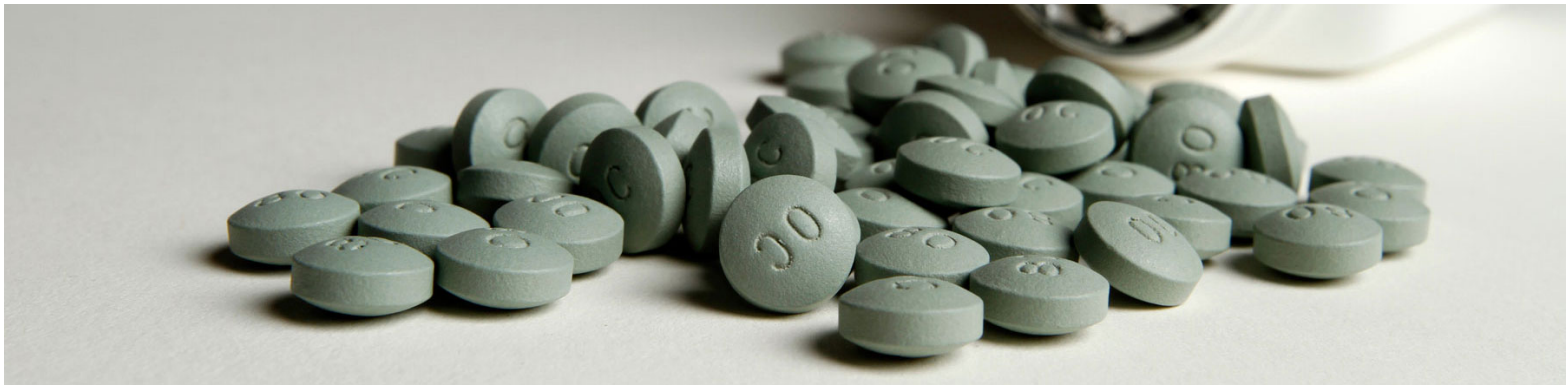


OxyContin 80 pills (Liz Baylen / Los Angeles Times)

A TIMES INVESTIGATION

‘YOU WANT A DESCRIPTION OF HELL?’ OXYCONTIN’S 12-HOUR PROBLEM

by HARRIET RYAN (HTTP://WWW.LATIMES.COM/LA-BIO-HARRIET-RYAN-STAFF.HTML), LISA GIRION AND SCOTT GLOVER

MAY 5, 2016

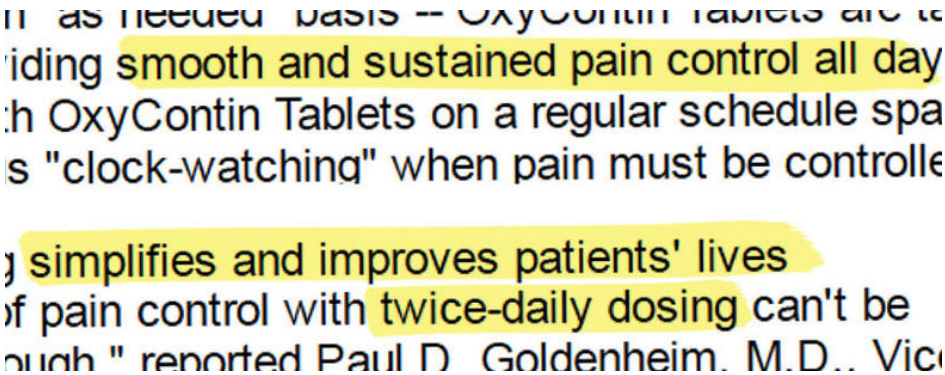
The drugmaker Purdue Pharma launched OxyContin two decades ago with a bold marketing claim: One dose relieves pain for 12 hours, more than twice as long as generic medications.

Patients would no longer have to wake up in the middle of the night to take their pills, Purdue told doctors. One OxyContin tablet in the morning and one before bed would provide “smooth and sustained pain control all day and all night.”

1996

OxyContin Press Release

When Purdue unveiled OxyContin in 1996, it touted 12-hour duration.



(http://documents.latimes.com/oxycontin-press-release-1996/)

On the strength of that promise, OxyContin became America’s bestselling painkiller, and Purdue reaped $31 billion in revenue.

But OxyContin’s stunning success masked a fundamental problem: The drug wears off hours early in many people, a Los Angeles Times investigation found. OxyContin is a chemical cousin of heroin, and when it doesn’t last, patients can experience excruciating symptoms of withdrawal, including an intense craving for the drug.

The problem offers new insight into why so many people have become addicted to OxyContin, one of the most abused pharmaceuticals in U.S. history.

The Times investigation, based on thousands of pages of confidential Purdue documents and other records, found that:

- Purdue has known about the problem for decades. Even before OxyContin went on the market, clinical trials showed many patients weren't getting 12 hours of relief. Since the drug's debut in 1996, the company has been confronted with additional evidence, including complaints from doctors, reports from its own sales reps and independent research.
- The company has held fast to the claim of 12-hour relief, in part to protect its revenue. OxyContin's market dominance and its high price — up to hundreds of dollars per bottle — hinge on its 12-hour duration. Without that, it offers little advantage over less expensive painkillers.
- When many doctors began prescribing OxyContin at shorter intervals in the late 1990s, Purdue executives mobilized hundreds of sales reps to "refocus" physicians on 12-hour dosing. Anything shorter "needs to be nipped in the bud. NOW!!" one manager wrote to her staff.
- Purdue tells doctors to prescribe stronger doses, not more frequent ones, when patients complain that OxyContin doesn't last 12 hours. That approach creates risks of its own. Research shows that the more potent the dose of an opioid such as OxyContin, the greater the possibility of overdose and death.
- More than half of long-term OxyContin users are on doses that public health officials consider dangerously high, according to an analysis of nationwide prescription data conducted for The Times.

Over the last 20 years, more than 7 million Americans have abused OxyContin, according to the federal government's National Survey on Drug Use and Health. The drug is widely blamed for setting off the nation's prescription opioid epidemic, which has claimed more than 190,000 lives from overdoses involving OxyContin and other painkillers since 1999.

GET INVOLVED

Tell us your story↗ (/oxycontin-your-story)

I have had an experience with OxyContin (/oxycontin-your-story/#my-experience)

I know someone who has had an experience with OxyContin (/oxycontin-your-story/#friend-family-experience)

The internal Purdue documents reviewed by The Times come from court cases and government investigations and include many records sealed by the courts. They span three decades, from the conception of OxyContin in the mid-1980s to 2011, and include emails, memos, meeting minutes and sales reports, as well as sworn testimony by executives, sales reps and other employees.

The documents provide a detailed picture of the development and marketing of OxyContin, how Purdue executives responded to complaints that its effects wear off early, and their fears about the financial impact of any departure from 12-hour dosing.

Reporters also examined Food and Drug Administration records, Patent Office files and medical journal articles, and interviewed experts in pain treatment, addiction medicine and pharmacology.

Experts said that when there are gaps in the effect of a narcotic like OxyContin, patients can suffer body aches, nausea, anxiety and other symptoms of withdrawal. When the agony is relieved by the next dose, it creates a cycle of pain and euphoria that fosters addiction, they said.

PURDUE'S RESPONSE

Purdue Pharma issues statement on OxyContin report; L.A. Times responds↗ (/purdue-response)

OxyContin taken at 12-hour intervals could be "the perfect recipe for addiction," said Theodore J. Cicero, a neuropharmacologist at the Washington University School of Medicine in St. Louis and a leading researcher on how opioids affect the brain.

Patients in whom the drug doesn't last 12 hours can suffer both a return of their underlying pain and "the beginning stages of acute withdrawal," Cicero said. "That becomes a very powerful motivator for people to take more drugs."

Video | 0:27
The cycle of addiction

Peter Przekop, a neuroscientist and physician who oversees the treatment of painkiller addicts at the Betty Ford Center in Rancho Mirage, said that repeated episodes of withdrawal from OxyContin "absolutely" raise the risk that patients will abuse the medication.

"You are messing with those areas of the brain that are involved in addiction, and you are going to get the person dependent on it," he said.

The Times sought comment from Purdue's scientists and executives. At the company's request, the newspaper submitted detailed questions in writing. Purdue responded with a one-page statement noting that the FDA approved OxyContin as a 12-hour drug.

"Scientific evidence amassed over more than 20 years, including more than a dozen controlled clinical studies, supports FDA's approval of 12-hour dosing for OxyContin," Purdue's chief medical officer, Dr. Gail Cawkwell, said.

Company officials said in the same statement that "the people at Purdue have dedicated themselves to helping address our nation's opioid epidemic."

'I have it under control. I know what I'm doing.'

As an LAPD officer, Ernest Gallego was fearless. He broke up bar fights and street brawls. During a torrential rainstorm in 1980, he waded into a flooded intersection to rescue two motorists.

He was on duty in Echo Park seven years later when a tow truck slammed into his patrol car, leaving him with a career-ending back injury. He had several surgeries and tried various pain medications over the next two decades.

By 2012, he was on OxyContin. His parents and siblings watched and worried as the strong, fastidiously neat man they knew became wobbly on his feet and unkempt. His father, an attorney, wrote letters on his law office letterhead pleading with his son's doctor to take him off the drug, and his mother hid any OxyContin bottles she found, Gallego's sister, Kathryn Galvan, recalled.

"He was having car accidents, fender benders. Very groggy all the time," she said. He spent much of his day sleeping. When confronted, "He would say, 'I have it under control. I know what I'm doing.'"

(Kathryn Galvan)

“I have it under control. I know what I’m doing.”

— Kathryn Galvan recalling the words of her brother, Ernest P. Gallego

Gallego died. A toxicology test showed lethal levels of oxycodone in his blood.

When his mother died in 2012, Gallego showed up at the funeral disheveled and confused.

A month and a half later, a police officer found him slumped over the steering wheel of his car in a convenience store parking lot and took him to the hospital, according to a coroner’s report and his sister. The next evening, he laid down on the floor of his father’s living room in La Verne, as he often did to relieve his pain. He never awoke. He was 58.

A toxicology test showed lethal levels of oxycodone in his blood. The label on an OxyContin bottle found nearby directed Gallego to take an 80 milligram pill every 12 hours, according to the coroner’s office. Based on the date Gallego filled the prescription, there should have been 44 pills left. There were 7.

‘Remember, effective relief just takes two’

Purdue developed OxyContin as a cure for pain — and for a financial problem.

The company’s owners were the Sacklers, a New York family of physicians and philanthropists who bought Purdue in 1952. By the late 1980s, the patent on its main source of revenue, a morphine pill for cancer patients called MS Contin, was running out.

Executives anticipated a massive loss of revenue as generic versions drove down the price of MS Contin, according to internal company correspondence from the period.

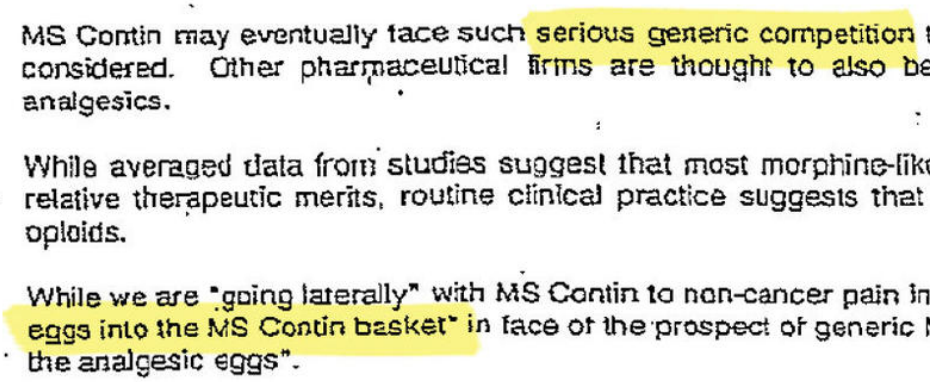
The company was focused on finding a new moneymaker. In a 1990 memo, Robert F. Kaiko, vice president for clinical research, laid out why it was important to develop a second painkiller.

“MS Contin may eventually face such serious generic competition that other controlled-release opioids must be considered,” Kaiko wrote.

1990

Purdue's Need for a New Painkiller

In this 1990 memo, Robert Kaiko, the scientist who would go on to help invent OxyContin, explains why Purdue needs another painkiller.



MS Contin may eventually face such serious generic competition
considered. Other pharmaceutical firms are thought to also be
analgesics.

While averaged data from studies suggest that most morphine-like
relative therapeutic merits, routine clinical practice suggests that
opioids.

While we are "going laterally" with MS Contin to non-cancer pain in
eggs into the MS Contin basket" in face of the prospect of generic
the analgesic eggs".

(http://documents.latimes.com/purdues-need-new-painkiller-1990/)

Purdue already had developed a technique to stretch a drug’s release over time. In MS Contin, the technique made morphine last eight to 12 hours. Kaiko and his colleagues decided to use it on an old, cheap narcotic, oxycodone.

Sold under several names and formulations, including Percocet and Roxicodone, oxycodone controls pain for up to six hours.

With the delayed-release technique, executives theorized, the drug would last 12 hours — at least twice as long as generics and the high end of MS Contin’s range.

Over the next decade, Purdue sunk more than $40 million into development of OxyContin, Paul D. Goldenheim,then-vice president of scientific and medical affairs, wrote in a 2003 court declaration.

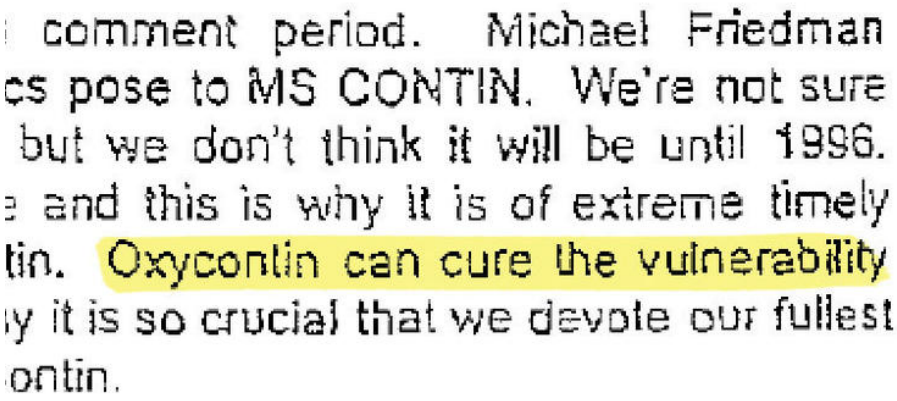
Sales and marketing representatives gathered at the company’s headquarters, then in Norwalk, Conn., in March 1995 to start planning the roll-out of the new drug.

“OxyContin can cure the vulnerability of the ... generic threat and that is why it is so crucial that we devote our fullest efforts now to a successful launch of OxyContin,” then chief executive Michael Friedman told the group, according to minutes of the meeting.

1995

OxyContin Launch

At a 1995 meeting, Purdue executives described how OxyContin could "cure" the "vulnerability" of generic competition and laid out how they planned to market the drug.


comment period. Michael Friedman
cs pose to MS CONTIN. We're not sure
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(http://documents.latimes.com/oxycontin-launch-1995/)

The first patients to use OxyContin were women recuperating from abdominal and gynecological surgery at two hospitals in Puerto Rico in 1989. In the clinical study, designed and overseen by Purdue scientists and paid for by the company, 90 women were given a single dose of the drug while other patients were given short-acting painkillers or placebos. None of the women were regular users of painkillers, so they were more susceptible to the effects of narcotics.

Even so, more than a third of the women given OxyContin started complaining about pain in the first eight hours and about half required more medication before the 12-hour mark, according to an FDA analysis of the study.

The study found that OxyContin was safe, relieved pain and lasted longer than the short-acting painkillers.

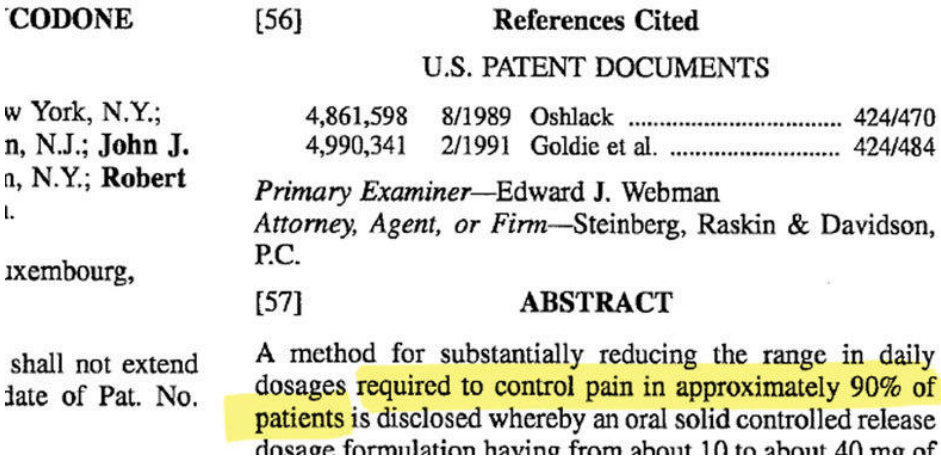
Purdue moved ahead on two paths: seeking patents for its new drug and running additional clinical trials to secure FDA approval.

In a 1992 submission to the Patent Office, the company portrayed OxyContin as a medical breakthrough that controlled pain for 12 hours “in approximately 90% of patients.” Applying for a separate patent a few years later, Purdue said that once a person was a regular user of OxyContin, it “provides pain relief in said patient for at least 12 hours after administration.”

1992

OxyContin Patent

Applying for a patent in 1992, Purdue said OxyContin controlled pain for 12 hours "in approximately 90% of patients."



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[56] **References Cited**

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4,861,598	8/1989	Oshlack	424/470
4,990,341	2/1991	Goldie et al.	424/484

Primary Examiner—Edward J. Webman
Attorney, Agent, or Firm—Steinberg, Raskin & Davidson, P.C.

[57] **ABSTRACT**

A method for substantially reducing the range in daily dosages required to control pain in approximately 90% of patients is disclosed whereby an oral solid controlled release dosage formulation having from about 10 to about 40 mg of

(http://documents.latimes.com/oxycontin-patent-1992/)

Purdue's researchers, meanwhile, were conducting at least a half dozen clinical trials, according to the company's FDA application. In study after study, many patients given OxyContin every 12 hours would ask for more medication before their next scheduled dose.

For example, in one study of 164 cancer patients, one third of those given OxyContin dropped out because they found the treatment "ineffective," according to an FDA analysis of the study. Researchers then changed the rules of the study to allow patients to take supplemental painkillers, known as "rescue medication," in between 12-hour doses of OxyContin.

In another study of 87 cancer patients, "rescue was used frequently in most of the patients," and 95% resorted to it at some point in the study, according to a journal article detailing the clinical trial.

A Tennessee pain specialist whom Purdue selected to field-test the drug in 1995 as part of the FDA approval process eventually moved 8 of 15 chronic pain patients to 8-hour dosing because they were not getting adequate relief taking the drug twice a day.

This prompted a letter from Purdue's medical director.

"This situation concerns me as OxyContin has been developed for q12h dosing," Dr. Robert Reder wrote to the Memphis physician, using medical shorthand for 12-hour dosing. "I request that you not use a q8h dosing regimen."

Narcotic painkillers work differently in different people. Some drug companies discuss that variability on their product labels and recommend that doctors adjust the frequency with which patients take the drugs, depending on their individual response.

The label for Purdue's MS Contin, for instance, recommends that doctors prescribe the drug every eight or 12 hours to suit the patient. The morphine tablet, Kadian, manufactured by Actavis, is designed to be taken once a day, but the label states that some patients may need a dose every 12 hours.

BEHIND THE STORY

How we reported the investigation↗ (/oxycontin-about)

Despite the results of the clinical trials, Purdue continued developing OxyContin as a 12-hour drug. It did not test OxyContin at more frequent intervals.

To obtain FDA approval, Purdue had to demonstrate that OxyContin was safe and as effective as other pain drugs on the market. Under agency guidelines for establishing duration, the company had to show that OxyContin lasted 12 hours for at least half of patients. Purdue submitted the Puerto Rico study, which showed that.

The FDA approved the application in 1995.

Dr. Curtis Wright, who led the agency's medical review of the drug, declined to comment for this article. Shortly after OxyContin's approval, he left the FDA and, within two years, was working for Purdue in new product development, according to his sworn testimony in a lawsuit a decade ago.

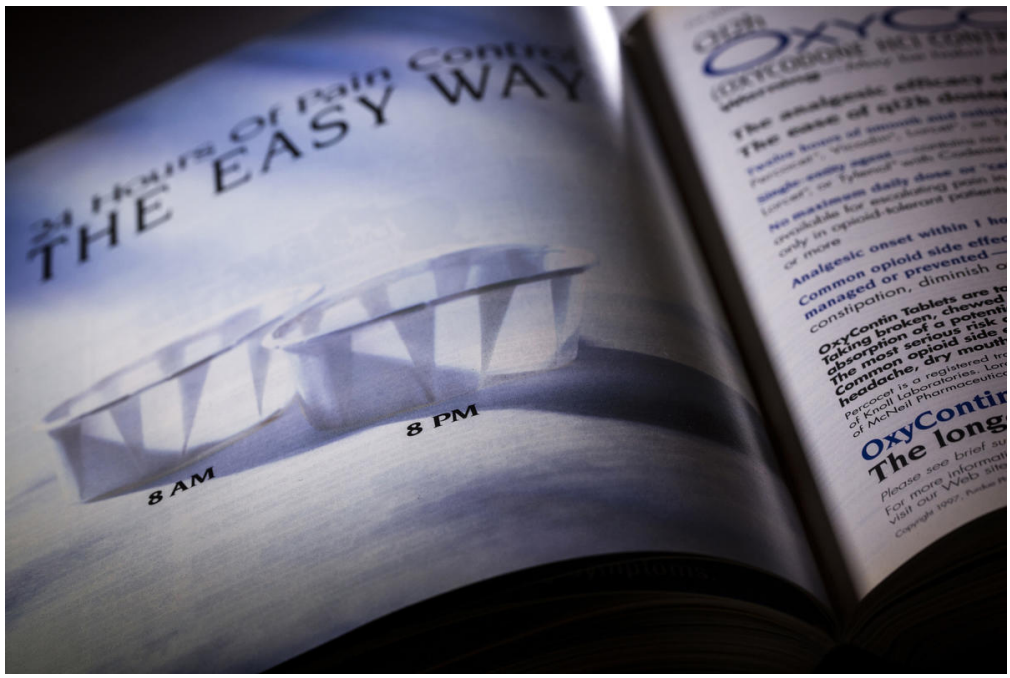
The Times asked the FDA for comment on the drug's failure to provide 12 hours of relief for many patients. Officials at the agency declined to be interviewed.

In a written statement, spokeswoman Sarah Peddicord said that although the FDA approved OxyContin for use every 12 hours, "it should be well understood by physicians that there will be some individual variability in the length of time that patients respond to this drug...

"While the labeled dosing regimen is a reasonable starting point, physicians should carefully individualize their approach to patients based on how quickly they metabolize the drug," Peddicord wrote.

After OxyContin hit the market in 1996, ads in medical journals left no ambiguity about how long it lasted. A spotlight illuminated two dosage cups, one marked 8 AM and the other 8 PM.

"REMEMBER, EFFECTIVE RELIEF JUST TAKES TWO," the ads said.



A 1997 OxyContin advertisement in the American Family Physician shows marketing promoting the benefits of 12-hour dosing. (Liz. O. Baylen / Los Angeles Times)

'What time is it? Oh, God, I have to medicate'

The year OxyContin was introduced, Elizabeth Kipp, a 42-year-old stay-at-home mom, went to her doctor in Kansas City, Kan. She had struggled with back pain since age 14, when she was thrown from a horse while practicing for an equestrian competition.

In the intervening decades, she'd taken short-acting generic painkillers. On that day in 1996, her physician said he had something new for her to try.

He told her to take OxyContin every 12 hours. Kipp, who had a bachelor's degree in plant science from the University of Delaware, said she followed his instructions precisely.

"I'm a scientist, very regimented," she said.

For the first two or three hours, she experienced a "modicum of relief." Then her pain roared back, accompanied by nausea, she said in an interview. Only the next pill would relieve her suffering.

She spent hours lying rigidly on her bed, waiting.

"I was watching the clock. 'What time is it? Oh, God, I have to medicate,' " she said. "My whole nervous system is on red alert."

(Dan Ray / For The Times)

“You want a description of hell? I can give it to you.”

— Elizabeth Kipp

Kipp began taking OxyContin in 1996 to cope with pain from a back injury sustained when she was 14.

When she complained to her doctor, he gave her stronger doses but kept her on the 12-hour schedule, as Purdue instructs physicians to do. The change had little effect.

For a year and a half, she spent each day cycling through misery and relief. Sometimes, she said, she contemplated suicide.

“You want a description of hell,” Kipp recalled. “I can give it to you.”

She eventually checked herself into rehab and said she no longer takes painkillers.

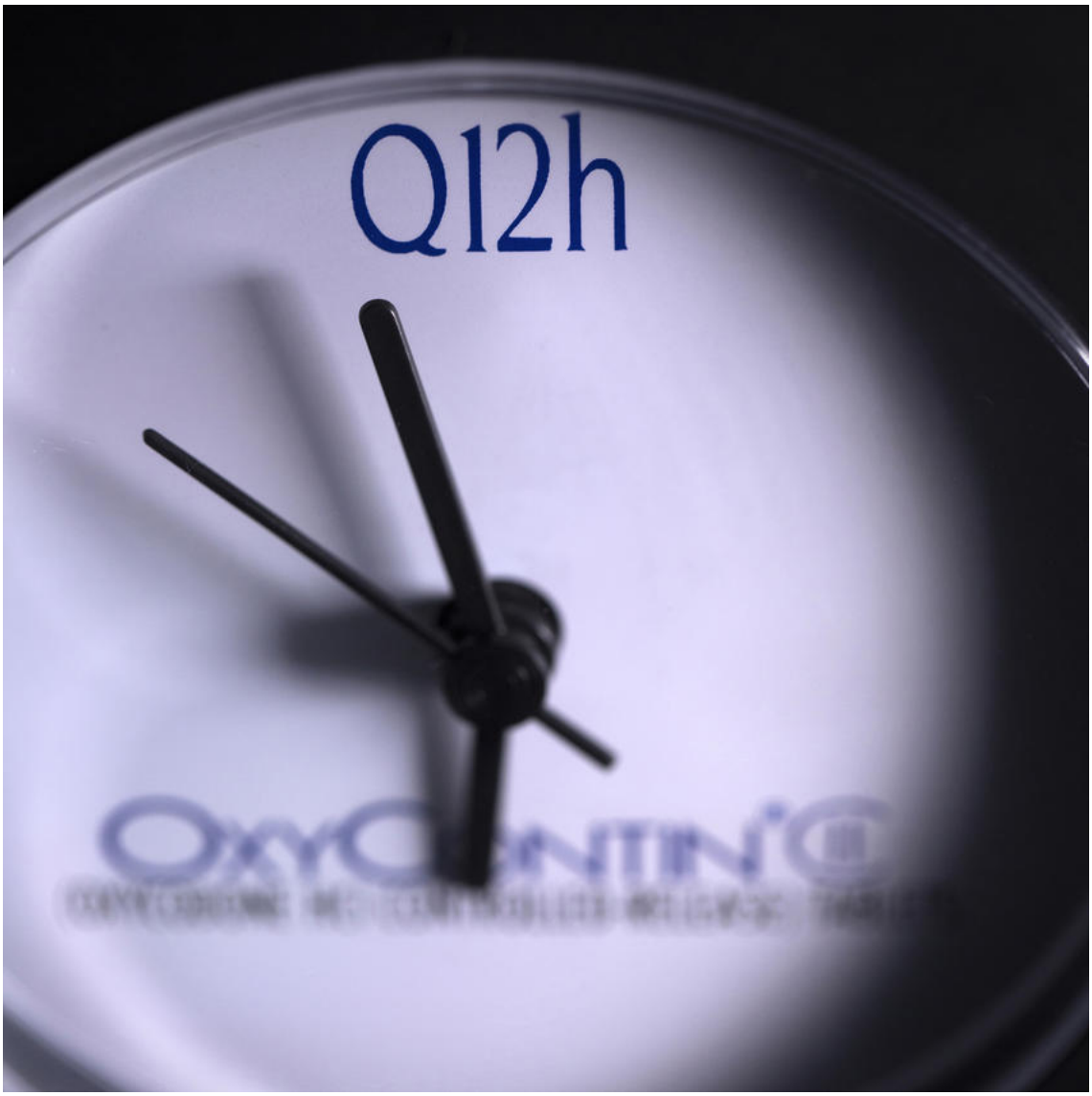
Before OxyContin, doctors had viewed narcotic painkillers as dangerously addictive and primarily reserved their long-term use for cancer patients and the terminally ill. Purdue envisioned a bigger market.

“We do not want to niche OxyContin just for cancer pain,” a marketing executive explained to employees planning the drug’s debut, according to minutes of the 1995 meeting.

The company spent $207 million on the launch, doubling its sales force to 600, according to a court declaration. Sales reps pitched the drug to family doctors and general practitioners to treat common conditions such as back aches and knee pain. Their hook was the convenience of twice-a-day dosing.

With Percocet and other short-acting drugs, patients have to remember to take a pill up to six times a day, Purdue told doctors. OxyContin “spares patients from anxious ‘clock-watching,’” a 1996 news release said.

Sales reps showered prescribers with clocks and fishing hats embossed with “Q12h.” The company invited doctors to dinner seminars and flew them to weekend junkets at resort hotels, where they were encouraged to prescribe OxyContin and promote it to colleagues back home.



A clock that Purdue distributed to doctors and healthcare professionals to promote OxyContin. (Liz. O. Baylen / Los Angeles Times)

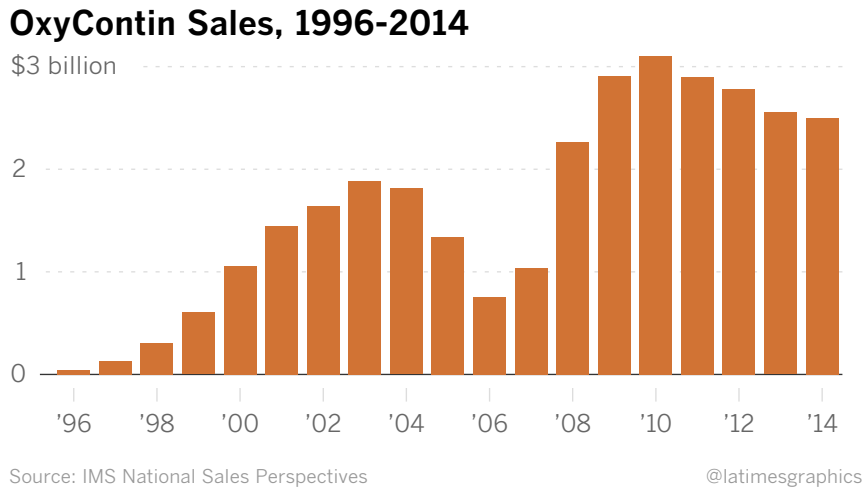
The marketing succeeded in ways that astonished even Purdue executives. OxyContin didn’t just replace MS Contin revenues. It dwarfed them.

By the third year, sales were more than double MS Contin's peak, according to sworn testimony by a Purdue executive. By the fifth, OxyContin was generating annual revenue of more than $1 billion. Sales would continue to climb until 2010, when they leveled off at $3 billion.

Purdue's owners, the Sackler family, were already rich — the family name adorns a wing of the Metropolitan Museum of Art and several galleries in the British Museum. The success of OxyContin brought a whole new level of wealth. Forbes magazine last year estimated the Sacklers' worth at $14 billion, which, the magazine noted, put the family ahead of American dynasties such as the Mellons and Rockefellers.

OxyContin's impact on the practice of medicine was similarly transformative. Other drug companies began marketing their own narcotic painkillers for routine injuries. By 2010, one out of every five doctor's visits in the U.S. for pain resulted in a prescription for narcotic painkillers, according to a Johns Hopkins University study.

OxyContin accounted for a third of all sales revenue from painkillers that year, according to industry data.



Rates of addiction and overdose have soared alongside the rise in prescriptions. News coverage of these problems in Appalachia and New England in the late 1990s made OxyContin notorious. Purdue dispatched representatives to Virginia, Maine and elsewhere to defend its drug. They blamed misuse of OxyContin and insisted their pill was a godsend for pain sufferers when taken as directed.

"A lot of these people say, 'Well, I was taking the medicine like my doctor told me to,' and then they start taking them more and more and more," Purdue senior medical director, Dr. J. David Haddox, told a reporter in 2001. "I don't see where that's my problem."

The U.S. Justice Dept. launched a criminal investigation, and in 2007 the company and three top executives pleaded guilty to fraud for downplaying OxyContin's risk of addiction. Purdue and the executives were ordered to pay $635 million. The case centered on elements of Purdue's marketing campaign that suggested to doctors that OxyContin was less addictive than other painkillers.

In the years after the settlement, Purdue funded programs to prevent pharmacy robberies and keep teenagers from stealing relatives' pills. The company eventually rolled out a tamper-resistant version of the painkiller that was harder to crush and snort.

But in all the scrutiny of Purdue and OxyContin, the problem of the drug wearing off early was not addressed.

Purdue sales reps who spent their days visiting doctors to talk up OxyContin heard repeatedly that the drug didn't last. In reports to headquarters, they wrote that many physicians were prescribing it for three or even four doses a day.

Company officials worried that if OxyContin wasn't seen as a 12-hour drug, insurance companies and hospitals would balk at paying hundreds of dollars a bottle.

Some already were.

Dr. Lawrence Robbins started prescribing OxyContin at his Chicago migraine clinic shortly after it hit the market. The neurologist recalled in an interview that "70 to 80%" of his patients reported that the drug "just lasts four, five, six, seven hours." Robbins started telling people to take it more frequently. But insurance carriers often refused to cover the pharmacy bill for more than two pills a day, he said.

Over the years, he wrote insurance companies more than 25 times on behalf of patients who he believed needed OxyContin more frequently than every 12 hours, he said. In some cases, the insurers relented. When others did not, Robbins switched the patients to another drug.

Robbins said he had no choice: "If they are having a real struggle with opioid withdrawal, sure, you have to do something."

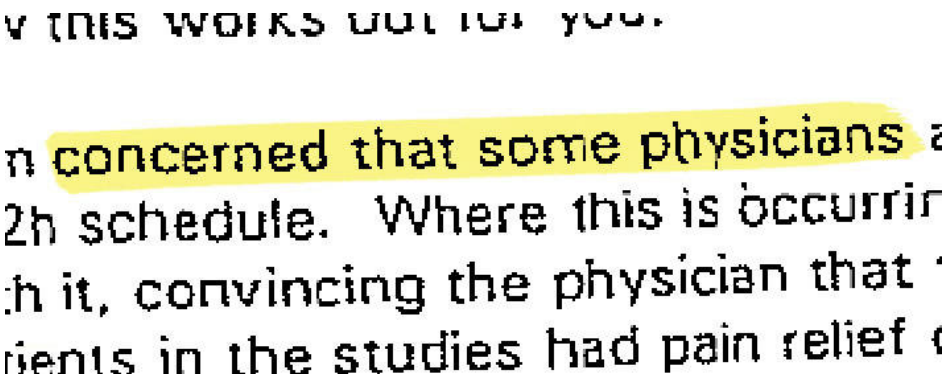
For Purdue, doctors like Robbins were a problem that had to be confronted.

"I am concerned that some physicians are using OxyContin on a q8h schedule rather than a q12h schedule," a regional manager in Atlanta, Windell Fisher, wrote in November 1996 — 11 months after OxyContin went on sale.

1996

Sales Manager on Q12 dosing

In this 1996 letter, a Purdue regional manager writes that he is concerned about doctors prescribing OxyContin at 8-hour intervals. Sales reps should visit those physicians and convince them to go back to 12-hour dosing, he writes.


v this works out for you.

n concerned that some physicians
2h schedule. Where this is occurrir
:h it, convincing the physician that
nients in the studies had pain relief

(http://documents.latimes.com/sales-manager-on12-hour-dosing-1996/)

In the memo, Fisher told a district sales manager what to do:

"Where this is occurring, you need to educate the representative on how to deal with it," convincing the physician that there is no need to do this, and that 100% of the patients in the studies had pain relief on a q12h dosing regimen."

By 2000, it was clear that chiding memos to sales reps weren't enough. Data analyzed by company employees showed that one in five OxyContin prescriptions was for use every eight hours, or even more frequently.

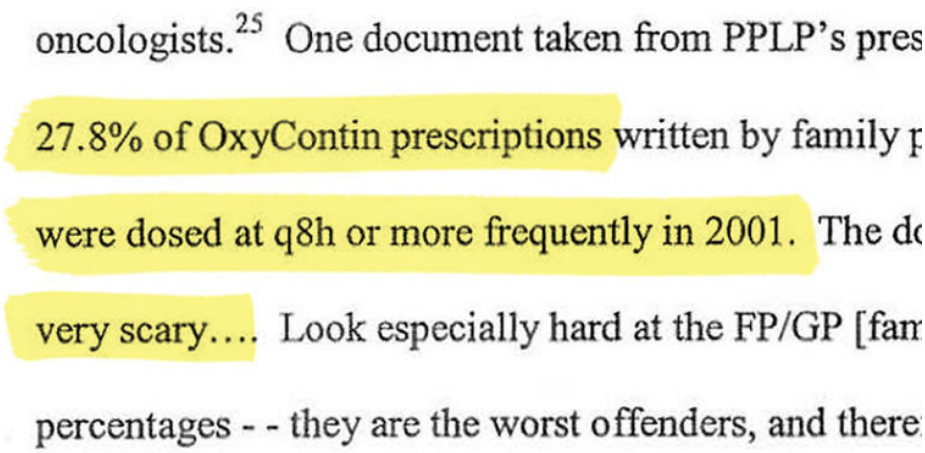
Purdue held closed-door meetings to retrain its sales force on the importance of 12-hour dosing, according to training documents, some included in sealed court files and others described in FDA files.

"These numbers are very scary," managers warned sales reps during one workshop.

2004

FDA Filing

In a 2004 petition to the FDA, attorneys for the state of Connecticut described the alarm inside Purdue when some doctors began prescribing OxyContin at more frequent intervals. "These numbers are very scary," sales reps were told.


oncologists.[25] One document taken from PPLP's pres

27.8% of OxyContin prescriptions written by family p

were dosed at q8h or more frequently in 2001. The do

very scary.... Look especially hard at the FP/GP [fam

percentages - - they are the worst offenders, and there

(http://documents.latimes.com/fda-filing-2004/)

"Managed care plans are beginning to refuse to fill prescriptions," they were told in another presentation. Reps were ordered to visit doctors and "refocus the clinician back to q12h." Doctors needed to be reminded "on every call," they were told.

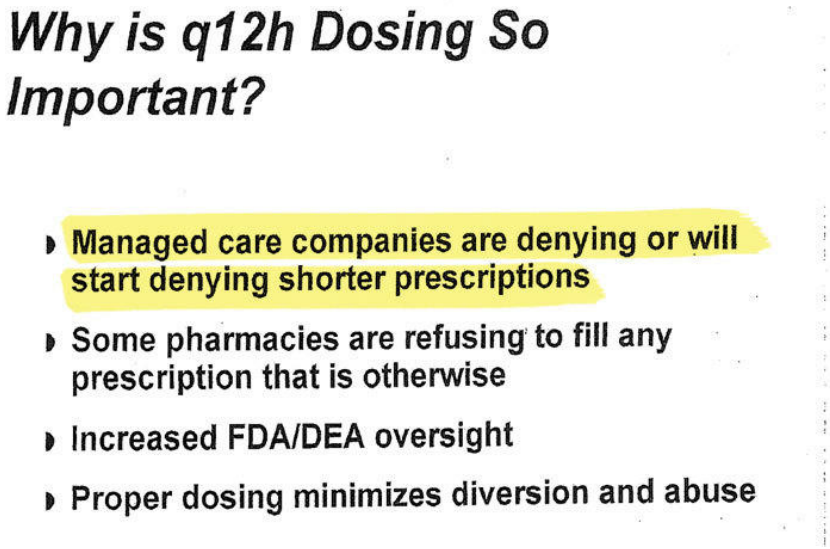
"There is no Q8 dosing with OxyContin," one sales manager told her reps, according to a memo cited in an FDA filing. She added that 8-hour dosing "needs to be nipped in the bud. NOW!!"

If a doctor complained that OxyContin didn't last, Purdue reps were to recommend increasing the strength of the dose rather than the frequency. There is no ceiling on the amount of OxyContin a patient can be prescribed, sales reps were to remind doctors, according to the presentation and other training materials.

2001

Workshop Presentation

After some physicians began prescribing OxyContin more frequently than every 12 hours, Purdue summoned its sales force to special seminars. As this 2001 presentation shows, company officials were concerned more frequent dosing would hurt business.



(http://documents.latimes.com/q12-workshops-2001/)

Boosting the dosage could extend the duration to some degree, but it didn't guarantee 12 hours of relief. Higher doses did mean more money for Purdue and its sales reps. The company charged wholesalers on average about $97 for a bottle of the 10-milligram pills, the smallest dosage, while the maximum strength, 80 milligrams, ran more than $630, according to 2001 sales data the company disclosed in litigation with the state of West Virginia. Commissions and performance evaluations for the sales force were based in part on the proportion of sales from high-dose pills.

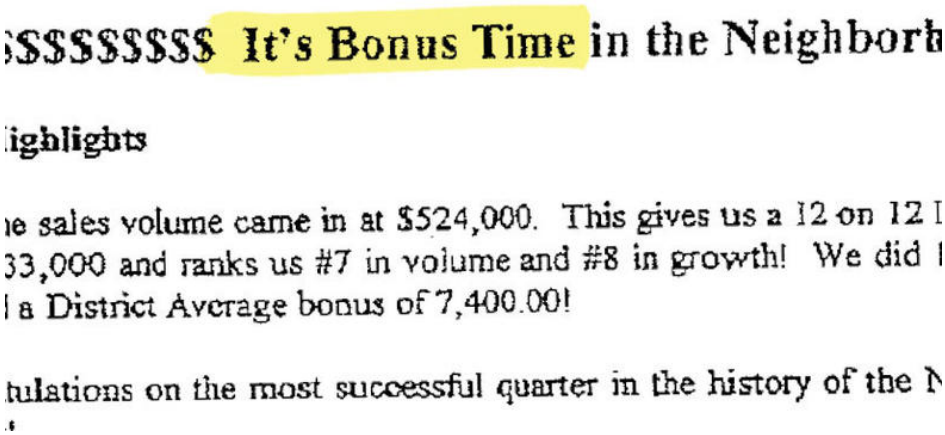
A West Virginia supervisor told one of his highest performing sales reps in a 1999 letter that she could "blow the lid off" her sales and earn a trip to Hawaii if she persuaded more doctors to write larger doses.

In an August 1996 memo headlined "$$$$$$$$$$$$ It's Bonus Time in the Neighborhood!" a manager reminded Tennessee reps that raising dosage strength was the key to a big payday.

1996

Letter to Sales Reps

In this 1996 memo entitled "It's Bonus Time in the Neighborhood," a Purdue sales manager told her staff to talk up stronger doses of OxyContin in conversations with doctors.



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ıe sales volume came in at $524,000. This gives us a 12 on 12 I
33,000 and ranks us #7 in volume and #8 in growth! We did
l a District Average bonus of 7,400.00!

tulations on the most successful quarter in the history of the N

(http://documents.latimes.com/letter-sales-reps-1996/)

"He who sells 40mg" the largest pill available at the time "will win the battle," the manager wrote.

By 2004, Purdue was seeing "a trend away from prescribing OxyContin" more frequently than every 12 hours, according to a company filing with the FDA.

In the training materials reviewed by The Times, little was said about the effect of higher doses on patient health. Those on higher doses of opioids are more likely to overdose, according to numerous research studies. An analysis of the medical records of more than 32,000 patients on OxyContin and other painkillers in Ontario, Canada, found that one in 32 patients on high doses fatally overdosed.

"In other words," the lead researcher, David Juurlink, said in an interview, "they are more likely to die as a result of their medication than almost anything else."

'Death was looking real good to me'

As a varsity athlete at the University of Central Florida and later a public school teacher, Burgess MacNamara was used to following rules.

That changed in 1999 when he had knee surgery and his doctor put him on OxyContin. MacNamara, then a 27-year-old gym teacher at an elementary school near Orlando, was familiar with painkillers. He'd been given Percocet and Vicodin for sports injuries, but he said OxyContin was unlike anything he'd ever experienced.

"The first six hours, it is awesome," he said. Then the effect began to "teeter off" and he became preoccupied with his next dose: "That's all you think about. Your whole day revolves around that."

MacNamara said he soon began taking pills early.

"I can't even tell you the times I actually waited 12 hours," he said. "There weren't many of them."

(Christopher Berkey for the Los Angeles Times)

> “Death was looking real good to me. ”
>
> **— Burgess MacNamara**

MacNamara began taking OxyContin in 1999, after a knee surgery.

Within a month, he was crushing and snorting the pills. Within a year, he was forging prescriptions. He eventually tried heroin, which was cheaper, and other drugs. MacNamara was arrested for forging prescriptions, possession of controlled substances, stealing pills from a school clinic and other drug-fueled crimes. He lost his teaching career and spent 19 months behind bars.

“Death was looking real good to me,” recalled MacNamara, who said he has been sober for the last two and a half years.

As OxyContin's popularity grew, a handful of scientists outside Purdue published research raising questions about the 12-hour claim. Scientists affiliated with the Oklahoma University College of Medicine found in 2002 that nearly 87% of those prescribed OxyContin at a school pain clinic were taking it more frequently than every 12 hours. The reason, researchers wrote, was "perceived end-of-dose failure."

A separate study underwritten by a Purdue competitor, Janssen Pharmaceutica, reached a similar conclusion. Researchers surveyed chronic pain patients treated with OxyContin and reported that less than 2% said the drug lasted 12 hours and nearly 85% said it wore off before eight, according to a 2003 journal article detailing the research.

In the real world practice of medicine, some doctors turned away from OxyContin entirely. San Francisco public health clinics stopped dispensing the painkiller in 2005, based in part on feedback from patients who said it wore off after eight hours. The clinics switched to generic morphine, which has a similar duration and costs a lot less.

"What I had come to see was the lack of evidence that it was any better than morphine," Dr. Mitchell Katz, then head of the San Francisco public health department, said in an interview.

"What I had come to see was the lack of evidence that it was any better than morphine," Dr. Mitchell Katz, then head of the San Francisco public health department, said in an interview. (Christina House / For The Times)

Patients began filing lawsuits in the early 2000s that accused Purdue of overstating OxyContin's duration, among other complaints. One of the plaintiffs was a retired Alabama businessman named H. Jerry Bodie.

His doctor had Bodie on 30 milligrams of OxyContin every eight hours for chronic back pain. A Purdue sales rep persuaded him to switch Bodie to a higher dose every 12 hours, according to a judge's summary of the evidence.

Bodie returned to his doctor repeatedly, saying the drug wasn't working, according to their sworn testimony. The doctor kept raising the dose, eventually putting Bodie on 400 milligrams a day.

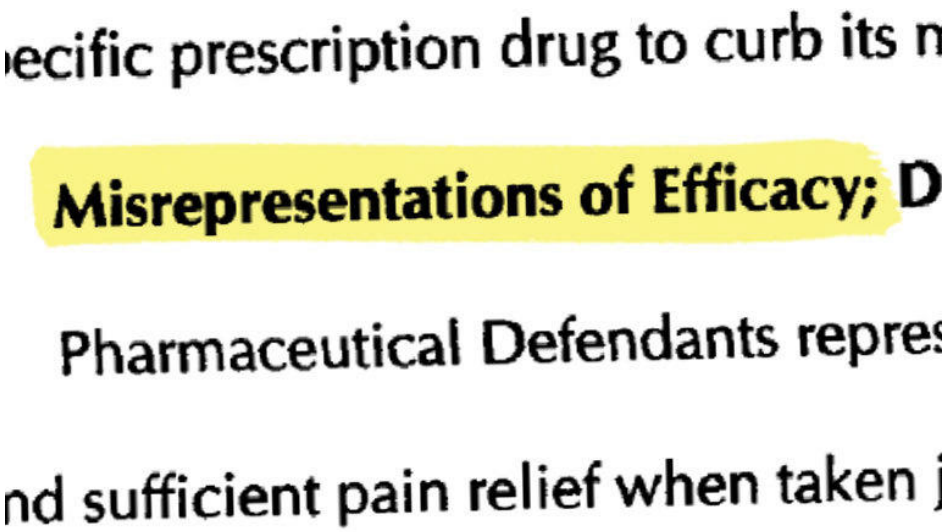
"I was more or less just a zombie," Bodie said in a deposition.

Bodie's lawsuit and hundreds of others filed by OxyContin users and their families never got before a jury. Purdue got suits dismissed by asserting, among other defenses, a legal doctrine which shields drug companies from liability when their products are prescribed by trained physicians. Purdue settled other lawsuits on confidential terms.

2002

Bodie Lawsuit

In a 2002 federal suit, Alabama businessman H. Jerry Bodie accused Purdue of overstating the duration of OxyContin, among other complaints. The lawsuit was dismissed.



(http://documents.latimes.com/bodie-lawsuit-2002/)

In these legal battles, the company successfully petitioned courts to have evidence sealed, citing the need to protect trade secrets. The sealed materials included internal memos to members of the Sackler family and others, FDA correspondence, testimony from executives and sales reps' reports.

They remain sealed to this day. The Times reviewed thousands of pages of them.

In the fall of 2004, in a remote courthouse in Appalachia, the 12-hour dosing issue came close to a public airing. The West Virginia attorney general was pressing a lawsuit against Purdue demanding reimbursement of "excessive prescription costs" paid by the state through programs for the poor and elderly. The state accused the company of deceptive marketing, including the 12-hour claim.

Frances Hughes, then the state's chief deputy attorney general, said the last allegation grew out of investigators' interviews with addicts and their families. In describing problems with OxyContin, many said the drug wore off hours early.

"What was happening was that they were taking more than they were prescribed because the pain medication wasn't working," Hughes recalled in an interview.

Purdue's legal team made numerous attempts to get the suit dismissed or moved from state to federal court, where the company had succeeded in getting many cases tossed out. All these efforts failed.

Purdue had one final shot at avoiding trial: A motion for summary judgment. The judge hearing the case in rural McDowell County was Booker T. Stephens, son of a local coal miner and the first African American elected to the West Virginia circuit court.

To make this critical argument, the company tapped Eric Holder Jr., who had been the nation's first African American deputy attorney general. On Oct. 13, 2004, the man who would become President Obama's attorney general argued that West Virginia prosecutors didn't have sufficient evidence to warrant a trial.

Eric Holder, later the Attorney General, appeared in 2004 for Purdue Pharma in a West Virginia court case. (Francine Orr / Los Angeles Times)

Stephens disagreed. He ruled that there was enough evidence that a jury could find Purdue had made deceptive claims about OxyContin, including how long it lasted.

"Most of the patients in the clinical trials required additional medication, so called 'rescue medications,' that accompanied their 12-hour OxyContin dose," the judge wrote in his Nov. 5, 2004 ruling. "Plaintiff's evidence shows Purdue could have tested the safety and efficacy of OxyContin at eight hours, and could have amended their label, but did not."

EXHIBIT 52

NEW HOPE FOR MILLIONS OF AMERICANS SUFFERING FROM PERSISTENT PAIN: LONG-ACTING OXYCONTIN TABLETS NOW AVAILABLE TO RELIEVE PAIN

NORWALK, Conn., May 31 /PRNewswire/ -- For patients suffering from moderate to severe pain which requires treatment for more than a few days, such as the pain associated with arthritis, cancer, injuries, lower back problems, and other musculoskeletal conditions, now there is new OxyContin(TM) (oxycodone HCl controlled-release) Tablets C-II (Warning: May be habit forming) -- the first and only 12-hour oxycodone pain medicine.

Purdue Pharma L.P., a leader in pain management, today announced that long-acting OxyContin Tablets (for the treatment of moderate to severe pain lasting more than a few days) is available in U.S. pharmacies with a doctor's prescription.

OxyContin -- the first and only 12-hour oxycodone analgesic

New OxyContin is a significant advance in the treatment of persistent pain. Millions of Americans suffer from moderate to severe chronic pain serious enough to have an impact on their lives. Among the most common causes of persistent, debilitating pain are arthritis, lower back conditions, injuries and cancer. For example, more than eight million Americans are permanently disabled by back pain -- with 65,000 new cases diagnosed each year. Cancer is diagnosed in over one million Americans each year. In advanced stages, nearly 75% of cancer patients have pain that is moderate, severe or very severe. In earlier stages, 30% to 45% of cancer patients experience moderate to severe pain.

Unlike short-acting pain medications, which must be taken every 3 to 6 hours -- often on an "as needed" basis -- OxyContin Tablets are taken every 12 hours, providing smooth and sustained pain control all day and all night. Dosing with OxyContin Tablets on a regular schedule spares patients from anxious "clock-watching" when pain must be controlled over long periods.

Twice-daily dosing simplifies and improves patients' lives

"The importance of pain control with twice-daily dosing can't be stressed strongly enough," reported Paul D. Goldenheim, M.D., Vice President of Purdue Pharma. "Until now, patients with persistent pain had to take products such as Percocet(R), Vicodin(R), and Tylenol(R) with Codeine as often as six times a day. Now, with every twelve-hour OxyContin dose, many patients may experience pain relief and may enjoy daytime activities and nighttime rest without the inconvenience of taking tablets every four to six hours. Moreover, we've discovered that the simplicity and convenience of twice-daily dosing also enhances patient compliance with their doctor's instructions."

Patient benefits demonstrated in clinical studies

In clinical trials of OxyContin Tablets, involving more than 700 patients, key findings included:

-- Onset of pain relief occurred within 1 hour for most patients.

-- 12 hours of smooth and sustained pain control were provided by

OxyContin Tablets.

-- Common opioid-related side effects (except constipation)

diminished over time, even as daily doses increased.

-- By relieving their pain, OxyContin improved patients' quality of

life, mood and sleep, as compared to placebo treatment.

"Because of its effectiveness and good acceptability to patients, our studies suggest that OxyContin is an ideal choice in progressive pain management when around-the-clock therapy is indicated," added Dr. Goldenheim.

OxyContin allows flexible dosing

OxyContin is available in three tablet strengths (10 mg, 20 mg, 40 mg) -- ideal for long-term control over a broad range of pain. Small, color-coded tablets make the product easy to swallow and easy to identify.

OxyContin Tablets are available by prescription only. OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids, including OxyContin, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritis, headache, dry mouth, sweating, and weakness.

Headquartered in Norwalk, Connecticut, Purdue Pharma L.P. is a leader in the research and development of long-acting pharmaceuticals, with a special emphasis on pain relief. Through Partners Against Pain(R) and other programs, the company is also committed to providing effective professional and patient education services.

Purdue Pharma, its international associated companies and affiliates distribute pharmaceuticals to more than 100 countries. Associated companies maintain production and research facilities in the United States, Canada, the United Kingdom, Germany and Israel, as well as marketing and distribution centers in Ireland, Austria and Switzerland.

NOTE: Percocet is a registered trademark of the DuPont Merck Pharmaceutical Co. Vicodin is a registered

trademark of Knoll Pharmaceutical Company. Tylenol with Codeine is a registered trademark of McNeil Pharmaceutical.

Please see brief summary of prescribing information which follows the background information.

BACKGROUND

Persistent Pain Goes Largely Untreated

Millions of Americans suffer from moderate to severe persistent pain. Arthritis, lower back conditions, cancer and injuries are among the most common causes of persistent, debilitating pain.

For example, more than eight million Americans are permanently disabled by back pain -- with 65,000 new cases diagnosed each year. Cancer is diagnosed in over one million Americans each year. At the time of diagnosis and at the intermediate stage, 30%-45% of cancer patients experience moderate to severe pain. Nearly 75% of patients with advanced cancer have pain; of these, 40%-50% describe it as moderate to severe; another 25% -30% report their pain as very severe or excruciating.

Despite the availability of medications to control or alleviate pain, the underreporting and undertreatment of pain remains one of the most pressing issues affecting the quality of patient care today.

Why is pain undertreated?

The reasons why pain remains so inadequately managed are many, but several have been identified: 1) poor assessment by healthcare professionals, 2) underreporting by patients who accept pain as an inevitable consequence of disease, and 3) underuse of pain medications because of unwarranted fears of uncontrollable side effects and/or addiction by physicians and patients alike.

What is being done about this problem?

In response to these concerns, new guidelines for the treatment of acute pain and cancer pain were published in the December 20, 1995 issue of Journal of the American Medical Association (JAMA), encouraging patients to become more active in managing their personal pain.

Patients must communicate with physicians/nurses.

According to Mitchell B. Max, M.D., chairman of the American Pain Society Quality of Care Committee, which developed the new guidelines, "Patients should let their doctor or nurse know when they are in pain; if the current treatment is not working, it should be adjusted. Outpatients should be able to talk to a doctor or nurse by telephone 24 hours a day to adjust their pain medication if needed."

The fear of addiction is exaggerated.

One cause of patient resistance to appropriate pain treatment -- the fear of addiction -- is largely unfounded. According to Dr. Max, "Experts agree that most pain caused by surgery or cancer can be relieved, primarily by carefully adjusting the dose of opioid (narcotic) pain reliever to each patient's need, and that there is very little risk of addiction from the proper uses of these drugs for pain relief."

Paul D. Goldenheim, M.D., Vice President of Purdue Pharma L.P. in Norwalk, Connecticut, agrees with this assessment. "Proper use of medication is an essential weapon in the battle against persistent pain. But too often fear, misinformation and poor communication stand in the way of their legitimate use."

Brief summary on q12h OxyContin(TM)
(oxycodone HCl controlled-release) Tablets
Warning -- May be habit forming
10 mg * 20 mg * 40 mg

Before prescribing, see complete prescribing information, including DOSAGE AND ADMINISTRATION

INDICATIONS AND USAGE:

For the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days.

CONTRAINDICATIONS:

OxyContin is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS:

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED. OxyContin TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF OXYCODONE.

Respiratory Depression

Respiratory depression, the chief hazard from all opioid agonist preparations, occurs most frequently in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure. Oxycodone produces effects which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

OxyContin, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. OxyContin may produce orthostatic hypotension in ambulatory patients. OxyContin, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS:

General -- OxyContin tablets are intended for use in patients who require oral pain therapy with an opioid agonist of more than a few days duration. As with any opioid analgesic, it is critical to adjust the dosing regimen individually for each patient.

Selection of patients for treatment with OxyContin should be governed by the same principles that apply to the use of similar controlled-release opioid analgesics. Opioid analgesics given on a fixed-dosage schedule have a narrow therapeutic index in certain patient populations, especially when combined with other drugs, and should be

reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension. Physicians should individualize treatment in every case, using non-opioid analgesics, prn opioids and/or combination products, and chronic opioid therapy with drugs such as OxyContin in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Health Care Policy and Research, and the American Pain Society.

Use of OxyContin is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone, like all opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

OxyContin, like all opioid analgesics, should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery

OxyContin is not recommended pre-operatively (preemptive analgesia) or for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

Patients who are already receiving OxyContin tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given and the temporary changes in physiology caused by the surgical intervention (see PRECAUTIONS: Drug-Drug Interactions).

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is the occurrence of withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

Significant tolerance should not occur in most of the patients treated with the lowest doses of oxycodone. It should be expected, however, that a fraction of cancer patients will develop some degree of tolerance and require progressively higher dosages of OxyContin to maintain pain control during chronic treatment. Regardless of whether this occurs as a result of increased pain secondary to disease progression or pharmacological tolerance, dosages can usually be increased safely by adjusting the patient's dose to maintain an acceptable balance

between pain relief and side effects. The dosage should be selected according to the patient's individual analgesic response and ability to tolerate side effects. Tolerance to the analgesic effect of opioids is usually paralleled by tolerance to side effects, except for constipation.

Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with opioid antagonist activity (see OVERDOSAGE). If OxyContin is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. This is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate or heart rate.

If signs and symptoms of withdrawal occur, patients should be treated by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of OxyContin combined with symptomatic support.

Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin should be given the following information by the physician:

1. OxyContin tablets were designed to work properly only if swallowed whole. They may release all their contents at once if broken, chewed or crushed, resulting in a risk of overdose.

2. Report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.

3. Do not adjust the dose of OxyContin without consulting the prescribing professional.

4. OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).

5. Do not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because additive effects may occur.

6. Women of childbearing potential who become, or are planning to become, pregnant should consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.

7. OxyContin is a potential drug of abuse. Patients should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.

8. Patients may pass empty matrix "ghosts" (tablets) via colostomy or in the stool; this is of no concern since the active medication has already been absorbed.

9. If patients have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.

Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids or illicit drugs which cause central nervous system depression.

Use in Drug and Alcohol Addiction

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including OxyContin, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

OxyContin, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers and alcohol because respiratory depression, hypotension and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Mutagenicity

Studies of oxycodone in animals to evaluate its carcinogenic and mutagenic potential have not been conducted owing to the length of clinical experience with the drug substance.

Pregnancy

Teratogenic Effects -- Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg (48 mg/m2) and 125 mg/kg (1375 mg/m2), respectively. These doses are 4 and 60 times a human dose of 120 mg/day (74 mg/m2), based on mg/kg of a 60 kg adult (0.7 and 19 times this human dose based upon mg/m2). The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects -- Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Labor and Delivery

OxyContin is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin since oxycodone may be excreted in the milk.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 have not been established with this dosage form of oxycodone. However, oxycodone has been used extensively in the pediatric population in other dosage forms, as have the excipients used in this formulation. No specific increased risk is expected from the use of this form of oxycodone in pediatric patients old enough to safely take tablets if dosing is adjusted for the patient's weight. It must be remembered that OxyContin tablets cannot be crushed or divided for administration.

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15%. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen based on age, and the usual doses and dosing intervals are appropriate for the geriatric patient. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients.

Hepatic Impairment

A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (less than 60 mL/min.), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials

ADVERSE REACTIONS:

Serious adverse reactions which may be associated with OxyContin tablet therapy in clinical use are those observed with other opioid analgesics, including: respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension or shock (see OVERDOSE).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose- dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (more than 5%) include constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

In clinical trials comparing OxyContin with immediate-release oxycodone and placebo, the most common adverse events (more than 5%) reported by patients (pts) at least once during therapy were:

	OxyContin		Immediate-Release		Placebo
	n=227		n=225		n=45
	# pts	(%)	# pts	(%)	# pts (%)
Constipation	52	(23)	58	(26)	3 (7)
Nausea	52	(23)	60	(27)	5 (11)
Somnolence	52	(23)	55	(24)	2 (4)
Dizziness	29	(13)	35	(16)	4 (9)
Pruritus	29	(13)	28	(12)	1 (2)
Vomiting	27	(12)	31	(14)	3 (7)

Headache	17	(7)	19	(8)	3 (7)
Dry Mouth	13	(6)	15	(7)	1 (2)
Asthenia	13	(6)	16	(7)	-- --
Sweating	12	(5)	13	(6)	1 (2)

The following adverse experiences were reported in OxyContin treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials:

General: accidental injury, chest pain, facial edema, malaise, neck

pain, pain

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal

disorder, increased appetite, nausea and vomiting, stomatitis

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, peripheral edema,

thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization,

depression, emotional lability, hallucination, hyperkinesia,

hypesthesia, hypotonia, malaise, paresthesia, speech disorder,

stupor, tinnitus, tremor, vertigo, withdrawal syndrome

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis

Special Senses: abnormal vision, taste perversion

Urogenital: dysuria, hematuria, impotence, polyuria, urinary

retention, urination impaired

DRUG ABUSE AND DEPENDENCE (Addiction):

OxyContin is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone products are common targets for both drug abusers and drug addicts. Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug.

Drug addiction (drug dependence, psychological dependence) is characterized by a preoccupation with the procurement, hoarding, and abuse of drugs for non-medicinal purposes. Drug dependence is treatable, utilizing a multi-disciplinary approach, but relapse is common. Iatrogenic "addiction" to opioids legitimately used in the management of pain is very rare.

OxyContin consists of a dual-polymer matrix, intended for oral use only. Parenteral venous injection of the tablet constituents, especially talc, can be expected to result in local tissue necrosis and pulmonary granulomas.

OVERDOSAGE:

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. They should be administered cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including OxyContin. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

SAFETY AND HANDLING:

OxyContin tablets are solid dosage forms that pose no known health risk to health-care providers beyond that of any controlled substance. As with all such drugs, care should be taken to prevent diversion or abuse by proper handling.

CAUTION:

DEA Order Form Required. Federal law prohibits dispensing without prescription.

Manufactured by The PF Laboratories, Inc., Totowa, N.J. 07512.

Distributed by Purdue Pharma L.P., Norwalk, CT 06850-3590

Copyright 1995, Purdue Pharma L.P.

U.S. Patent Numbers 4,861,598; 4,970,075; and 5,266,331

December 5, 1995 A4909-BS
-0- 5/31/96

/CONTACT: Mike Innaurato of Purdue Pharma L.P., 203-854-7332/

CO: Purdue Pharma L.P. ST: Connecticut IN: MTC SU: PDT

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Product introduction

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EXHIBIT 53

The New York Times

BUSINESS DAY

In Guilty Plea, OxyContin Maker to Pay $600 Million

By BARRY MEIER MAY 10, 2007

ABINGDON, Va., May 10 — The company that makes the narcotic painkiller OxyContin and three current and former executives pleaded guilty today in federal court here to criminal charges that they misled regulators, doctors and patients about the drug's risk of addiction and its potential to be abused.

To resolve criminal and civil charges related to the drug's "misbranding," the parent of Purdue Pharma, the company that markets OxyContin, agreed to pay some $600 million in fines and other payments, one of the largest amounts ever paid by a drug company in such a case.

Also, in a rare move, three executives of Purdue Pharma, including its president and its top lawyer, pleaded guilty today as individuals to misbranding, a criminal violation. They agreed to pay a total of $34.5 million in fines.

OxyContin is a powerful, long-acting narcotic that provides relief of serious pain for up to 12 hours. Initially, Purdue Pharma contended that OxyContin, because of its time-release formulation, posed a lower threat of abuse and addiction to patients than do traditional, shorter-acting painkillers like Percocet or Vicodin.

That claim became the linchpin of the most aggressive marketing campaign ever undertaken by a pharmaceutical company for a narcotic painkiller. Just a few years after the drug's introduction in 1996, annual sales reached $1 billion. Purdue Pharma heavily promoted OxyContin to doctors like general practitioners, who had often had little training in the treatment of serious pain or in recognizing signs of drug abuse in patients.

But both experienced drug abusers and novices, including teenagers, soon discovered that chewing an OxyContin tablet or crushing one and then snorting the powder or injecting it with a needle produced a high as powerful as heroin. By 2000, parts of the United States, particularly rural areas, began to see skyrocketing rates of addiction and crime related to use of the drug.

More details about the plea agreements were expected to be announced at a news conference this afternoon in Roanoke, Va., by John L. Brownlee, the United States attorney for the Western District of Virginia. "Misbranding" is a broad statute that makes it a crime to mislabel a drug, fraudulently promote it or market it for an unapproved use.

In a proceeding this morning in United States District Court here, both Purdue Pharma and the three executives acknowledged that the company fraudulently marketed OxyContin for six years as a drug that was less prone to abuse, as well as one that also had fewer narcotic side effects.

In a statement, the company said: "Nearly six years and longer ago, some employees made, or told other employees to make, certain statements about OxyContin to some health care professionals that were inconsistent with the F.D.A.-approved prescribing information for OxyContin and the express warnings it contained about risks associated with the medicine. The statements also violated written company policies requiring adherence to the prescribing information."

"We accept responsibility for those past misstatements and regret that they were made," the statement said.

The time period covered by the guilty pleas runs from late 1995, when the Food and Drug Administration approved OxyContin for sale, to mid-2001, when Purdue

Pharma, faced with both public criticism and regulatory scrutiny, dropped its initial marketing claims for the drug.

Federal officials said that internal Purdue Pharma documents show that company officials recognized even before the drug was marketed that they would face stiff resistance from doctors who were concerned about the potential of a high-powered narcotic like OxyContin to be abused by patients or cause addiction.

As a result, company officials developed a fraudulent marketing campaign designed to promote OxyContin as a time-released drug that was less prone to such problems. The crucial ingredient in OxyContin is oxycodone, a narcotic that has been used for many years. But unlike other medications like Percocet that contain oxycodone along with other ingredients, OxyContin is pure oxycodone, with a large amount in each tablet because of the time-release design.

The drug has proven to be valuable in treating serious, long-lasting pain.

Purdue Pharma acknowledged in the court proceeding today that "with the intent to defraud or mislead," it marketed and promoted OxyContin as a drug that was less addictive, less subject to abuse and less likely to cause other narcotic side effects than other pain medications.

For instance, when the painkiller was first approved, F.D.A. officials allowed Purdue Pharma to state that the time-release of a narcotic like OxyContin "is believed to reduce" its potential to be abused.

But according to federal officials, Purdue sales representatives falsely told doctors that the statement, rather than simply being a theory, meant that OxyContin had a lower potential for addiction or abuse than drugs like Percocet. Among other things, company sales officials were allowed to draw their own fake scientific charts, which they then distributed to doctors, to support that misleading abuse-related claim, federal officials said.

Between 1995 and 2001, OxyContin brought in $2.8 billion in revenue for Purdue Pharma, a closely held company based in Stamford, Conn. At one point, the drug accounted for 90 percent of the company's sales.

As part of the plea agreement, Purdue Frederick, a holding company for Purdue Pharma that is also closely held, pleaded guilty to a felony charge of misbranding OxyContin. Of the $600 million the company agreed to pay in criminal and civil penalties, some $470 million represents fines to federal and state agencies. The remaining $130 million represents payments to settle civil litigation brought by patients and other private plaintiffs.

Purdue Pharma has also agreed, among other things, to subject itself to independent monitoring of its practices. The three top former and current Purdue Pharma executives pleaded guilty to criminal misdemeanor charges of misbranding, a charge that does not require prosecutors to show knowledge or intent on the executives' part. However, the three individuals ran Purdue Pharma during the period in question.

Those executives are: Michael Friedman, the company's president, who agreed to pay $19 million in fines; Howard R. Udell, its top lawyer, who agreed to pay $8 million; and Dr. Paul D. Goldenheim, its former medical director, who agreed to pay $7.5 million.

In a separate statement, Purdue said: "Mr. Friedman, Dr. Goldenheim (while at Purdue) and Mr. Udell neither engaged in nor tolerated the misconduct at issue in this investigation. To the contrary, they took steps to prevent any misstatements in the marketing or promotion of OxyContin and to correct any such misstatements of which they became aware."

EXHIBIT 54

A TIMES INVESTIGATION

More than 1 million OxyContin pills ended up in the hands of criminals and addicts. What the drugmaker knew

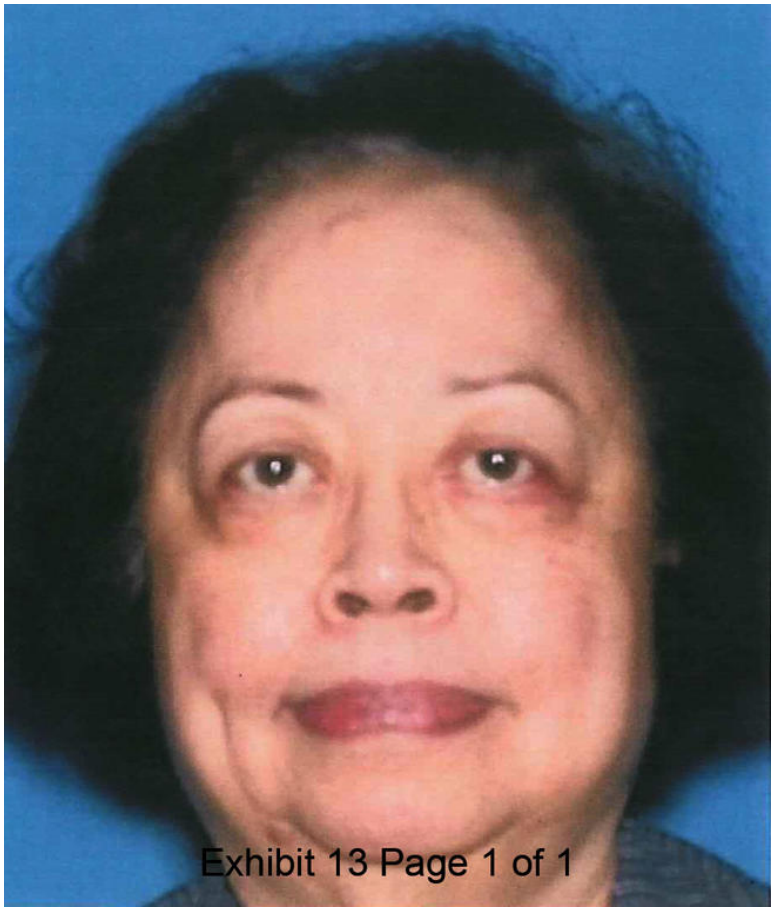
By HARRIET RYAN, LISA GIRION AND SCOTT GLOVER

JULY 10, 2016

In the waning days of summer in 2008, a convicted felon and his business partner leased office space on a seedy block near MacArthur Park. They set up a waiting room, hired an elderly physician and gave the place a name that sounded like an ordinary clinic: Lake Medical.

The doctor began prescribing the opioid painkiller OxyContin – in extraordinary quantities. In a single week in September, she issued orders for 1,500 pills, more than entire pharmacies sold in a month. In October, it was 11,000 pills. By December, she had prescribed more than 73,000, with a street value of nearly $6 million.

At its headquarters in Stamford, Conn., Purdue Pharma, the maker of OxyContin, tracked the surge in prescriptions. A sales manager went to check out the clinic and the company launched an investigation. It eventually concluded that Lake Medical was working with a corrupt pharmacy in Huntington Park to obtain large quantities of OxyContin.



During a single week in September 2008, Eleanor Santiago of Lake Medical, issued orders for 1,500 pills, more than entire pharmacies sold in a month. (Court exhibit)

“Shouldn’t the DEA be contacted about this?” the sales manager, Michele Ringler, told company officials in a 2009 email. Later that evening, she added, “I feel very certain this is an organized drug ring…”

Purdue did not shut off the supply of highly addictive OxyContin and did not tell authorities what it knew about Lake Medical until several years later when the clinic was out of business and its leaders indicted.

By that time, 1.1 million pills had spilled into the hands of Armenian mobsters, the Crips gang and other criminals.

A Los Angeles Times investigation found that, for more than a decade, Purdue collected extensive evidence suggesting illegal trafficking of OxyContin and, in many cases, did not share it with law enforcement or cut off the flow of pills. A former Purdue executive, who

investigated pharmacies for criminal activity, acknowledged that even when the company had evidence pharmacies were colluding with drug dealers, it did not stop supplying distributors selling to those stores.

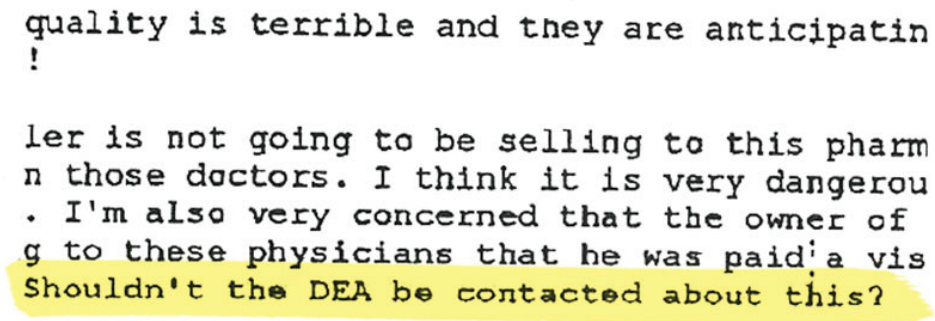
Purdue knew about many suspicious doctors and pharmacies from prescribing records, pharmacy orders, field reports from sales representatives and, in some instances, its own surveillance operations, according to court and law enforcement records, which include internal Purdue documents, and interviews with current and former employees.

Sounding the alarm

September 1, 2009

"Shouldn't the DEA be contacted about this?"

Purdue district manager Michele Ringler urges company officials to alert the DEA. She later recalled a previous visit to the clinic and said, "I feel very certain this is an organized drug ring..."



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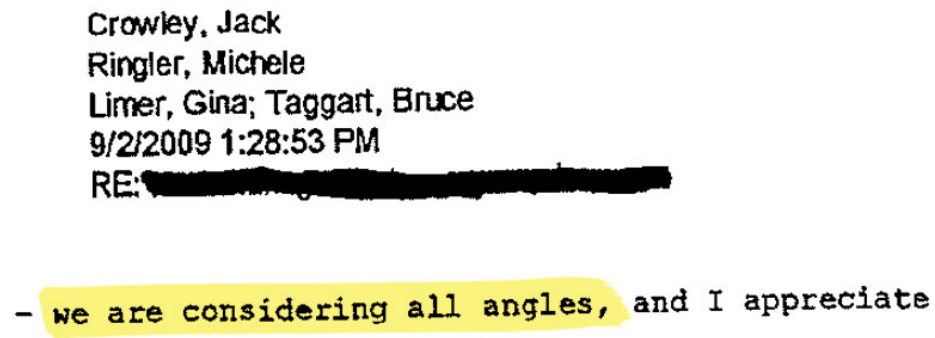
g to these physicians that he was paid a vis
Shouldn't the DEA be contacted about this?

(http://documents.latimes.com/sounding-alarm/)

September 2, 2009

A Purdue officials response

Jack Crowley responds to Ringler's concern.



Crowley, Jack
Ringler, Michele
Limer, Gina; Taggart, Bruce
9/2/2009 1:28:53 PM
RE: [redacted]

- we are considering all angles, and I appreciate

(http://documents.latimes.com/sounding-alarm/)

Joseph Rannazzisi, who was the top DEA official responsible for drug company regulation until last year, said he was not aware of the scope of evidence collected by Purdue. Under federal law, drugmakers must alert the DEA to suspicious orders. The agency interprets that

law, he said, to include a duty to report orders from customers if the company suspects pills are going to the black market.

“They have an obligation, a legal one but also a moral one,” he said.

The federal government has not accused Purdue of any wrongdoing in the case of Lake Medical or other suspected drug operations.

In a statement (http://documents.latimes.com/purdues-response-july-2016/), a Purdue lawyer said the company had “at all times complied with the law.” General counsel Phil Strassburger said Purdue had reduced supplies of OxyContin to distributors servicing some pharmacies it suspected of corruption, but had to be careful such reductions did not interfere with legitimate patients getting medication.

This is the second part of an L.A. Times investigation of OxyContin, the nation’s best-selling and widely abused painkiller.

The story is based on interviews with current and former Purdue employees, law enforcement officials, medical professionals, pharmaceutical industry experts and others as well as court filings, law enforcement records and internal Purdue documents. The company records come from court cases and government investigations and include many records sealed by the courts.

He defended the company’s decision not to share all its evidence with authorities.

“It would be irresponsible to direct every single anecdotal and often unconfirmed claim of potential misprescribing to these organizations,” Strassburger said.

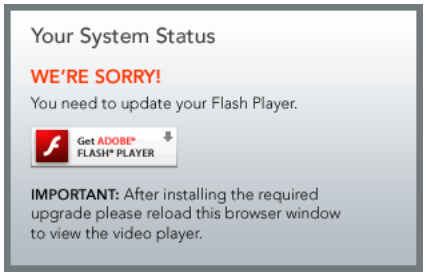
What Purdue knew

More than 194,000 people have died since 1999 from overdoses involving opioid painkillers, including OxyContin. Nearly 4,000 people start abusing those drugs every day, according to government statistics. The prescription drug epidemic is fueling a heroin crisis, shattering communities and taxing law enforcement officers who say they would benefit from having information such as that collected by Purdue.

A private, family-owned corporation, Purdue has earned more than $31 billion from OxyContin, the nation’s bestselling painkiller (/projects/oxycontin-part1). A year before Lake Medical opened, Purdue and three of its executives pleaded guilty to federal charges of misbranding OxyContin in what the company acknowledged was an attempt to mislead doctors about the risk of addiction. It was ordered to pay $635 million in fines and fees.

WATCH THE VIDEO

Inside an OxyContin ring



(http://www.adobe.com/go/getflash/)

After the settlement, Purdue touted a high-powered internal security team it had set up to guard against the illicit use of its drug. Drugmakers like Purdue are required by law to establish and maintain "effective controls" against the diversion of drugs from legitimate medical purposes.

That anti-diversion effort at Purdue was run by associate general counsel Robin Abrams, a former assistant U.S. attorney in New York who had prosecuted healthcare fraud and prescription drug cases. Jack Crowley, who held the title of executive director of Controlled Substances Act compliance and had spent decades at the DEA, was also on the team.

Purdue had access to a stream of data showing how individual doctors across the nation were prescribing OxyContin. The information came from IMS, a company that buys prescription data from pharmacies and resells it to drugmakers for marketing purposes.

That information was vital to Purdue's sales department. Representatives working on commission used it to identify doctors writing a small number of OxyContin prescriptions who might be persuaded to write more.

By combing through the data, Purdue also could identify physicians writing large numbers of prescriptions – a potential sign of drug dealing.

Soon after Lake Medical opened, Purdue zeroed in on prescriptions of 80-milligram, maximum-strength OxyContin written by Eleanor Santiago. Once a respected physician, the 70-year-old was in failing health and drowning in debt when she took the job of clinic medical director alongside several other doctors.

The 80-milligram pills Santiago prescribed had the strength of 16 Vicodin tablets. Doctors generally reserved those pills for patients with severe, chronic pain who had built up a tolerance over months or years.

In the illegal drug trade, however, "80s" were the most in demand.

During the years that Lake Medical was in business, the pills could be crushed and smoked or snorted, producing a high similar to the drug's chemical cousin, heroin. On the street, the pills went for up to $80 apiece.

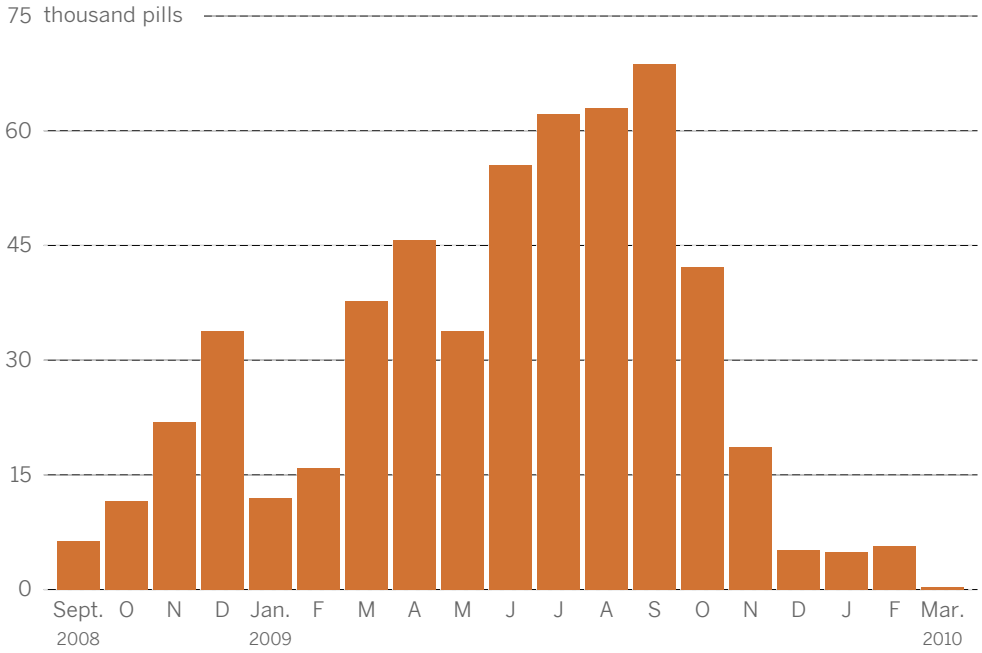
A physician writing a high volume of 80s was a red flag for anyone trying to detect how OxyContin was getting onto the black market.

The number of prescriptions Santiago was writing wasn't merely high. It was jaw-dropping. Many doctors would go their entire careers without writing a single 80s prescription. Santiago doled out 26 in a day.

Purdue was tracking her prescriptions.

Pills prescribed by Santiago

At the Lake Medical Clinic, Dr. Eleanor Santiago prescribed nearly 2,000 mg OxyContin, the strength favored by addicts.



INSIGHTS

Dec. 2008: Purdue lawyers put Santiago in "Region Zero," a company database of doctors suspected of misprescribing narcotics.

Sept. 2009: Purdue sales manager raises alarm about Lake Medical after visiting Huntington Park pharmacy.

March 2010: The clinic closes.

Source: California state prescribing records
Raoul Rañoa, Armand Emamdjomeh / @latimesgraphics

Michele Ringler, the district sales manager for Los Angeles and a company veteran, went to Lake Medical to investigate. When she and one of her sales reps arrived, they found a building that looked abandoned, according to company emails recounting the visit. Inside, the hallways were strewn with trash and lined with a crowd of men who looked like they'd "just got out of L.A. County jail," according to the emails. Feeling uncomfortable, Ringler and the rep left without speaking to Santiago.

When a Purdue security committee met in Stamford in December 2008, less than five months after Lake Medical opened, Santiago was under review, according to internal records and interviews. The panel, comprised of three company lawyers, could have reported her to the DEA. Instead it opted to add her name to a confidential roster of physicians suspected of recklessly prescribing to addicts or dealers.

Purdue calls that list Region Zero and has been adding names to it since 2002. A Times investigation in 2013 (http://www.latimes.com/local/la-me-rx-purdue-20130811-story.html) revealed the existence of the list. At that time, the company acknowledged that there were more than 1,800 doctors in Region Zero.

Purdue directed its sales reps to avoid those doctors, and it didn't tell physicians they had been placed on the list. Company executives told The Times in a 2013 interview that Purdue had reported about 8% of the doctors on the list to authorities.

One doctor Purdue put in Region Zero was Eric Jacobson, a Long Island, N.Y., physician prescribing huge amounts of OxyContin. The company stopped sending sales reps to his office in 2010. The following year, one of Jacobson's patients killed four people, including a high school student, in a pharmacy robbery.

In the investigation, authorities discovered that Jacobson had been selling prescriptions to dealers and addicts for years. The doctor "directly contributed to the tragedy of prescription drug abuse that has swept our district and our nation," said Loretta Lynch, then the region's top federal prosecutor, now the U.S. Attorney General.

Jacobson was convicted of unlawful distribution of oxycodone. The prosecutor and lead investigator told the Times that Purdue did not disclose what it knew about Jacobson to them either before or after the pharmacy slayings.

Following the pills

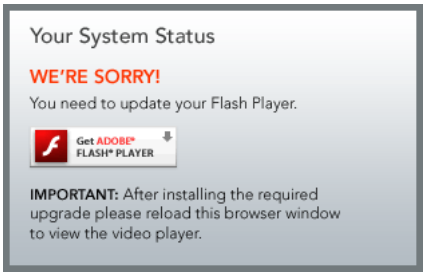
In L.A., Santiago kept writing prescriptions in ever larger numbers.

To keep the OxyContin flowing, Lake Medical needed people. Lots of them. Age, race and gender didn't matter. Just people whose time was cheap. For that, there was no place better than skid row.

Low-level members of the Lake Medical ring known as cappers would set up on Central Avenue or San Pedro Street. The stench of urine was everywhere. People were lying in doorways, sleeping in tents, fighting, shooting up. Who wants to make some money, the cappers would shout.

For as little as $25, homeless people served as straw patients and collected prescriptions for 80s. It required just a few hours at the clinic, filling out a few forms and sitting through a sham examination. They were then driven, often in groups, to a pharmacy, where a capper acting as a chaperone paid the bill in cash. He then took the pills back to the Lake Medical ring leaders who packaged them in bulk for sale to drug dealers.

The skid row connection



(http://www.adobe.com/go/getflash/)

The pills from Lake Medical coursed out of L.A. An informant would later tell an FBI agent that East Hollywood's White Fence gang trafficked pills to Chicago, according to the agent's report. A Crips leader from the Inland Empire also bought OxyContin from Lake Medical, according to law enforcement records.

In the months after the Lake Medical ring started, Purdue was informed that homeless people were being used in an OxyContin ring. In December 2008, the same month Santiago was placed on the Region Zero list, a company sales rep visited Central Care Pharmacy, an Encino store filling Lake Medical prescriptions. The pharmacist said there appeared to be some kind of scam going on with 80-milligram pills, according to the sales representative's report to headquarters. They're shuttling homeless people around to pharmacies, the pharmacist said.

Purdue sent Ringler to follow up and her report on the pharmacist's concerns reached Purdue's security and risk management teams the next day.

Pharmacist complaints

Pharmacist complaints about Santiago kept piling up.

"The first few of these prescriptions…looked legitimate…[but] after those were filled, a steady flow of younger, more ambulatory, customers came in with the same prescriptions," a Temple Street pharmacist told a Purdue representative, according to a January 2009 field report.

Encino pharmacist Tihana Skaricic raised questions about prescriptions from the Lake Medical clinic. (Liz O. Baylen / Los Angeles Times)

Pharmacists from La Canada-Flintridge, Glendale, Moreno Valley and elsewhere also complained to Purdue. Company executives and lawyers received at least 11 reports about Santiago in the four months after they placed her in Region Zero.

On June 10, the Encino pharmacist sent an email to her Purdue sales rep with the subject line "urgent question." The pharmacist said she was being asked to fill prescriptions written by Santiago and other Lake Medical doctors for "lots of Oxy patients."

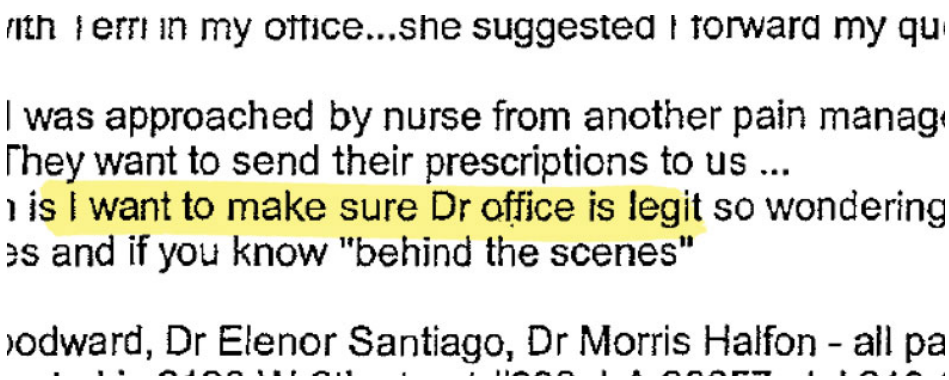
"I want to make sure Dr office is legit," Shaun Skaricic wrote. "So wondering, if you know 'behind the scenes.'"

Reports of concern

June 10, 2009

Pharmacist's letter

In June 2009, an Encino pharmacist emailed a Purdue sales rep and her manager asking for help determining whether OxyContin prescriptions from Lake Medical were legitimate. Purdue did not respond, the pharmacist said in an interview.

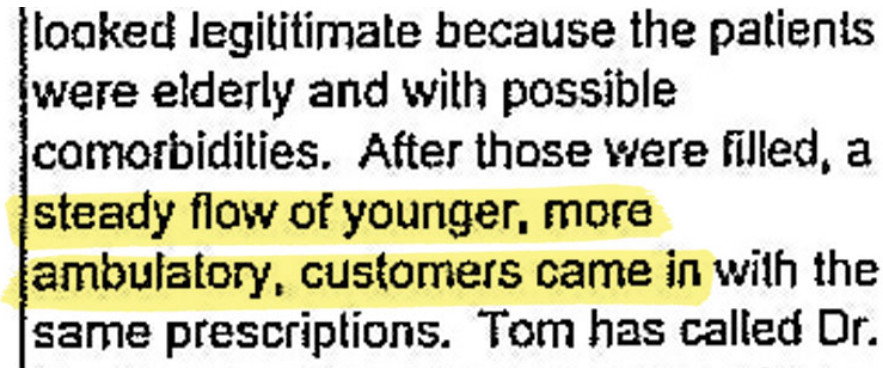


(http://documents.latimes.com/pharmacists-letter/)

January 9, 2009

Suspicious prescriptions

In January 2009, a Purdue sales rep filed a report after paying a sales call to a Temple Street pharmacy. The pharmacy was getting "many suspicious prescriptions from Dr. Eleanor Santiago" for OxyContin.



(http://documents.latimes.com/suspicious-prescriptions/)

The email was forwarded to Ringler, who sent it to a company lawyer, who sent it to Crowley, an executive responsible for compliance with the federal controlled substances law. No one at Purdue ever got back to Skaricic, she said in an interview. Eventually she and some other pharmacists decided on their own to turn away business from Lake Medical.

Had Purdue passed on its concerns, Skaricic said, "I would have stopped filling these prescriptions way earlier."

was sitting on a gold mine.”

With a few keystrokes on his computer at Purdue, Jack Crowley could identify pharmacies around the country that were moving a staggering volume of 80s and almost nothing else.

“I could punch it in at any time…Bang,” Crowley told the Times. “I was sitting on a gold mine.”

Crowley retired from Purdue in 2013 and works in Georgia for a pharmaceutical consulting company. After The Times approached him, he agreed to a series of interviews in which he talked at length about the inner workings of Purdue’s security operation.

Until a decade ago, Purdue, like most drug manufacturers, didn't monitor pharmacies for criminal activity. The DEA has held wholesalers, not drugmakers, responsible for identifying and reporting suspicious orders from their customer pharmacies.

In 2007, the DEA pressured drug manufacturers to do more to stem the prescription drug crisis and warned that it would be looking at every step in the supply chain. In response, Purdue decided to gather detailed information about pharmacies, Crowley said.

The company approached wholesalers and struck agreements allowing the company access to their sales reports. With the new data, the security team in Stamford could see all wholesalers’ OxyContin sales to individual pharmacies, down to the pill.

“I can look at something and say, ‘Geez, that stinks’ without me even visiting the place,” Crowley recalled.

The DEA had access to similar pharmacy purchasing data, but many investigators regarded the database as unwieldy because it encompassed dozens of drugs sold by more than a thousand companies and could be up to six months out of date.

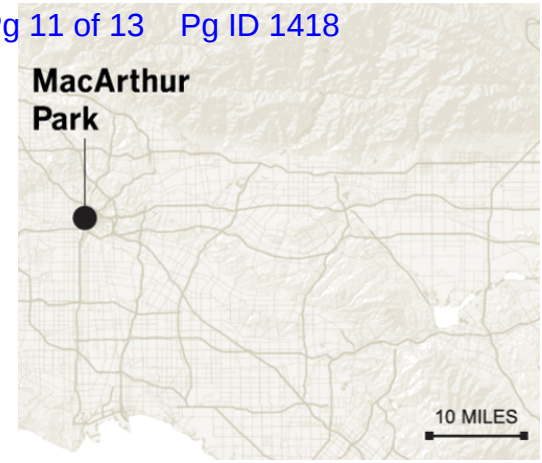
As Lake Medical entered its second year, Crowley’s computer screen showed a handful of small pharmacies in the L.A. area suddenly ordering eye-popping amounts of maximum-strength OxyContin.

At one San Marino store, Huntington Pharmacy, monthly orders for 80s were up nearly 20-fold over the previous year. At another in East L.A., orders jumped 400% in two months. A small shop in Panorama City, Mission Pharmacy, became the top seller of OxyContin in the entire state of California.

Following the pills

Using a doctor and homeless people, ringleaders had prescriptions for OxyContin filled at pharmacies across the L.A. region.

Purdue added those store names to a long list of problematic pharmacies across the country. Each month, a group called the Order Monitoring System committee — Crowley, company lawyer Abrams, the chief security officer, a sales executive and others — met to discuss what to do about the stores, according to security team memos.



(Raoul Rañoa / Los Angeles Times Graphics)

Some on the committee argued for reporting suspicious pharmacies to the DEA and instructing distributors to stop selling to those stores, Crowley said. But he and others felt it was up to the distributors to take action, he said, noting that company policy prohibited employees from reporting pharmacies to the DEA without first consulting their distributors.

In the case of Mission in Panorama City, a top supplier to the Lake Medical ring, the committee decided the best course was for Crowley to "continue to watch" the situation, according to an internal company email.

In an interview, Crowley said that in the five years he spent investigating suspicious pharmacies, Purdue never shut off the flow of pills to any store.

Pharmacies were allowed to buy OxyContin even in cases when Purdue security staffers personally witnessed suspicious behavior. Crowley said during visits to two San Francisco pharmacies, he saw homeless people filling prescriptions and then handing the bottles off to men he suspected were drug dealers. In 2009, he and a Purdue investigator went to Las Vegas to check on Lam's, a pharmacy next to a bar in a mini-mall that Crowley said was one of the top five sellers of OxyContin in the nation.

He and his colleague sat in their rental car watching crowds of young people come and go with pills, Crowley said.

"It was terrible," he recalled. "It was just a drug-distribution operation."

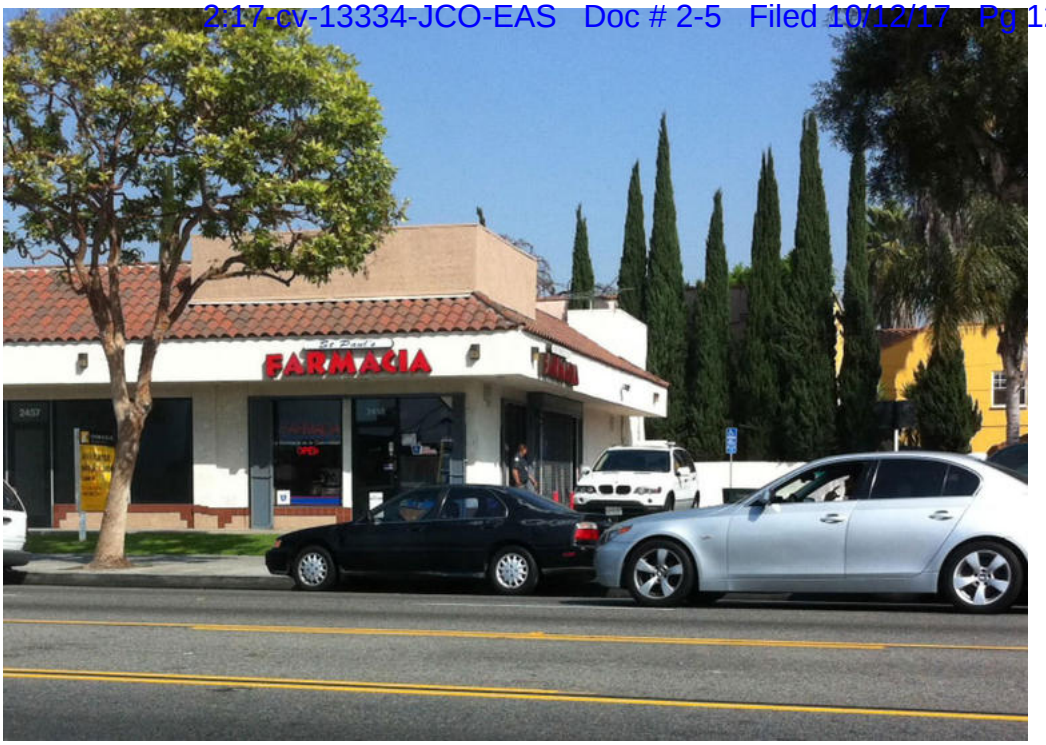
Crowley said he phoned in a tip to a DEA agent he knew in San Francisco, and Mark Geraci, the company's security chief, wrote a letter to the DEA about Lam's. But the company did not share the telltale sales data with the DEA or others in law enforcement, Crowley said. With Lam's, some wholesalers decided to stop supplying the store and Purdue ultimately limited the amount of OxyContin the pharmacy's remaining wholesaler could buy. But in that case, and in San Francisco, the company did not cut off the wholesalers completely.

Federal prosecutors in Las Vegas later targeted Lam's, charging a local drug dealer, an 87-year-old doctor, a pharmacist and others with participating in a criminal ring that furnished pills to addicts as far away as Ohio and New Hampshire. Several were convicted. Others are awaiting trial.

In Southern California, one of Purdue's OxyContin distributors eventually noticed a troubling spike in sales at St. Paul's Pharmacy in Huntington Park, which was filling prescriptions for Lake Medical.

"They are buying a lot of Oxycontin 80s from us," the security chief for distributor HD Smith emailed Crowley in August 2009.

Purdue knew St. Paul's orders for 80s were up nearly 1400%. But the company's monitoring committee "hadn't gotten around to discussing" the store, Crowley wrote in an email to colleagues, and he asked Ringler, the L.A. district manager, to investigate.



St. Paul's pharmacy in Huntington Park was among those that filled prescriptions from Lake Medical for 80mg OxyContin pills. (Court exhibit)

The pharmacist told Ringler his business "exploded" when he started filling 80s for Lake Medical doctors, according to series of emails and reports on her August 2009 visit.

Ringler asked the pharmacist if the cash transactions for maximum-strength OxyContin concerned him, according to the emails, but he declined to answer. When she suggested he call law enforcement, "he said he didn't want to get audited by the DEA," Ringler told supervisors. "I told him that eventually the DEA will track down where these Rxes are getting filled."

HD Smith cut off shipments to the pharmacy after her visit, but other distributors still filled orders from the store and other pharmacies were filling prescriptions from doctors at Lake Medical.

In an email to Crowley and others at Purdue, Ringler said the drug sales were "clearly diversion" – illegal use or distribution of pharmaceuticals.

Reaching out to the DEA "is under serious consideration," Crowley replied. Ringler pushed back, telling him that Lake Medical was "very dangerous" and "an organized drug ring."

"It just seems that trained professionals like the DEA would be better equipped to do further investigation of this clinic," she wrote.

"Thanks, Michele," Crowley replied. "We are considering all angles."

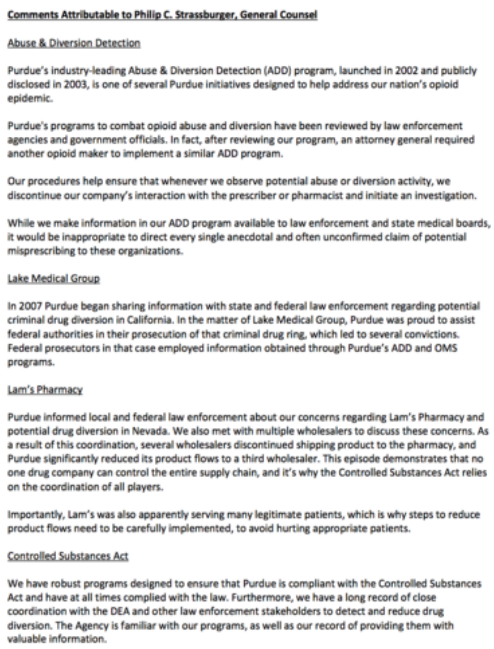
In his statement to The Times, Purdue's general counsel, Strassburger, acknowledged that the company is "required to monitor and report suspicious orders to the DEA," but he noted that "Purdue does not ship prescription products directly to retail pharmacies; it sells only to authorized wholesalers, who maintain their own order monitoring programs."

Purdue's statement↗ (http://documents.latimes.com/purdues-response-july-2016/)

Purdue provided a statement for this story. Read it here. (http://documents.latimes.com/purdues-response-july-2016/)

"Once Purdue identifies the potential suspicious activity of a wholesaler's customer, Purdue informs the wholesaler, so they can perform their due diligence...," Strassburger said.

In the case of Lake Medical, Purdue didn't notify some distributors that it suspected St. Paul's was part of a drug ring. Five months after HD Smith stopped shipments, another wholesaler selling large quantities of 80s to St. Paul's reached out to Crowley seeking information about the store.



Comments Attributable to Philip C. Strassburger, General Counsel

Abuse & Diversion Detection

Purdue's industry-leading Abuse & Diversion Detection (ADD) program, launched in 2002 and publicly disclosed in 2003, is one of several Purdue initiatives designed to help address our nation's opioid epidemic.

Purdue's programs to combat opioid abuse and diversion have been reviewed by law enforcement agencies and government officials. In fact, after reviewing our program, an attorney general required another opioid maker to implement a similar ADD program.

Our procedures help ensure that whenever we observe potential abuse or diversion activity, we discontinue our company's interaction with the prescriber or pharmacist and initiate an investigation.

While we make information in our ADD program available to law enforcement and state medical boards, it would be inappropriate to direct every single anecdotal and often unconfirmed claim of potential misprescribing to these organizations.

Lake Medical Group

In 2007 Purdue began sharing information with state and federal law enforcement regarding potential criminal drug diversion in California. In the matter of Lake Medical Group, Purdue was proud to assist federal authorities in their prosecution of that criminal drug ring, which led to several convictions. Federal prosecutors in that case employed information obtained through Purdue's ADD and OMS programs.

Lam's Pharmacy

Purdue informed local and federal law enforcement about our concerns regarding Lam's Pharmacy and potential drug diversion in Nevada. We also met with multiple wholesalers to discuss these concerns. As a result of this coordination, several wholesalers discontinued shipping product to the pharmacy, and Purdue significantly reduced its product flows to a third wholesaler. This episode demonstrates that no one drug company can control the entire supply chain, and it's why the Controlled Substances Act relies on the coordination of all players.

Importantly, Lam's was also apparently serving many legitimate patients, which is why steps to reduce product flows need to be carefully implemented, to avoid hurting appropriate patients.

Controlled Substances Act

We have robust programs designed to ensure that Purdue is compliant with the Controlled Substances Act and have at all times complied with the law. Furthermore, we have a long record of close coordination with the DEA and other law enforcement stakeholders to detect and reduce drug diversion. The Agency is familiar with our programs, as well as our record of providing them with valuable information.

(http://documents.latimes.com/purdues-response-july-2016/)

'It really takes the 'G' a long time to catch up with these jokers'

In the end, the Lake Medical ring was brought down by a team of state, federal and local investigators who collected tips from citizens and spent hours staking out the clinic, interviewing witnesses and turning junior ring members into informants. When Lake Medical closed in 2010, after a year and a half in business, Purdue had still not shared its wealth of information on the clinic with the authorities, according to law enforcement sources.

In an email to a distributor after the arrest of Santiago and the clinic operators, Crowley criticized the pace of the government investigation.

"It really takes the 'G' a long time to catch up with these jokers," he wrote.

In a memo to supervisors after the clinic was shuttered, Ringler noted that more than 20 doctors in her territory were still doling out large amounts of 80s, some using the same pharmacies Lake Medical had used. She suggested that Purdue use its databases to "proactively" report suspicious prescribing, across the country, to insurers as well as law enforcement.

Purdue did not respond to questions about the proposal. Crowley said he was never told about her plan. Ringler declined to speak to The Times.

The company introduced a new, tamper-resistant OxyContin tablet in August 2010. Addicts found them almost impossible to smoke or snort. Within months, the old 80s were gone from the streets and many dependent on the pills switched to heroin, which was chemically similar and readily available.

In December 2011, two months after the Lake Medical arrests, Purdue lawyer Abrams emailed a DEA official in LA the names of local doctors it suspected of misprescribing OxyContin. Santiago, who had already been arrested, was on the list.

"Basically, it was old news," said Mike Lewis, then the agency's diversion program manager in L.A. The doctors were "people we were already actively investigating or cases we had taken action on."

Two years later, in 2013, Abrams called the U.S. Attorney's Office in L.A. with an offer of

EXHIBIT 55

stamford advocate http://www.stamfordadvocate.com/business/article/Purdue-Pharma-agrees-to-restrict-marketing-of-6464800.php

Purdue Pharma agrees to restrict marketing of opioids

By Bill Fallon, Fairfield County Business Journal **Published 3:32 pm, Tuesday, August 25, 2015**

IMAGE 1 OF 2

Between 2008 and 2011, OxyContin, from Stamford-based Purdue Pharma, accounted for approximately 10 percent of the total oxycodone prescriptions in New York state.

New York state Attorney General **Eric T. Schneiderman** recently announced an agreement with Stamford-based **Purdue Pharma LP** to restrict its opioid marketing efforts. Purdue Pharma had already begun the process.

Purdue Pharma makes the long-acting opioid Oxy-Contin, its brand name for oxycodone pills.

The agreement strengthens and makes permanent an internal Purdue program aimed at preventing the company's sales staff from promoting the powerful painkiller to health care providers who may be involved in abuse and illegal diversion of opioids, according to Schneiderman.

The deal requires Purdue to disclose financial relationships with any individuals, including doctors and other health care professionals, who appear on the company's "unbranded" websites that endorse the benefits of pain treatment. Schneiderman, in a prepared statement, cited inthefaceofpain.com as such a website. He said the company had agreed to "important business practice changes" to help stave off both overprescription and the "opioid addiction epidemic."

"Over the past two decades, New York has experienced a sharp increase in opioid addiction and that has coincided with the substantially increased sale of oxycodone," Schneiderman said. "The public health crisis created by opioid overprescribing in New York remains pervasive and extremely dangerous. My office will work to ensure that prescription drugs are marketed and prescribed responsibly — and that consumers get the information they need about the risks of addiction to painkillers."

Between the 1990s and 2011, prescriptions of oxycodone more than doubled in the U.S. and sales of the product increased more than tenfold.

Between 2008 and 2011, OxyContin accounted for approximately 10 percent of the total oxycodone prescriptions in New York state, Schneiderman said. During that time, according to the **New York City Department of Health and Mental Hygiene**, the number of opioid painkiller prescriptions filled by New York City residents increased by 31 percent, from approximately 1.6 million to approximately 2.2 million, with oxycodone accounting for 53 percent of those prescriptions.

Between 1997 and 2011, there was also a sharp increase in the prevalence of opioid addiction, which in turn has been associated with a rise in overdose deaths and heroin use. According to the federal **Centers for Disease Control and Prevention**, in New York state, from 2003 to 2012, deaths involving opioid analgesics increased five-fold, from 179 in 2003 to 883 in 2012.

Purdue's "Abuse and Diversion Detection" program requires its sales representatives to report to the company any facts that suggest a health care provider to whom it markets opioids may be involved in the abuse or illegal diversion of opioid products. When a provider is reported under the program, Purdue conducts an internal inquiry regarding the provider to determine whether he or she should be placed on a "no-call" list. If a provider is placed on this list, Purdue sales representatives may no longer contact the provider to promote the company's opioid products.

Purdue and the attorney general's office additionally agreed to require Purdue's sales representatives who market Purdue opioid products to health care providers to ask whether the provider has completed an FDA-approved training program regarding the appropriate prescribing of opioids and to provide information about such training. Purdue will also provide, upon request, information regarding addiction treatment resources to providers to whom it markets its opioid products.

As part of the settlement, Purdue Pharma will pay $75,000 in penalties and costs.

Bill Fallon is editor of the Fairfield County Business Journal. For more of his work and that of the journal, see www.westfaironline.com.

EXHIBIT 56

Safe and Effective Opioid Rotation - Perry Fine, M.D.

213 views 1 0 SHARE

OnlineSymposia
Published on Nov 8, 2012

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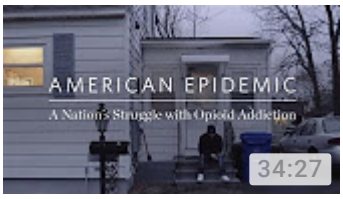
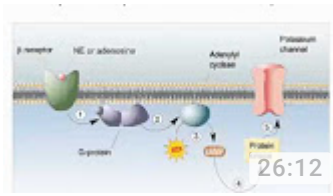


American Epidemic: The Nation's Struggle With Opioid Addiction
Wall Street Journal
375K views

Why Opiod Rotation and the Management of Breakthrough Pain
European Pain Federation - EFIC
15 views

Risks and Rewards of Opioid Rotation
MD Magazine
134 views

Opioid Safety 1
Knut Westlye



PSYC2050 Week 11 Lecture Essentials - Opioids

Chris Goode

12K views

Opioid Manager

MacHealthSci

7K views

Choosing an Opioid for Chronic Pain

MIPharmacists

3K views

Judges Suspect She Lip Sync & Demand her to Stop. What She Did

imryanang

Recommended for you

Newer Opioid Formulations Deter Drug Abuse

MD Magazine

196 views

Chief medical officer interview questions and answers

monivi Ravulapalli

3.4K views

Briarpatch: Dec. 9, 2009 - Opiate Rotation and the Head People

JackScheper

73 views

Melania Trump moved to tears during worship song!

Jonathan Hodges

2.1M views

4:25

TIM ALLEN talks about God

Jesus Daily

3.5M views

5:43

169 views

4:03

Dr. Jose A. Contreras Discusses Rotating Opioids

PainLiveTV
1.1K views

1:06

Shy School Girls Bring The House To TEARS with Their Voices!

imryanang
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8:37

Success in Prescribing Opioids for Chronic Pain

MD Magazine
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▸ 21-Year Old Car Mechanic MAKES Simon Cowell CRY With His Voice

Faith's Channel
Recommended for you

6:23

Dr. Perry Fine American Pain Foundation on Back Pain

GoodNewsBroadcast
983 views

14:43

Great Lifetime Movies 2017 - Rural Girl - Based On a True Story 2017

Callie Stone
783K views

1:28:00

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0 Comments SORT BY

Add a public comment...

EXHIBIT 57

POWERED BY GUIDESTAR

American Pain Foundation

Also Known As: APF
201 N Charles St
Ste 710
Baltimore, MD 21201

- This organization is a 501(c)(3) Public Charity
- Financial information in this report is derived from the organization's December 31, 2010 Form 990.

GENERAL INFORMATION

EIN:	52-2002328
Contact:	Eric Hauth
Year Founded:	Information not available
Ruling Year:	1997
Fiscal Year :	December 31, 2010
Assets:	$2,340,690 (from Dec 31, 2010 Form 990)
Income:	$4,879,865 (from Dec 31, 2010 Form 990)
No. of Board Members:	
No. of Full-Time Employees:	6
No. of Part-Time Employees:	1
No. of Volunteers:	21

Mission and Programs

Mission

APF works to eliminate the undertreatment of pain in America, and prevent needless human suffering. Over 50 million Americans live with devestating chronic pain. APF provides free information and support to help educate people about pain and support them as they advocate for better pain care. APF works locally and nationally to raise awareness about pain, remove barriers to effective pain care, stimulate research, and give pain sufferers a voice. We fight together for the rights of people with pain.

Programs

Program:
Budget: NaN
Category:
Population Served:

Program Description:

The American Pain Foundation's programs include an extensive website full of helpful information for people with pain, caregivers and healthcare professionals. You can search our online library, search other organizations that might be helpful for a particular pain condition, and view clinical pain trials. Ever expanding "spotlights on pain" focus on particular groups or conditions that have pain issues. APF's Veterans and Pain program is an expample of this. A website within a website, the veterans program provides information and support to help veterans in pain and their family members who support them. Via email or our toll-free info-line 1-888-615-7246 people can request FREE educational materials including the Pain

Action Guide, Pain Care Bill of Rights(English and Spanish versions), the Target Card and companion Pain Notebook (designed to stimulate dialogue between pain patients and their healthcare providers), our newsletter - Pain Community News, and our Pain Bulletin. Additionally, online you can receive our APF Pain Monitor, a monthly e-newsletter to keep people in touch with the latest news and resources. Pain Aid - our online pain support group program includes over 100 chat/discussion rooms, "ask the expert" chats, and topic-oriented message boards moderated by professionals who also are affected by pain. Though our "Power Over Pain" program we are working with state orgs on a grassroots level to educate people about pain and motivate them to take action on their own behalf and others. APF's Mobilization program works locally and nationally to harness the energy of millions of people affected by pain to bring voice to this silent epidemic and speak out for the right to quality pain treatment.

Program: PainSAFE
Budget: NaN
Category:
Population Served: Adults

Program Description:

Educating and empowering consumers and health care providers about the responsibility of each person in the safe use of treatments to minimize risk and improve access to quality pain care.

Program: APF Military/Veteran Pain Initiative
Budget: NaN
Category:
Population Served: Military/Veterans

Program Description:

The American Pain Foundation (APF) launched the Military/Veterans Pain Initiative to reach out to members of the military who are living with pain and their families t Provide free educational materials and peer-to-peer support; Reduce feelings of isolation; Ensure the unique needs of returning and retired soldiers are being addressed; Empower those living with pain to seek appropriate care for themselves and other comrades.

Program: PainAid
Budget: NaN
Category:
Population Served: Adults

Program Description:

The American Pain Foundation's interactive online community. Here you will find: Chat Rooms(http://painaid.painfoundation.org/chat/default.htm) : regularly scheduled live chats on a range of issues --- Chat Room Info(http://discuss.painfoundation.org/topiclist.aspx?cbbsid=31) --- Expert Chat Logs(http://discuss.painfoundation.org/topiclist.aspx?cbbsid=21) Discussion Boards(http://discuss.painfoundation.org/) : message boards on a broad range of topics Ask-the-Experts(http://discuss.painfoundation.org/) : message boards moderated by licensed healthcare professionals Military/Veteran's Discussion Board(http://discuss.painfoundation.org/) : message boards specially for people in the military, veterans and their caregivers Hemophilia Pain Support Board(http://discuss.painfoundation.org/) monitored by PA Theo! Please check it out! International Board(http://discuss.painfoundation.org/) . Please check out our new board focusing on all of our international members. Topics range from illness-specific pain, traditional and complementary treatments, to depression and family matters, to financial issues such as disability and workers compensation. This free service is an online forum for people living with pain, and their caregivers. It is staffed(http://painaid.painfoundation.org/Default.aspx?pageId=3) entirely by highly qualified volunteers with a range of backgrounds, all of whom either live with chronic pain or care for people who do.

FINANCIAL DATA

Revenues and Expenses: Fiscal Year Ending December 31, 2010

REVENUE	
Contributions	$1,884,059
Government Grants	$0
Program Services	$0

Investments	$229,092
Special Events	$83,710
Sales	$5,326
Other	$697
Total Revenue	**$2,202,884**
EXPENSES	
Program Services	$1,427,334
Administration	$217,445
Other	$129,631
Total Expenses	**$1,774,410**
Net Gain/Loss	**$428,474**

Balance Sheet Fiscal Year Ending December 31, 2010

Note: The balance sheet gives a snapshot of the financial health of an organization at a particular point in time. An organization's total assets should generally exceed its total liabilities, or it cannot survive long, but the types of assets and liabilities also must be considered. For instance, an organization's current assets (cash, receivables, securities, etc.) should be sufficient to cover its current liabilities (payables, deferred revenue, current year loan, and note payments). Otherwise, the organization may face solvency problems. On the other hand, an organization whose cash and equivalents greatly exceed its current liabilities might not be putting its money to best use.

ASSETS	**January 1, 2007**	**December 31, 2010**	**Change**
Cash Equivalent	$5,010	$2,980	($2,030)
Accounts Receivable	$32,588	$0	($32,588)
Pledges Grants Receivable	$795,049	$1,103,715	$308,666
Receivable / Other	$0	$0	$0
Inventories for Sale or Use	$0	$0	$0
Investment/Securities	$1,274,785	$1,195,863	($78,922)
Investment/Other	$0	$0	$0
Fixed Assets	$10,862	$14,606	$3,744
Other	$24,778	$18,172	($6,606)
Total Assets	**$2,143,072**	**$2,335,336**	**$192,264**

LIABILITIES	**January 1, 2007**	**December 31, 2010**	**Change**
Accounts Payable	$110,591	$130,297	$19,706
Grants Payable	$0	$0	$0
Deferred Revenue	$0	$0	$0
Loans and Notes	$163,882	$3,524	($160,358)
Tax-Exempt Bond Liabilities	$0	$0	$0
Other	$10,000	$10,000	$0
Total Liabilities	**$284,473**	**$143,821**	**($140,652)**
FUND BALANCE	**$1,858,599**	**$2,191,515**	**$332,916**

- FAQs on financial data
- Digitizing IRS Form 990 Data

FORM 990 AND EDOCS

Forms 990 from the IRS:

- 2010 Form 990
- 2009 Form 990
- 2008 Form 990
- 2007 Form 990
- 2006 Form 990
- 2005 Form 990
- 2004 Form 990
- 2003 Form 990
- 2002 Form 990
- 2001 Form 990
- 2000 Form 990
- 1999 Form 990
- 1998 Form 990
- 1997 Form 990

Additional Documents from the Organization:

- 2008 Financial Statement
- 2009 Financial Statement
- Letter of Determination
- 2008 Annual Report
- 2009 Annual Report
- 2010 Annual Report

EXHIBIT 58

U.S. Department of Justice

United States Attorney
Western District of Virginia

STATEMENT OF UNITED STATES ATTORNEY JOHN BROWNLEE ON THE GUILTY PLEA OF THE PURDUE FREDERICK COMPANY AND ITS EXECUTIVES FOR ILLEGALLY MISBRANDING OXYCONTIN

May 10, 2007

One of the oldest and most challenging medical mysteries is the treatment of pain. For centuries, scientists and doctors have searched for a drug that would safely relieve patients of their chronic pain without inflicting the dangerous side effects that routinely come from the use of addictive narcotics. The discovery of this "wonder" drug would bring hope and relief to millions of suffering patients and wealth beyond one's imagination to its creators.

In 1996, Purdue and its top executives claimed that they had developed such a drug; a safe drug that would help those suffering in pain. The name of that drug was OxyContin. Backed by an aggressive marketing campaign, Purdue's OxyContin became the new pain medication of choice for many doctors and patients. Purdue claimed it had created the miracle drug – a low risk drug that could provide long acting pain relief but was less addictive and less subject to abuse. Purdue's marketing campaign worked, and sales for OxyContin skyrocketed – making billions for Purdue and millions for its top executives.

But OxyContin offered no miracles to those suffering in pain. Purdue's claims that OxyContin was less addictive and less subject to abuse and diversion were false – and Purdue knew

its claims were false. The result of their misrepresentations and crimes sparked one of our nation's greatest prescription drug failures. OxyContin is nothing more than pure oxycodone – a habit forming narcotic derived from the opium poppy. Purdue's OxyContin never lived up to its hype and never offered a low risk way of reducing pain as promised. Simply put, the genesis of OxyContin was not the result of good science or laboratory experiment. OxyContin was the child of marketeers and bottom line financial decision making.

Accordingly, this morning, in a federal courtroom in Abingdon, Virginia, the Purdue Frederick Company, the manufacturer and distributor of OxyContin, pleaded guilty to a felony charge of illegally misbranding OxyContin in an effort to mislead and defraud physicians and consumers. Purdue has agreed to pay over $600 million in criminal and civil penalties, fines and forfeitures, subjected itself to independent monitoring and an extensive remedial action program, and acknowledged that it illegally marketed and promoted OxyContin by falsely claiming that OxyContin was less addictive, less subject to abuse and diversion, and less likely to cause withdrawal symptoms than other pain medications – all in an effort to maximize its profits. Also, Purdue's Chief Executive Officer Michael Friedman, General Counsel Howard Udell, and former Chief Medical Officer Paul Goldenheim pleaded guilty to a misdemeanor charge of misbranding OxyContin and collectively agreed to pay $34.5 million in penalties. With its OxyContin, Purdue unleashed a highly abusable, addictive, and potentially dangerous drug on an unsuspecting and unknowing public. For these misrepresentations and crimes, Purdue and its executives have been brought to justice.

We have released a Criminal Information, Plea Agreements, a Corporate Integrity Agreement, a Statement of Facts, and a Complaint for Forfeiture that have been filed in U.S. District Court in Abingdon. Purdue and its top three executives have pleaded guilty to illegally misbranding

OxyContin from 1996 thru 2001. The company has admitted that it misbranded OxyContin with the intent to defraud and mislead the public.

As part of this plea agreement, Purdue and its top three executives will pay $634.5 million in criminal and civil fines, penalties, and forfeitures, to be distributed as follows. First, Purdue will forfeit to the United States $276.1 million, a portion of which will be shared with the state and federal law enforcement agencies for their work during this investigation.

Second, Purdue will pay $130 million for compensation and settlement of private civil liabilities related to OxyContin. Any part of the $130 million that Purdue fails to distribute within two years will be immediately paid to the United States. Third, Purdue will pay $100.6 million to the United States as reimbursement for payments made by government agencies for the settlement of false claims related to the misbranding of OxyContin. Those federal agencies include the Department of Health and Human Services, the Department of Labor, the Department of Defense, the Office Personnel Management, and the Veterans Administration.

Fourth, Purdue will pay $59.3 million to the State Medicaid programs as reimbursement for payments made by Medicaid for the settlement of false claims related to the misbranding of OxyContin. This money is available to any state to settle claims related to Purdue's criminal conduct. Fifth, Purdue and its top three executives will pay $39.8 million to the Virginia Attorney General's Medicaid Fraud Control Unit Program Income fund. Virginia's MFCU is an important partner in our efforts to fight fraud against our medicaid programs. Sixth, Purdue will pay $20 million to the Virginia Department of Health Professionals' operation of the Virginia Prescription Monitoring Program. The prescription monitoring program was initiated in part because of the big spike in prescription drug abuse that accompanied the illegal marketing of OxyContin. Currently,

the program is largely funded by the Virginia taxpayers, and the $20 million payment by Purdue should endow the program for the foreseeable future. Seventh, Purdue will pay $4.6 million to cover the costs of the five year internal monitoring program that is a part of the company's Corporate Integrity Agreement with the Health and Human Services Office of the Inspector General. Eighth, Purdue will pay $3.4 million to the federal and state Medicaid programs for improperly calculated Medicaid rebates for years 1998 and 1999, and finally, Purdue and the three executives will pay $515,475 in criminal fines and special assessments to the court.

In addition to the guilty pleas and monetary penalties, the United States has directed Purdue, as part of the Corporate Integrity Agreement, to retain and pay for an Independent Monitor and staff to monitor Purdue's compliance with this agreement and federal law. The monitor and staff will be independent from Purdue's management and must file periodic reports with the government concerning Purdue's conduct and business practices. We believe this monitoring program, in conjunction with the Corporate Integrity Agreement, will ensure that in the future Purdue will market and promote its products in an honest and responsible manner. The public must be confident that we will keep close watch on how Purdue sells its most dangerous products.

I would now like to provide to you a brief summary of the investigation and some of our findings. The main violations of the law revealed by the government's criminal investigation are set forth in detail in the Statement of Facts released to you today.

The defendant The Purdue Frederick Company, a New York corporation headquartered in Connecticut, was created in 1892 and purchased by its current owners in 1952. Defendant Michael Friedman joined Purdue in 1985 and was appointed President and Chief Executive Officer in 2003. It is our understanding that Mr. Friedman has announced his intention to leave Purdue this year.

Defendant Howard Udell joined Purdue in 1977 and is presently Purdue's Executive Vice President and Chief Legal Officer. Defendant Dr. Paul Goldenheim joined Purdue in 1985 as its Medical Director. Dr. Goldenheim left Purdue in 2004.

This case began in early 1995, when Purdue used focus groups of primary care physicians and surgeons to determine whether physicians would be willing to prescribe OxyContin for patients with non-cancer pain. According to Purdue's research, many of these physicians had great reservations about prescribing OxyContin because of the drug's addictive potential and side effect profile, and its abuse potential. It was clear from these focus groups that physicians were concerned about the safety and risks of OxyContin.

Purdue also learned from these focus groups that physicians wanted a long lasting pain reliever that was less addictive and less subject to abuse and diversion. Purdue understood that the company that marketed and sold that drug would dominate the pain management market. And that is exactly what Purdue tried to do.

Despite knowing that OxyContin contained high concentrations of oxycodone HCL, had an abuse potential similar to that of morphine, and was at least as addictive as other pain medications on the market, Purdue, beginning in January 1996, with the intent to defraud and mislead, falsely marketed and promoted OxyContin as less addictive, less subject to abuse and diversion, and less likely to cause tolerance and withdrawal than other pain medications. Purdue did so in the following ways:

First, Purdue trained its sales representatives to falsely inform health care providers that it was more difficult to extract the oxycodone from an OxyContin tablet for the purpose of intravenous abuse. Purdue ordered this training even though its own study showed that a drug abuser

could extract approximately 68% of the oxycodone from a single 10 mg OxyContin tablet by simply crushing the tablet, stirring it in water, and drawing the solution through cotton into a syringe.

Second, Purdue falsely instructed its sales representatives to inform health care providers that OxyContin could create fewer chances for addiction than immediate-release opioids.

Third, Purdue sponsored training that falsely taught Purdue sales supervisors that OxyContin had fewer "peak and trough" blood level effects than immediate-release opioids resulting in less euphoria and less potential for abuse than short-acting opioids.

Fourth, Purdue falsely told certain health care providers that patients could stop therapy abruptly without experiencing withdrawal symptoms and that patients who took OxyContin would not develop tolerance to the drug.

And fifth, Purdue falsely told health care providers that OxyContin did not cause a "buzz" or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used to "weed out" addicts and drug seekers.

The results of Purdue's crimes were staggering. According to DEA, the number of oxycodone related deaths increased 400 percent between 1996 and 2001. During that same time period, the annual number of prescriptions for OxyContin increased from approximately 300,000 to nearly 6 million. Also, in February of 2002, the DEA released a report detailing the death rates caused by OxyContin abuse up to that time. According to the DEA, there were 146 deaths in which OxyContin was determined to be the direct "cause of" or "a contributing factor to." DEA identified an additional 318 deaths that were "most likely" caused by OxyContin. In Virginia, our medical examiner reported that 228 people died in western Virginia from overdoses of oxycodone from 1996

to 2005.

For some communities, the danger went beyond just addiction and death. Beginning in 2000, localities began to report dramatically higher crime rates – some up as much as 75% from the year before. This sharp increase in crime was directly attributable to the abuse of OxyContin. Tazewell County estimated that OxyContin was behind 80-95% of all crimes that were committed there. From 1998 to 2003, burglaries, robberies, and larcenies jumped 131% in Buchanan County and 102% in Russell County.

During the last 10 years, Virginia's law enforcement community has fought hard against the devastating effects OxyContin has had on our citizens and communities. During that time, we have convicted the OxyContin addicts who committed serious crimes to get money to buy more OxyContin, and we convicted street dealers who preyed upon the addicts' craving for this powerful narcotic. We also convicted pharmacists and physicians who illegally diverted OxyContin for personal gain and profit. With today's conviction of the maker of OxyContin, we have finally brought to justice the main component involved in this ring of abuse. The conviction of Purdue and its executives will end the misbranding and fraudulent marketing of OxyContin, deter other companies from committing like crimes, and provide desperately needed resources to fight addiction and abuse that threatens the health of millions of Virginians.

Thank you.

NEWS RELEASE

UNITED STATES ATTORNEY'S OFFICE
WESTERN DISTRICT OF VIRGINIA

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May 10, 2007

THE PURDUE FREDERICK COMPANY, INC. AND TOP EXECUTIVES PLEAD GUILTY TO MISBRANDING OXYCONTIN, WILL PAY OVER $600 MILLION

John L. Brownlee, United States Attorney for the Western District of Virginia, and Virginia Attorney General Bob McDonnell announced today that The Purdue Frederick Company, Inc., along with its President, Chief Legal Officer, and former Chief Medical Officer have pleaded guilty to charges of misbranding Purdue's addictive and highly abusable drug OxyContin. Purdue and the three executives will pay a total of $634,515,475. OxyContin is a Schedule II prescription pain relief medication, classified as having the highest potential for abuse of legally available drugs. The Purdue Frederick Company, Inc., and the three executives have admitted that Purdue fraudulently marketed OxyContin by falsely claiming that OxyContin was less addictive, less subject to abuse, and less likely to cause withdrawal symptoms than other pain medications when there was no medical research to support these claims and without Food and Drug Administration approval of these claims.

"Even in the face of warnings from health care professionals, the media, and members of its own sales force that OxyContin was being widely abused and causing harm to our citizens, Purdue, under the leadership of its top executives, continued to push a fraudulent marketing campaign that promoted Oxycontin as less addictive, less subject to abuse, and less likely to cause withdrawal, " said United States Attorney John Brownlee. "In the process, scores died as a result of OxyContin abuse and an even greater number of people became addicted to OxyContin; a drug that Purdue led many to believe was safer, less abusable, and less addictive than other pain medications on the market. Today's convictions are a testament to the outstanding work of the prosecutors and agents who spent years investigating this important case."

The Purdue Frederick Company, Inc. and Purdue Pharma, L.P. are part of a worldwide group of related and associated entities engaged in the pharmaceutical business. These entities manufacture, market, and distribute OxyContin, an extended-release form of oxycodone.

"Purdue put its desire to sell OxyContin above the interests of the public," said Assistant Attorney General Peter D. Keisler. "Purdue abused the drug approval process which relies on drug manufacturers to be forthright in reporting clinical data and, instead, misled physicians about the addiction and withdrawal issues involved with Oxycontin."

"The criminal behavior exhibited in this case damages the reputation of a critically important industry. Pharmaceutical companies have an obligation to patients, physicians, and those in the industry they serve to market prescription drugs in accordance with the law and FDA regulations." said Virginia Attorney General Bob McDonnell, " I applaud John Brownlee and his team for their leadership, as well as the Virginia Medicaid Fraud Control Unit, FDA and all of the other state and federal law enforcement agencies that worked so hard over the past four years to investigate this complex criminal scheme and bring the wrongdoers to justice."

"FDA will not tolerate practices that falsely promote drug products and place consumers at health risk," said Margaret O.K. Glavin, Associate Commissioner for Regulatory Affairs, FDA. "We will continue to do all we can to protect the public against drug companies and their representatives who are not truthful and bilk consumers of precious health care dollars."

The Purdue Frederick Company, Inc., pleaded guilty to felony misbranding OxyContin with the intent to defraud and mislead. President and Chief Operating Officer Michael Friedman, Executive Vice President and Chief Legal Officer Howard Udell, and former Executive Vice President of Worldwide Medical Affairs Paul D. Goldenheim, pleaded guilty to a misdemeanor charge of misbranding OxyContin. All the pleas were entered in United States District Court in Abingdon this morning.

"Purdue's illegal sales and marketing practices concealed information from patients and many health care providers regarding the potency and abuse potential of OxyContin for corporate profit," said Daniel R. Levinson, Inspector General for the U.S. Department of Health and Human Services. "We commend the highly qualified team of prosecutors and investigators from a variety of Federal and State agencies for developing a global resolution that addresses the criminal violations of the past, ensures strict compliance in the future, and serves as a strong warning to others who may consider illegally marketing pharmaceuticals."

"The falsification of drug product information is a very serious breach of the public's trust. IRS Criminal Investigation will continue to concentrate its resources on the tax and money laundering aspects of these types of investigations in cooperation with the United States Attorney's Office and other federal, state, and local authorities," said Charles R. Pine, Special Agent in Charge.

"Today's guilty pleas mark a significant milestone in the fight against corruption by company officials who seek to illegally enrich corporate profits at taxpayers' expense," stated Gordon S. Heddell, Inspector General, U.S. Department of Labor. "These convictions demonstrate our steadfast resolve to investigate any individuals who would defraud Labor programs, such as the Office of Workers' Compensation Programs, by overcharging them. My office remains committed to working with other law enforcement agencies and the U.S. Attorney to fight this type of corruption."

Pursuant to written plea agreements, Purdue and the executives will pay a total of $634,515,475.00. Purdue's payments will include:

$276.1 million forfeited to the United States

$160 million paid to federal and state government agencies to resolve liability for false claims made to Medicaid and other government healthcare programs

$130 million set aside to resolve private civil claims (monies remaining after 36 months will be paid to the United States)

$5.3 million paid to the Virginia Attorney General's Medicaid Fraud Control Unit to fund future health care fraud investigations

$20 million paid to fund the Virginia Prescription Monitoring Program for the foreseeable future

In addition, Purdue will pay the maximum statutory criminal fine of $500,000.

Purdue's top executives will pay the following amounts to the Virginia Attorney General's Medicaid Fraud Control Unit:

$19 million paid by Michael Friedman

$8 million paid by Howard R. Udell

$7.5 million paid by Dr. Paul D. Goldenheim

Each executive will also pay a $5,000 criminal fine.

The Director of the Defense Criminal Investigative Service, Mr. Chuck Beardall, stated, "It is unthinkable that purely for greed, addictive drugs were fraudulently marketed to the public, and in so doing threatened the health and safety of our citizens. Among those endangered were soldiers, sailors, airmen, marines, and their families, all of whom avail themselves of the military health system. At a time when our military personnel and their loved ones are sacrificing so much, something like this is incomprehensible and grossly reprehensible."

According to the Statement of Facts filed with the Court, beginning in January 1996 and continuing through June 30, 2001, Purdue's market research found that "[t]he biggest negative of [OxyContin] was the abuse potential." Despite this finding, Purdue's supervisors and employees falsely and misleadingly marketed OxyContin as less addictive, less subject to abuse, and less likely to cause withdrawal than other pain medications. Purdue misbranded OxyContin in three specific ways:

1. Purdue sales representatives falsely told some health care providers that OxyContin had less euphoric effect and less abuse potential than short-acting opioids. This message was

presented to some health care providers through the use of graphs that exaggerated the differences between blood plasma levels achieved by OxyContin compared to the levels of other pain relief medications. Purdue supervisors and employees participated in the misbranding in the following ways:

A. Purdue supervisors and employees sponsored training that used graphs that exaggerated the differences between the blood plasma levels of OxyContin as compared to immediate-release opioids. These graphs were used to falsely teach Purdue sales supervisors that OxyContin had fewer "peak and trough" blood level effects than immediate-release opioids and that would result in less euphoria and less potential for abuse than short-acting opioids.

B. Purdue supervisors and employees permitted new Purdue sales representatives to use similar exaggerated graphical depictions during role-play training at Purdue's headquarters in Stamford, Connecticut.

2. Purdue supervisors and employees drafted an article about a study of the use of OxyContin in osteoarthritis patients that was published in a medical journal on March 27, 2000. On June 26, 2000, each sales representative was provided a copy of the article together with a "marketing tip" that stated that the article was available for use in achieving sales success. Sales representatives distributed copies of the article to health care providers to falsely or misleadingly represent that patients taking OxyContin at doses below 60 milligrams per day can always be discontinued abruptly without withdrawal symptoms. The article also indicated that patients on such doses would not develop tolerance. The marketing tip that accompanied the article stated that one of the twelve key points was, "There were 2 reports of withdrawal symptoms after patients abruptly stopped taking CR [controlled release] oxycodone at doses of 60 or 70 mg/d. Withdrawal syndrome was not reported as an adverse event during scheduled respites indicating that CR oxycodone at doses below 60 mg/d [milligrams per day] can be discontinued without tapering the dose if the patient condition so warrants." These marketing claims were made even though Purdue representatives were well aware of the following information:

A. The year before the article was published and distributed to sales representatives, Purdue received an analysis of the osteoarthritis study and a second study from a United Kingdom company affiliated with Purdue that listed eight patients in the osteoarthritis study "who had symptoms recorded that may possibly have been related to opioid withdrawal," and stated that "[a]s expected, some patients did become physically dependent on OxyContin tablets but this is not expected to be a clinical problem so long as abrupt withdrawal of drug is avoided."

B. In May of 2000, Purdue received a report of a patient who said he or she was unable to stop taking OxyContin 10 mg every 12 hours without experiencing withdrawal symptoms. Executives also learned that "this type of question,

patients not being able to stop OxyContin without withdrawal symptoms ha[d] come up quite a bit . . . in Medical Services lately (at least 3 calls in the last 2 days)."

C. In February 2001, Purdue received a review of the accuracy of the withdrawal data in the osteoarthritis study that listed eleven study patients who reported adverse experience due to possible withdrawal symptoms during the study's respite periods and stated "[u]pon a review of all comments for all enrolled patients, it was noted that multiple had comments which directly stated or implied that an adverse experience was due to possible withdrawal symptoms;" Even after receiving this information, on March 28, 2001, supervisors and employees decided not to write up the findings because of a concern that it might "add to the current negative press."

D. Supervisors and employees stated that while they were well aware of the incorrect view held by many physicians that oxycodone was weaker than morphine, they did not want to do anything "to make physicians think that oxycodone was stronger to or equal to morphine" or to "take any steps in the form of promotional materials, symposia, clinicals, publications, conventions, or communications with the field force that would affect the unique position that OxyContin ha[d] in many physicians['] mind[s]."

3. Purdue sales representatives, while promoting and marketing OxyContin, falsely told health care providers that the statement in the OxyContin package insert that "[d]elayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug," meant that OxyContin did not cause a "buzz" or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used to "weed out" addicts and drug seekers.

The statement was later amended to read, "[d]elayed absorption, as provided by OxyContin tablets, when used properly for the management of pain, is believed to reduce the abuse liability of a drug." Nevertheless, Purdue continued to market OxyContin in the same manner as described above.

Purdue supervisors and employees took part in the misbranding in the following ways:

A. Supervisors instructed Purdue sales representatives to use the reduced abuse liability statement and the amended statement to market and promote OxyContin.

B. Supervisors told Purdue sales representatives they could tell health care providers that OxyContin potentially creates less chances for addiction than immediate-release opioids.

C. Supervisors trained Purdue sales representatives and told some health care providers that it was more difficult to extract the oxycodone from an OxyContin tablet for the purpose of intravenous abuse, although Purdue's own study showed that a drug abuser could extract approximately 68% of the oxycodone from a single 10 mg OxyContin tablet merely by crushing the tablet, stirring it in water, and drawing the solution through cotton into a syringe.

D. By March 2000, Purdue had received reports of OxyContin abuse and diversion occurring in different communities but allowed sales staff to continue promoting and marketing OxyContin in this manner.

The case was investigated by the Virginia Attorney General's Medicaid Fraud Control Unit; Food and Drug Administration, Office of Criminal Investigations; Internal Revenue Service Criminal Investigation; the Department of Health and Human Services Office of Inspector General; Department of Labor, Office of Inspector General; Defense Criminal Investigative Service; Virginia State Police; and West Virginia State Police. The case was prosecuted by Assistant United States Attorneys Rick Mountcastle, Randy Ramseyer and Sharon Burnham and U.S. Department of Justice, Office of Consumer Litigation, Trial Attorneys Barbara Wells and Elizabeth Stein.

END

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
ABINGDON DIVISION

UNITED STATES OF AMERICA	)	
	)	
v.	)	**Dkt. No. _____**
	)	
THE PURDUE FREDERICK COMPANY, INC.	)	**21 U.S.C. §§ 331(a), 352(a), 333(a)(2)**
D/B/A The Purdue Frederick Company	)	
MICHAEL FRIEDMAN	)	**21 U.S.C. §§ 331(a), 352(a), 333(a)(1)**
HOWARD R. UDELL	)	**21 U.S.C. §§ 331(a), 352(a), 333(a)(1)**
PAUL D. GOLDENHEIM	)	**21 U.S.C. §§ 331(a), 352(a), 333(a)(1)**

INFORMATION

INTRODUCTION

The United States Attorney charges that at all times relevant to this Information:

Description of Defendants

1. Defendant The PURDUE FREDERICK COMPANY, INC. (referred to in this Information as "PURDUE"), doing business as The Purdue Frederick Company, was a New York corporation, headquartered in Connecticut. It was created in 1892 and was purchased by its current owners in 1952. At all times relevant to this Information, PURDUE and other related and associated entities were engaged in the pharmaceutical business throughout the United States.

2. PURDUE developed and originally marketed OxyContin Tablets ("OxyContin"), an opioid analgesic approved to be taken every twelve hours. OxyContin is a controlled-release form of oxycodone and is a Schedule II controlled substance with an abuse liability similar to morphine.

3. Defendant MICHAEL FRIEDMAN joined PURDUE in 1985 as Vice President and Assistant to the President and Chairman. He was appointed Group Vice President in 1988, Executive Vice President and Chief Operating Officer in 1999, and President and Chief Executive

Officer in 2003.

4. Defendant HOWARD R. UDELL joined PURDUE in 1977 as General Counsel. He was appointed Group Vice President and General Counsel in 1989, Executive Vice President and General Counsel in 1999, and Executive Vice President and Chief Legal Officer in 2003.

5. Defendant PAUL D. GOLDENHEIM joined PURDUE in 1985 as Medical Director. He was appointed Vice President and Medical Director in 1986, Vice President of Scientific and Medical Affairs and Executive Director of Purdue Frederick Research Center in 1988, Group Vice President of Scientific and Medical Affairs in 1989, Executive Vice President of Medical and Scientific Affairs in 1999, Executive Vice President of Worldwide Research & Development in 2000, and Executive Vice President of Worldwide Research & Development and Chief Scientific Officer in 2003. He left PURDUE in 2004.

6. From January 1996 through June 30, 2001, PURDUE received approximately $2.8 billion in revenue from the sale of OxyContin.

Statutory Framework

7. The United States Food and Drug Administration ("FDA") is the agency of the United States responsible for protecting the public health by ensuring the safety, efficacy, and security of human drugs and for enforcing the Federal Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301, *et seq.*

8. The FDCA, 21 U.S.C. § 355, required a sponsor of a new drug to receive FDA approval of a New Drug Application ("NDA"), before the sponsor could distribute the drug in interstate commerce.

9. The FDCA, 21 U.S.C. § 321(m), defined labeling to include "all labels and other

written, printed, or graphic matter . . . accompanying [a drug]." Title 21, Code of Federal Regulations, Section 202.1(*l*)(2) provided that labeling included brochures, booklets, mailing pieces, detailing pieces, bulletins, letters, motion picture films, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug which were disseminated by or on behalf of a drug's manufacturer, packer, or distributor. Such items "accompanied" a drug if they were designed for use and used in the distribution and sale of the drug.

10. The FDCA, 21 U.S.C. § 352(a), provided that a drug was misbranded "[i]f its labeling [was] false or misleading in any particular." The FDCA, 21 U.S.C. § 321(n), provided that "[i]n determining whether the labeling . . . [was] misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling fails to reveal facts material in the light of such representation or material with respect to the consequences which may result from the use . . . to which the labeling . . . relates under the conditions of use prescribed in the labeling . . . or under such conditions of use as are customary or usual."

11. The FDCA, 21 U.S.C. § 331(a), prohibited the introduction or delivery for introduction into interstate commerce of a misbranded drug. 21 U.S.C. § 333(a)(2) provided that such a violation committed with the intent to defraud or mislead was punishable as a felony. Under 21 U.S.C. § 333(a)(1) and the applicable case law, an individual could be held criminally liable for a misdemeanor violation of § 331(a) without having knowledge of, or intent to cause, the misbranding if that individual was a responsible corporate officer at the time of the misbranding. A responsible corporate officer for these purposes was one who had responsibility and authority either to prevent in the first instance or to promptly correct certain conduct resulting in the

misbranding of a drug introduced or delivered for introduction into interstate commerce.

12. OxyContin was a drug within the meaning of the FDCA, 21 U.S.C. § 321(g)(1), and a new drug within the meaning of 21 U.S.C. § 321(p).

OxyContin Approval and Package Insert

13. On approximately December 28, 1994, PURDUE submitted the OxyContin NDA to the FDA. The NDA included clinical studies showing that OxyContin, when dosed every twelve hours, was as safe and as effective as immediate-release oxycodone dosed every six hours.

14. The NDA did not claim that OxyContin was safer or more effective than immediate-release oxycodone or other pain medications and PURDUE did not have, and did not provide the FDA with, any clinical studies demonstrating that OxyContin was less addictive, less subject to abuse and diversion, or less likely to cause tolerance and withdrawal than other pain medications.

15. On or about October 24, 1995, the FDA completed, with PURDUE's assistance, an internal Medical Officer Review ("MOR") of the Integrated Summary of Safety ("ISS") and a MOR of the Integrated Summary of Efficacy ("ISE"). While not binding on the company, the MORs were disclosed to certain PURDUE supervisors and employees. These MORs did not state that OxyContin was more effective than or superior to, safer, had less opioid effects, or caused fewer adverse events than any other marketed product.

16. The MOR of the ISS included these statements:

a. "The blood level data in clinical use suggests the opioid effects [of OxyContin and immediate-release oxycodone] would be similar;"

b. "The best conclusion is that the efficacy of [OxyContin] is equivalent to the [immediate-release oxycodone], with an adverse event profile that is as good as the [immediate-release oxycodone]. I would not allow a 'better' claim." (emphasis in original);

c. "The adverse experience profile of [OxyContin] is qualitatively similar to that of the parent drug, oxycodone;" and

d. "Withdrawal is possible in patients who have their dosage abruptly reduced or discontinued."

17. The MOR of the ISE included these statements:

a. "There is some evidence, both pharmacokinetic and clinical, that reduced acute opioid adverse effects may be expected in some patients, but there is not enough evidence to support an [adverse event] superiority claim [for OxyContin] against other marketed products." (emphasis in original); and

b. "Care should be taken to limit competitive promotion. [OxyContin] has been shown to be as good as current therapy, but has not been shown to have a significant advantage beyond reduction in frequency of dosing."

18. The FDA approved the OxyContin NDA on December 12, 1995, and from 1996 through June 30, 2001, the FDA-approved package insert for OxyContin stated that it was intended for "the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days." The package insert also included the statement: "Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug."

Misbranding of OxyContin

19. During the period February through March 1995, PURDUE supervisors and employees obtained market research that included focus groups of forty primary care physicians, rheumatologists, and surgeons to determine their receptivity to using OxyContin for non-cancer pain. According to this market research, some of these physicians had concerns, similar to their concerns about combination opioids, regarding OxyContin's addictive potential and side effect profile, including that "[t]he biggest negative of [OxyContin] was the abuse potential."

20. Beginning on or about December 12, 1995, and continuing until on or about June 30, 2001, certain PURDUE supervisors and employees, with the intent to defraud or mislead, marketed

and promoted OxyContin as less addictive, less subject to abuse and diversion, and less likely to cause tolerance and withdrawal than other pain medications, as follows:

a. Trained PURDUE sales representatives and told some health care providers that it was more difficult to extract the oxycodone from an OxyContin tablet for the purpose of intravenous abuse, although PURDUE's own study showed that a drug abuser could extract approximately 68% of the oxycodone from a single 10 mg OxyContin tablet by crushing the tablet, stirring it in water, and drawing the solution through cotton into a syringe;

b. Told PURDUE sales representatives they could tell health care providers that OxyContin potentially creates less chance for addiction than immediate-release opioids;

c. Sponsored training that taught PURDUE sales supervisors that OxyContin had fewer "peak and trough" blood level effects than immediate-release opioids resulting in less euphoria and less potential for abuse than short-acting opioids;

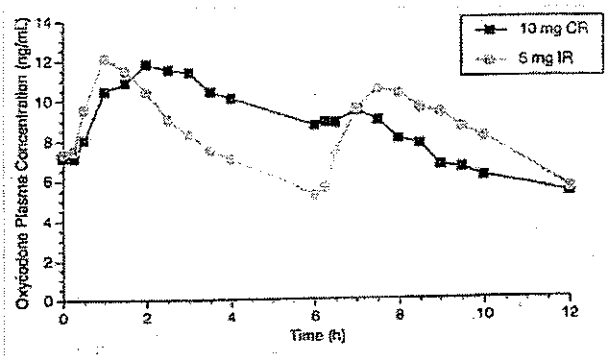
d. Told certain health care providers that patients could stop therapy abruptly without experiencing withdrawal symptoms and that patients who took OxyContin would not develop tolerance to the drug; and

e. Told certain health care providers that OxyContin did not cause a "buzz" or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used to "weed out" addicts and drug seekers.

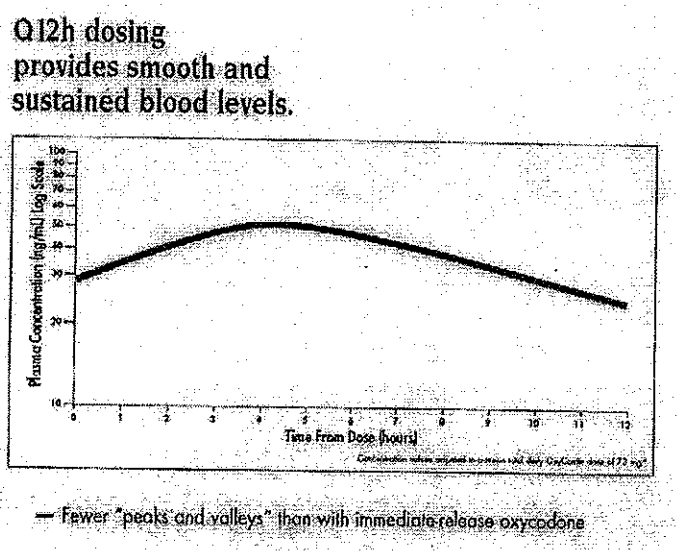
Misbranding of OxyContin: Use of Graphical Depictions by Sales Representatives

21. Data from one of PURDUE's clinical studies was used to create the following graphical demonstration of the difference in the plasma levels at steady state between patients who

took OxyContin every twelve hours (the "10 mg CR" line) and patients who took immediate-release oxycodone every six hours (the "5 mg IR" line):



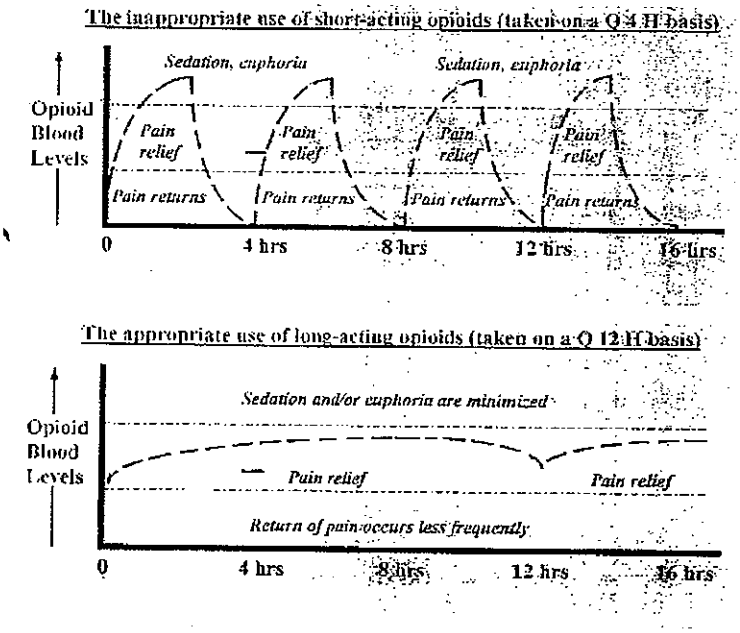
22. On October 12, 1995, PURDUE requested comments from the FDA's Division of Drug Marketing, Advertising, and Communication ("DDMAC") about its proposed launch marketing materials, which included the following graph and text showing the oxycodone plasma concentration provided by OxyContin on a logarithmic scale along with the statement that OxyContin's oxycodone blood plasma levels provided "fewer 'peaks and valleys' than with immediate-release oxycodone:"



23. On or about December 20, 1995, after reviewing the proposed OxyContin launch materials, DDMAC informed PURDUE that "[i]f [Purdue] wishes to compare blood levels in the text, then DDMAC suggests that the blood levels for both dosage forms be presented in the graphic so that the reader can accurately interpret this claim."

24. On or about January 11, 1996, PURDUE told DDMAC that it had "deleted" the statement "[f]ewer peaks and valleys than with immediate-release oxycodone."

25. In or about December 1998, PURDUE sponsored training for all of its district sales managers. During this meeting, a pharmacist retained by PURDUE to conduct a portion of the training used the following graphical demonstration (instead of the graphical demonstration of the actual clinical data described in paragraph 21 of the Introduction of this Information), and falsely stated that OxyContin had significantly fewer "peak and trough" blood level effects than immediate-release opioids resulting in less euphoria and less potential for abuse than short-acting opioids:



26. Beginning in or around 1999, some of PURDUE's new sales representatives were permitted, during training at PURDUE's headquarters, to draw their own blood level graphs to falsely represent that OxyContin, unlike immediate-release or short-acting opioids, did not swing up and down between euphoria and pain and resulted in less abuse potential.

27. During the period 1999 through June 30, 2001, certain PURDUE sales representatives used graphical depictions similar to the one described in paragraph 25 of the Introduction of this Information and falsely stated to some health care providers that OxyContin had less euphoric effect and less abuse potential than short-acting opioids.

Misbranding of OxyContin: Misleading Use of Article to Claim No Withdrawal or Tolerance

28. On or about January 16, 1997, certain PURDUE supervisors and employees sent to the FDA the results of a clinical study pertaining to the use of low doses of OxyContin by

osteoarthritis patients ("osteoarthritis study") and a final study report that included, in a section pertaining to respite periods, the statement "[n]o investigator reported 'withdrawal syndrome' as an adverse experience during the respite periods." In a section entitled "Adverse Experiences by Body System During Respite Periods," the report's summary of the major results listed the most frequently reported adverse experiences in respite periods to be nervousness, insomnia, nausea, pain, anxiety, depression, and diarrhea, followed by the statement: "Twenty-eight patients (26%) had symptoms recorded during 1 or more respite periods."

29. In or about May 1997, certain PURDUE supervisors and employees stated that while they were well aware of the incorrect view held by many physicians that oxycodone was weaker than morphine, they did not want to do anything "to make physicians think that oxycodone was stronger or equal to morphine" or to "take any steps in the form of promotional materials, symposia, clinicals, publications, conventions, or communications with the field force that would affect the unique position that OxyContin ha[d] in many physicians mind (*sic*)."

30. On or about February 12, 1999, certain supervisors and employees of a United Kingdom company affiliated with PURDUE provided certain PURDUE supervisors and employees with an analysis of the osteoarthritis study together with another clinical study. This analysis included a list of eight patients in the osteoarthritis study and eleven patients in the other study "who had symptoms recorded that may possibly have been related to opioid withdrawal," including one patient in the other study who required treatment for withdrawal syndrome. The "Discussion" section of this analysis included the following: "It is not surprising that some patients in the clinical trials developed some degree of physical dependence and consequently experienced withdrawal symptoms as a result of abrupt discontinuation of OxyContin tablets. All patients who were

suspected to have withdrawal symptoms have been reported but this may have resulted in a falsely high incidence. Of the patients who participated in [the osteoarthritis study] (in which patients entered respite periods without OxyContin tablets) many symptoms suspected to be due to opioid withdrawal may simply have resulted from the return of pain. After withdrawal of OxyContin tablets, patient 6007 complained of nervousness, patient 2004 complained of insomnia and felt restless and patients 2020 and 2028 were restless and anxious. Since these are symptoms which often accompany the return of significant pain, it may be wrong to label these as withdrawal symptoms. Nonetheless, the incidence of withdrawal syndromes in patients treated with OxyContin tablets is a concern and it is safer to over report, than under report this potential problem." The analysis' conclusions included the statement: "As expected, some patients did become physically dependent on OxyContin tablets but this is not expected to be a clinical problem so long as abrupt withdrawal of drug is avoided."

31. Certain PURDUE supervisors and employees participated in the drafting of an article regarding the osteoarthritis study that was published in a medical journal on or about March 27, 2000 ("osteoarthritis study article"). The "Results" section of the article included the following three statements pertaining to the incidence of withdrawal syndrome and withdrawal symptoms experienced by study patients: (1) One patient was hospitalized "for withdrawal symptoms . . . . The patient who was hospitalized with withdrawal symptoms had completed the study on the previous day and had been receiving CR oxycodone, 70 mg/d; symptoms resolved after 3 days." (2) "A second patient, who was receiving 60 mg/d CR oxycodone, experienced withdrawal symptoms after running out of study medication. The patient had not reported withdrawal symptoms during scheduled respites from doses of 30 or 40 mg/d." (3) "Withdrawal syndrome was not reported as

an adverse event for any patient during scheduled respites. Adverse experiences reported by more than 10% of patients during scheduled respites were nervousness (9 patients) and insomnia (8 patients)."

32. The osteoarthritis study article also included a "Comment" section. The statement regarding withdrawal in this section largely summarized the information in the three statements in the "Results" section and further suggested that patients taking low doses could have their OxyContin treatment abruptly discontinued without experiencing withdrawal if their condition so warranted: "There were 2 reports of withdrawal symptoms after patients abruptly stopped taking CR oxycodone at doses of 60 or 70 mg/d. Withdrawal syndrome was not reported as an adverse event during scheduled respites, indicating that [OxyContin] at doses below 60 mg [per day] can be discontinued without tapering the dose if the patient's condition so warrants."

33. On or about May 18, 2000, after millions of OxyContin tablets had been sold and used by patients, PURDUE's Medical Services Department reported to certain PURDUE supervisors and employees that it had recently received a report of a patient who said he or she was unable to stop taking OxyContin 10 mg every 12 hours without experiencing withdrawal symptoms and the report indicated that "this type of question, patients not being able to stop OxyContin without withdrawal symptoms has come up quite a bit here in Medical Services lately (at least 3 calls in the last 2 days)."

34. On or about June 26, 2000, certain PURDUE supervisors and employees sent the full text of the osteoarthritis study article together with a "marketing tip" to PURDUE's entire sales force. The marketing tip stated that a reprint of the osteoarthritis study article was available for use in achieving sales success. The marketing tip also included as one of the article's twelve key points:

"There were 2 reports of withdrawal symptoms after patients abruptly stopped taking CR oxycodone at doses of 60 or 70 mg/d. Withdrawal syndrome was not reported as an adverse event during scheduled respites indicating that CR oxycodone at doses below 60 mg/d can be discontinued without tapering the dose if the patient condition so warrants."

35. On or about February 13, 2001, certain PURDUE supervisors and employees received a review of the accuracy of the withdrawal data in the osteoarthritis study that stated: "Upon a review of all comments for all enrolled patients, it was noted that multiple had comments which directly stated or implied that an adverse experience was due to possible withdrawal symptoms." This was followed by a list of eleven study patients who reported adverse experience due to possible withdrawal symptoms during these periods. 106 patients initially participated in the osteoarthritis study, 32 of them withdrew because of adverse events (not necessarily related to withdrawal), and 38 patients remained in the study at 12 months.

36. On or about March 28, 2001, a PURDUE employee emailed a PURDUE supervisor regarding the review of withdrawal data described in paragraph 35 of the Introduction of this Information, asking: "Do you think the withdrawal data from the [osteoarthritis] study . . . is worth writing up (an abstract)? Or would this add to the current negative press and should be deferred?" The supervisor responded: "I would not write it up at this point." No abstract was prepared.

37. Between approximately June 26, 2000, and June 30, 2001, certain PURDUE supervisors and employees distributed copies of the reprint of the osteoarthritis study article to all of PURDUE's sales representatives for use in the promotion and marketing of OxyContin to health care providers, including the distribution of 10,615 copies to certain PURDUE sales representatives between February 13, 2001, and June 30, 2001.

38. During the period June 26, 2000, through June 30, 2001, certain PURDUE sales representatives distributed the reprint of the osteoarthritis study article to some health care providers and falsely or misleadingly stated that patients taking OxyContin at doses below 60 milligrams per day can always be discontinued abruptly without withdrawal symptoms and that patients on such doses would not develop tolerance.

Misbranding of OxyContin: Use of Reduced Abuse Liability Claim in Marketing

39. The original OxyContin package insert approved by the FDA stated: "Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug" (the *Reduced Abuse Liability Statement*). Certain PURDUE supervisors and employees instructed PURDUE sales representatives to use this statement to market and promote OxyContin.

40. Certain PURDUE sales representatives, while promoting and marketing OxyContin, falsely told some health care providers that the *Reduced Abuse Liability Statement* meant that OxyContin did not cause a "buzz" or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used to "weed out" addicts and drug seekers.

41. By March 2000, various PURDUE supervisors and employees in different parts of the company had received reports of OxyContin abuse and diversion occurring in different communities.

42. On or about November 27, 2000, certain PURDUE supervisors and employees amended the *Reduced Abuse Liability Statement* to state that "[d]elayed absorption, as provided by OxyContin tablets, when used properly for the management of pain, is believed to reduce the abuse liability of a drug," and instructed PURDUE sales representatives to use the amended statement to

promote and market OxyContin.

43. From March 2000 through June 30, 2001, certain PURDUE sales representatives, while promoting and marketing OxyContin, falsely told some health care providers that the *Reduced Abuse Liability Statement* and the amended statement meant that OxyContin did not cause a "buzz" or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used to "weed out" addicts and drug seekers.

COUNT ONE
Introduction of Misbranded Drug into Interstate Commerce
21 U.S.C. §§ 331(a), 352(a), 333(a)(2)

1. The Introduction of this Information is realleged and made a part of this Count.

2. In or about and between January 1996 and June 30, 2001, in the Western District of Virginia and elsewhere, defendant The PURDUE FREDERICK COMPANY, INC. doing business as The Purdue Frederick Company, with the intent to defraud or mislead, introduced and caused the introduction into interstate commerce of quantities of OxyContin from various locations outside the state of Virginia to various locations in the Western District of Virginia and elsewhere, which were misbranded within the meaning of 21 U.S.C. §§ 331(a), 333(a)(2), and 352(a), in that the matters described in paragraphs 19 through 43 of the Introduction of this Information constituted labeling within the meaning of 21 U.S.C. § 321(m) and were false and/or misleading.

All in violation of 21 U.S.C. §§ 331(a), 352(a), and 333(a)(2).

COUNT TWO
Introduction of Misbranded Drug in Interstate Commerce
21 U.S.C. §§ 331(a), 352(a), and 333(a)(1)

The United States Attorney charges that:

1. The Introduction of this Information is realleged and made a part of this Count.

2. Between in or about January 1996 and on or about June 30, 2001, defendants MICHAEL FRIEDMAN, HOWARD R. UDELL, and PAUL D. GOLDENHEIM, were senior executives of The PURDUE FREDERICK COMPANY, INC., doing business as The Purdue Frederick Company, and were responsible corporate officers under 21 U.S.C. §§ 331(a), 333(a)(1), and 352(a) during the time that THE PURDUE FREDERICK COMPANY, INC., introduced and caused the introduction into interstate commerce of quantities of OxyContin from various locations outside the state of Virginia to various locations in the Western District of Virginia and elsewhere, which were misbranded as described in paragraphs 19 through 43 of the Introduction and Count One of this Information.

All in violation of Title 21, United States Code, Sections 331(a), 352(a), and 333(a)(1).

Date: May 9, 2007

John L. Brownlee
United States Attorney
Western District of Virginia

Rick A. Mountcastle, Assistant United States Attorney
Randy Ramseyer, Assistant United States Attorney
Sharon Burnham, Assistant United States Attorney
Barbara T. Wells, Trial Attorney, U.S. Dept. Of Justice
Elizabeth Stein, Trial Attorney, U.S. Dept. Of Justice

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
ABINGDON DIVISION

UNITED STATES OF AMERICA	)	
	)	
v.	)	**Dkt. No. _____**
	)	
THE PURDUE FREDERICK COMPANY, INC.	)	
D/B/A The Purdue Frederick Company	)	
MICHAEL FRIEDMAN	)	
HOWARD R. UDELL	)	
PAUL D. GOLDENHEIM	)	

AGREED STATEMENT OF FACTS

Introduction

1. Defendant The PURDUE FREDERICK COMPANY, INC. (referred to in this Agreed Statement of Facts as "PURDUE"), doing business as The Purdue Frederick Company, was a New York corporation, headquartered in Connecticut. It was created in 1892 and was purchased by its current owners in 1952. At all times relevant to this Agreed Statement of Facts, PURDUE and other related and associated entities were engaged in the pharmaceutical business throughout the United States.

2. PURDUE developed and originally marketed OxyContin Tablets ("OxyContin"), an opioid analgesic approved to be taken every twelve hours. OxyContin is a controlled-release form of oxycodone and is a Schedule II controlled substance with an abuse liability similar to morphine.

3. Defendant MICHAEL FRIEDMAN joined PURDUE in 1985 as Vice President and Assistant to the President and Chairman. He was appointed Group Vice President in 1988, Executive Vice President and Chief Operating Officer in 1999, and President and Chief Executive Officer in 2003.

4. Defendant HOWARD R. UDELL joined PURDUE in 1977 as General Counsel. He was appointed Group Vice President and General Counsel in 1989, Executive Vice President and General Counsel in 1999, and Executive Vice President and Chief Legal Officer in 2003.

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14. The NDA did not claim that OxyContin was safer or more effective than immediate-release oxycodone or other pain medications and PURDUE did not have, and did not provide the FDA with, any clinical studies demonstrating that OxyContin was less addictive, less subject to abuse and diversion, or less likely to cause tolerance and withdrawal than other pain medications.

15. On or about October 24, 1995, the FDA completed, with PURDUE's assistance, an internal Medical Officer Review ("MOR") of the Integrated Summary of Safety ("ISS") and a MOR of the Integrated Summary of Efficacy ("ISE"). While not binding on the company, the MORs were disclosed to certain PURDUE supervisors and employees. These MORs did not state that OxyContin was more effective than or superior to, safer, had less opioid effects, or caused fewer adverse events than any other marketed product.

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c. "The adverse experience profile of [OxyContin] is qualitatively similar to that of the parent drug, oxycodone;" and

d. "Withdrawal is possible in patients who have their dosage abruptly reduced or discontinued."

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b. "Care should be taken to limit competitive promotion. [OxyContin] has been shown to be as good as current therapy, but has not been shown to have a significant advantage beyond reduction in frequency of dosing."

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Misbranding of OxyContin

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20. Beginning on or about December 12, 1995, and continuing until on or about June 30, 2001, certain PURDUE supervisors and employees, with the intent to defraud or mislead, marketed and promoted OxyContin as less addictive, less subject to abuse and diversion, and less likely to

cause tolerance and withdrawal than other pain medications, as follows:

a. Trained PURDUE sales representatives and told some health care providers that it was more difficult to extract the oxycodone from an OxyContin tablet for the purpose of intravenous abuse, although PURDUE's own study showed that a drug abuser could extract approximately 68% of the oxycodone from a single 10 mg OxyContin tablet by crushing the tablet, stirring it in water, and drawing the solution through cotton into a syringe;

b. Told PURDUE sales representatives they could tell health care providers that OxyContin potentially creates less chance for addiction than immediate-release opioids;

c. Sponsored training that taught PURDUE sales supervisors that OxyContin had fewer "peak and trough" blood level effects than immediate-release opioids resulting in less euphoria and less potential for abuse than short-acting opioids;

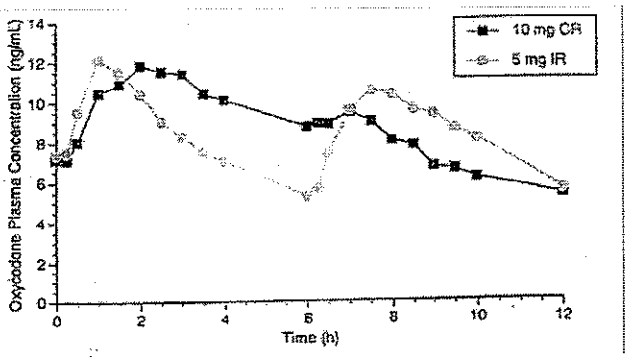
d. Told certain health care providers that patients could stop therapy abruptly without experiencing withdrawal symptoms and that patients who took OxyContin would not develop tolerance to the drug; and

e. Told certain health care providers that OxyContin did not cause a "buzz" or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used to "weed out" addicts and drug seekers.

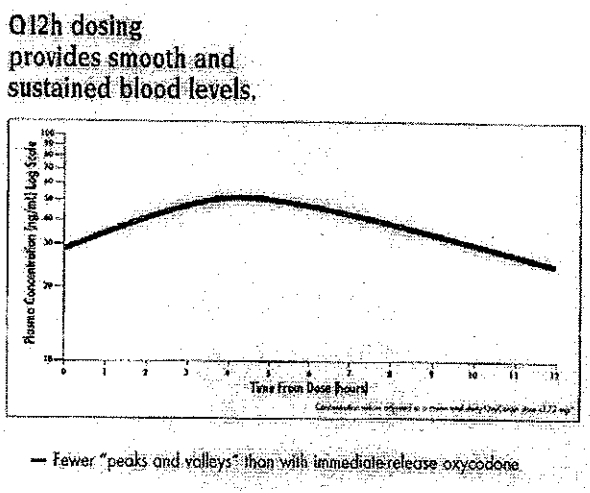
Misbranding of OxyContin: Use of Graphical Depictions by Sales Representatives

21. Data from one of PURDUE's clinical studies was used to create the following graphical demonstration of the difference in the plasma levels at steady state between patients who took OxyContin every twelve hours (the "10 mg CR" line) and patients who took immediate-release

oxycodone every six hours (the "5 mg IR" line):



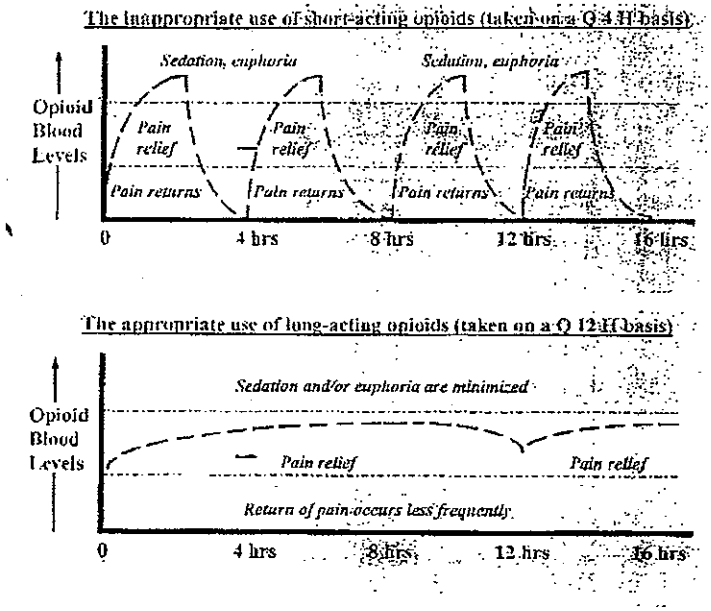
22. On October 12, 1995, PURDUE requested comments from the FDA's Division of Drug Marketing, Advertising, and Communication ("DDMAC") about its proposed launch marketing materials, which included the following graph and text showing the oxycodone plasma concentration provided by OxyContin on a logarithmic scale along with the statement that OxyContin's oxycodone blood plasma levels provided "fewer 'peaks and valleys' than with immediate-release oxycodone:"



23. On or about December 20, 1995, after reviewing the proposed OxyContin launch materials, DDMAC informed PURDUE that "[i]f [Purdue] wishes to compare blood levels in the text, then DDMAC suggests that the blood levels for both dosage forms be presented in the graphic so that the reader can accurately interpret this claim."

24. On or about January 11, 1996, PURDUE told DDMAC that it had "deleted" the statement "[f]ewer peaks and valleys than with immediate-release oxycodone."

25. In or about December 1998, PURDUE sponsored training for all of its district sales managers. During this meeting, a pharmacist retained by PURDUE to conduct a portion of the training used the following graphical demonstration (instead of the graphical demonstration of the actual clinical data described in paragraph 21 of this Agreed Statement of Facts), and falsely stated that OxyContin had significantly fewer "peak and trough" blood level effects than immediate-release opioids resulting in less euphoria and less potential for abuse than short-acting opioids:



26. Beginning in or around 1999, some of PURDUE's new sales representatives were permitted, during training at PURDUE's headquarters, to draw their own blood level graphs to falsely represent that OxyContin, unlike immediate-release or short-acting opioids, did not swing up and down between euphoria and pain, and resulted in less abuse potential.

27. During the period 1999 through June 30, 2001, certain PURDUE sales representatives used graphical depictions similar to the one described in paragraph 25 of this Agreed Statement of Facts and falsely stated to some health care providers that OxyContin had less euphoric effect and less abuse potential than short-acting opioids.

Misbranding of OxyContin: Misleading Use of Article to Claim No Withdrawal or Tolerance

28. On or about January 16, 1997, certain PURDUE supervisors and employees sent to the FDA the results of a clinical study pertaining to the use of low doses of OxyContin by osteoarthritis patients ("osteoarthritis study") and a final study report that included, in a section pertaining to respite periods, the statement "[n]o investigator reported 'withdrawal syndrome' as an adverse experience during the respite periods." In a section entitled "Adverse Experiences by Body System During Respite Periods," the report's summary of the major results listed the most frequently reported adverse experiences in respite periods to be nervousness, insomnia, nausea, pain, anxiety, depression, and diarrhea, followed by the statement: "Twenty-eight patients (26%) had symptoms recorded during 1 or more respite periods."

29. In or about May 1997, certain PURDUE supervisors and employees stated that while they were well aware of the incorrect view held by many physicians that oxycodone was weaker than morphine, they did not want to do anything "to make physicians think that oxycodone was stronger or equal to morphine" or to "take any steps in the form of promotional materials, symposia, clinicals,

publications, conventions, or communications with the field force that would affect the unique position that OxyContin ha[d] in many physicians mind (*sic*)."

30. On or about February 12, 1999, certain supervisors and employees of a United Kingdom company affiliated with PURDUE provided certain PURDUE supervisors and employees with an analysis of the osteoarthritis study together with another clinical study. This analysis included a list of eight patients in the osteoarthritis study and eleven patients in the other study "who had symptoms recorded that may possibly have been related to opioid withdrawal," including one patient in the other study who required treatment for withdrawal syndrome. The "Discussion" section of this analysis included the following: "It is not surprising that some patients in the clinical trials developed some degree of physical dependence and consequently experienced withdrawal symptoms as a result of abrupt discontinuation of OxyContin tablets. All patients who were suspected to have withdrawal symptoms have been reported but this may have resulted in a falsely high incidence. Of the patients who participated in [the osteoarthritis study] (in which patients entered respite periods without OxyContin tablets) many symptoms suspected to be due to opioid withdrawal may simply have resulted from the return of pain. After withdrawal of OxyContin tablets, patient 6007 complained of nervousness, patient 2004 complained of insomnia and felt restless and patients 2020 and 2028 were restless and anxious. Since these are symptoms which often accompany the return of significant pain, it may be wrong to label these as withdrawal symptoms. Nonetheless, the incidence of withdrawal syndromes in patients treated with OxyContin tablets is a concern and it is safer to over report, than under report this potential problem." The analysis' conclusions included the statement: "As expected, some patients did become physically dependent on OxyContin tablets but this is not expected to be a clinical problem so long as abrupt withdrawal of drug is avoided."

31. Certain PURDUE supervisors and employees participated in the drafting of an article regarding the osteoarthritis study that was published in a medical journal on or about March 27, 2000 ("osteoarthritis study article"). The "Results" section of the article included the following three statements pertaining to the incidence of withdrawal syndrome and withdrawal symptoms experienced by study patients: (1) One patient was hospitalized "for withdrawal symptoms . . . . The patient who was hospitalized with withdrawal symptoms had completed the study on the previous day and had been receiving CR oxycodone, 70 mg/d; symptoms resolved after 3 days." (2) "A second patient, who was receiving 60 mg/d CR oxycodone, experienced withdrawal symptoms after running out of study medication. The patient had not reported withdrawal symptoms during scheduled respites from doses of 30 or 40 mg/d." (3) "Withdrawal syndrome was not reported as an adverse event for any patient during scheduled respites. Adverse experiences reported by more than 10% of patients during scheduled respites were nervousness (9 patients) and insomnia (8 patients)."

32. The osteoarthritis study article also included a "Comment" section. The statement regarding withdrawal in this section largely summarized the information in the three statements in the "Results" section and further suggested that patients taking low doses could have their OxyContin treatment abruptly discontinued without experiencing withdrawal if their condition so warranted: "There were 2 reports of withdrawal symptoms after patients abruptly stopped taking CR oxycodone at doses of 60 or 70 mg/d. Withdrawal syndrome was not reported as an adverse event during scheduled respites, indicating that [OxyContin] at doses below 60 mg [per day] can be discontinued without tapering the dose if the patient's condition so warrants."

33. On or about May 18, 2000, after millions of OxyContin tablets had been sold and used by patients, PURDUE's Medical Services Department reported to certain PURDUE supervisors and

employees that it had recently received a report of a patient who said he or she was unable to stop taking OxyContin 10 mg every 12 hours without experiencing withdrawal symptoms and the report indicated that "this type of question, patients not being able to stop OxyContin without withdrawal symptoms has come up quite a bit here in Medical Services lately (at least 3 calls in the last 2 days)."

34. On or about June 26, 2000, certain PURDUE supervisors and employees sent the full text of the osteoarthritis study article together with a "marketing tip" to PURDUE's entire sales force. The marketing tip stated that a reprint of the osteoarthritis study article was available for use in achieving sales success. The marketing tip also included as one of the article's twelve key points: "There were 2 reports of withdrawal symptoms after patients abruptly stopped taking CR oxycodone at doses of 60 or 70 mg/d. Withdrawal syndrome was not reported as an adverse event during scheduled respites indicating that CR oxycodone at doses below 60 mg/d can be discontinued without tapering the dose if the patient condition so warrants."

35. On or about February 13, 2001, certain PURDUE supervisors and employees received a review of the accuracy of the withdrawal data in the osteoarthritis study that stated: "Upon a review of all comments for all enrolled patients, it was noted that multiple had comments which directly stated or implied that an adverse experience was due to possible withdrawal symptoms." This was followed by a list of eleven study patients who reported adverse experience due to possible withdrawal symptoms during these periods. 106 patients initially participated in the osteoarthritis study, 32 of them withdrew because of adverse events (not necessarily related to withdrawal), and 38 patients remained in the study at 12 months.

36. On or about March 28, 2001, a PURDUE employee emailed a PURDUE supervisor regarding the review of withdrawal data described in paragraph 35 of this Agreed Statement of Facts,

asking: "Do you think the withdrawal data from the [osteoarthritis] study . . . is worth writing up (an abstract)? Or would this add to the current negative press and should be deferred?" The supervisor responded: "I would not write it up at this point." No abstract was prepared.

37. Between approximately June 26, 2000, and June 30, 2001, certain PURDUE supervisors and employees distributed copies of the reprint of the osteoarthritis study article to all of PURDUE's sales representatives for use in the promotion and marketing of OxyContin to health care providers, including the distribution of 10,615 copies to certain PURDUE sales representatives between February 13, 2001, and June 30, 2001.

38. During the period June 26, 2000, through June 30, 2001, certain PURDUE sales representatives distributed the reprint of the osteoarthritis study article to some health care providers and falsely or misleadingly stated that patients taking OxyContin at doses below 60 milligrams per day can always be discontinued abruptly without withdrawal symptoms and that patients on such doses would not develop tolerance.

Misbranding of OxyContin: Use of Reduced Abuse Liability Claim in Marketing

39. The original OxyContin package insert approved by the FDA stated: "Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug" (the *Reduced Abuse Liability Statement*). Certain PURDUE supervisors and employees instructed PURDUE sales representatives to use this statement to market and promote OxyContin.

40. Certain PURDUE sales representatives, while promoting and marketing OxyContin, falsely told some health care providers that the *Reduced Abuse Liability Statement* meant that OxyContin did not cause a "buzz" or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used

to "weed out" addicts and drug seekers.

41. By March 2000, various PURDUE supervisors and employees in different parts of the company had received reports of OxyContin abuse and diversion occurring in different communities.

42. On or about November 27, 2000, certain PURDUE supervisors and employees amended the *Reduced Abuse Liability Statement* to state that "[d]elayed absorption, as provided by OxyContin tablets, when used properly for the management of pain, is believed to reduce the abuse liability of a drug," and instructed PURDUE sales representatives to use the amended statement to promote and market OxyContin.

43. From March 2000 through June 30, 2001, certain PURDUE sales representatives, while promoting and marketing OxyContin, falsely told some health care providers that the *Reduced Abuse Liability Statement* and the amended statement meant that OxyContin did not cause a "buzz" or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used to "weed out" addicts and drug seekers.

Introduction of Misbranded OxyContin Into Interstate Commerce

44. In or about and between January 1996 and June 30, 2001, PURDUE manufactured, marketed, and sold quantities of OxyContin in interstate commerce from various locations outside the state of Virginia to various locations in the Western District of Virginia and elsewhere, which were misbranded within the meaning of 21 U.S.C. §§ 331(a), 333(a)(2), and 352(a), as described in paragraphs 19 through 43 of this Agreed Statement of Facts.

45. Between in or about January 1996 and on or about June 30, 2001, defendants MICHAEL FRIEDMAN, HOWARD R. UDELL, and PAUL D. GOLDENHEIM, were responsible

corporate officers of PURDUE under 21 U.S.C. §§ 331(a), 333(a)(1), and 352(a).

46. Defendants MICHAEL FRIEDMAN, HOWARD R. UDELL, and PAUL D. GOLDENHEIM ("individual defendants") do not agree that they had personal knowledge of all of the matters set forth in paragraphs 1 through 44 of this Agreed Statement of Facts. However, they agree that the Court may accept these facts, as agreed to by defendant THE PURDUE FREDERICK COMPANY, INC., as part of the factual basis supporting the guilty pleas by the individual defendants.

The parties agree to the foregoing Agreed Statement of Facts.

Date: May 9, 2007

FOR THE UNITED STATES:

John L. Brownlee
John L. Brownlee
United States Attorney
Western District of Virginia

Rick A. Mountcastle, Assistant United States Attorney
Randy Ramseyer, Assistant United States Attorney
Sharon Burnham, Assistant United States Attorney
Barbara T. Wells, Trial Attorney, U.S. Dept. Of Justice
Elizabeth Stein, Trial Attorney, U.S. Dept. Of Justice

FOR DEFENDANT THE PURDUE FREDERICK COMPANY, INC.:

Date: May 7, 2007

Robin E. Abrams, Esquire
Vice-President and Director of
The Purdue Frederick Company, Inc. and
Vice-President and Associate General Counsel
of Purdue Pharma L.P.
Authorized Corporate Officer for
The Purdue Frederick Company, Inc.

Date: May 8, 2007

Howard M. Shapiro, Esquire
Counsel for The Purdue Frederick Company, Inc.

FOR DEFENDANT MICHAEL FRIEDMAN:

Date: May 7, 2007

Michael Friedman, Defendant

Date: _____

Mark D. Pomerantz, Esquire
Counsel for Michael Friedman

FOR DEFENDANT HOWARD R. UDELL:

Date: May 7, 2007

Howard R. Udell, Defendant

Date: _____

Mary Jo White, Esquire
Counsel for Howard R. Udell

FOR DEFENDANT PAUL D. GOLDENHEIM:

Date: _____

Paul D. Goldenheim, Defendant

Date: _____

Andrew Good, Esquire
Counsel for Paul D. Goldenheim

FOR DEFENDANT THE PURDUE FREDERICK COMPANY, INC.:

Date: _____

Robin E. Abrams, Esquire
Vice-President and Director of
The Purdue Frederick Company, Inc. and
Vice-President and Associate General Counsel
of Purdue Pharma L.P.
Authorized Corporate Officer for
The Purdue Frederick Company, Inc.

Date: _____

Howard M. Shapiro, Esquire
Counsel for The Purdue Frederick Company, Inc.

FOR DEFENDANT MICHAEL FRIEDMAN:

Date: 5/7/07

Michael Friedman, Defendant

Date: 5/8/07

Mark F. Pomerantz, Esquire
Counsel for Michael Friedman

FOR DEFENDANT HOWARD R. UDELL:

Date: _____

Howard R. Udell, Defendant

Date: _____

Mary Jo White, Esquire
Counsel for Howard R. Udell

FOR DEFENDANT PAUL D. GOLDENHEIM:

Date: _____

Paul D. Goldenheim, Defendant

Date: _____

Andrew Good, Esquire
Counsel for Paul D. Goldenheim

FOR DEFENDANT THE PURDUE FREDERICK COMPANY, INC.:

Date: _____

_____
Robin E. Abrams, Esquire
Vice-President and Director of
The Purdue Frederick Company, Inc. and
Vice-President and Associate General Counsel
of Purdue Pharma L.P.
Authorized Corporate Officer for
The Purdue Frederick Company, Inc.

Date: _____

_____
Howard M. Shapiro, Esquire
Counsel for The Purdue Frederick Company, Inc.

FOR DEFENDANT MICHAEL FRIEDMAN:

Date: _____

_____
Michael Friedman, Defendant

Date: _____

_____
Mark D. Pomerantz, Esquire
Counsel for Michael Friedman

FOR DEFENDANT HOWARD R. UDELL:

Date: 5/7/07

_____
Howard R. Udell, Defendant

Date: 5/8/07

_____
Mary Jo White, Esquire
Counsel for Howard R. Udell

FOR DEFENDANT PAUL D. GOLDENHEIM:

Date: _____

_____
Paul D. Goldenheim, Defendant

Date: _____

_____
Andrew Good, Esquire
Counsel for Paul D. Goldenheim

FOR DEFENDANT THE PURDUE FREDERICK COMPANY, INC.:

Date: _____

Robin E. Abrams, Esquire
Vice-President and Director of
The Purdue Frederick Company, Inc. and
Vice-President and Associate General Counsel
of Purdue Pharma L.P.
Authorized Corporate Officer for
The Purdue Frederick Company, Inc.

Date: _____

Howard M. Shapiro, Esquire
Counsel for The Purdue Frederick Company, Inc.

FOR DEFENDANT MICHAEL FRIEDMAN:

Date: _____

Michael Friedman, Defendant

Date: _____

Mark D. Pomerantz, Esquire
Counsel for Michael Friedman

FOR DEFENDANT HOWARD R. UDELL:

Date: _____

Howard R. Udell, Defendant

Date: _____

Mary Jo White, Esquire
Counsel for Howard R. Udell

FOR DEFENDANT PAUL D. GOLDENHEIM:

Date: May 8, 2007

Paul D. Goldenheim, Defendant

Date: May 8, 2007

Andrew Good, Esquire
Counsel for Paul D. Goldenheim

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
ABINGDON DIVISION

UNITED STATES OF AMERICA	)	
	)	
v.	)	**Case No.** _____
	)	
THE PURDUE FREDERICK COMPANY, INC.	)	

PLEA AGREEMENT

THE PURDUE FREDERICK COMPANY, INC. ("PURDUE") has entered into a Plea Agreement with the United States of America, by counsel, pursuant to Rule 11(c)(1)(C) of the Federal Rules of Criminal Procedure ("Fed. R. Crim. P."). The terms and conditions of this agreement are as follows:

1. CHARGE TO WHICH PURDUE IS PLEADING GUILTY AND WAIVER OF RIGHTS

PURDUE will enter a plea of guilty to Count One of an Information, charging it with the felony of misbranding a drug, with the intent to defraud or mislead, in violation of Title 21, United States Code, Sections 331(a) and 333(a)(2). The maximum statutory penalty is a fine of $500,000.00 or twice the gross gain or loss, pursuant to Title 18, United States Code, Sections 3571(c)(3) and 3571(d), plus a period of probation of up to five years, pursuant to Title 18, United States Code, Section 3561(c)(1). In addition, PURDUE's assets may be subject to forfeiture. PURDUE understands that fees may be imposed to pay for probation and that there will be a $400 special assessment, pursuant to Title 18, United States Code, Section 3013(a)(2)(B). PURDUE's attorney has informed it of the nature of the charge and the elements of the charge that must be proved by the United States beyond a reasonable doubt before PURDUE could be found guilty as charged.

PURDUE hereby waives its right to be proceeded against by indictment and consents to the filing of an Information charging it with a violation of Title 21, United States Code, Sections 331(a) and 333(a)(2).

PURDUE acknowledges that PURDUE has had all of its rights explained to it. PURDUE expressly recognizes that, as a corporation, PURDUE may have the following constitutional rights and, that by voluntarily pleading guilty, PURDUE knowingly waives and gives up these valuable constitutional rights:

The right to plead not guilty and persist in that plea.
The right to a speedy and public jury trial.
The right to assistance of counsel at that trial and in any subsequent appeal.
The right to remain silent at trial.
The right to testify at trial.

The right to confront and cross-examine witnesses.
The right to present evidence and witnesses.
The right to compulsory process of the court.
The right to compel the attendance of witnesses at trial.
The right to be presumed innocent.
The right to a unanimous guilty verdict.
The right to appeal a guilty verdict.

PURDUE is pleading guilty as described above because PURDUE is in fact guilty and because PURDUE believes it is in its best interest to do so and not because of any threats or promises, other than the terms of the Plea Agreement, described herein, in exchange for its plea of guilty. PURDUE agrees that all of the matters set forth in the Information are true and correct.

PURDUE understands that the plea is being entered in accordance with Fed. R. Crim. P. 11(c)(1)(C).

2. SENTENCING PROVISIONS

The parties agree and stipulate that the 2006 United States Sentencing Guidelines ("U.S.S.G.") Manual should be used and the following sentencing guidelines sections apply, exclusively.

The Offense Level is computed as follows:

6	§ 2B1.1(a)(2)	Base offense level (cross reference from §2N2.1(b)(1)).
+2	§ 2B1.1(b)(2)(A)(ii)	The offense was committed through mass-marketing.
+2	§ 2B1.1(b)(9)(C)	The offense involved sophisticated means.
10	Total	
12	§ 2B1.1(b)(9)	If the resulting offense level is less than level 12, increase to level 12.

Total Offense Level is 12

The Culpability Score is computed as follows:

5	§ 8C2.5(a)	Start with 5 points.
+4	§ 8C2.5(b)(2)(A)(ii)	The organization had 1,000 or more employees.
- 1	§ 8C2.5(g)(3)	The organization accepted responsibility for its criminal conduct.

Total Culpability Score is 8.

The Base Fine for an Offense Level of 12 is $40,000.00 (§ 8C2.4(d)).

The Minimum Multiplier for a Culpability Score of 8 is 1.60 (§ 8C2.6).
The Maximum Multiplier for a Culpability Score of 8 is 3.20 (§ 8C2.6).

The Guideline Fine Range is $64,000.00 to $128,000.00 ((1.60 x $40,000.00) to (3.20 x $40,000.00)) (§ 8C2.7).

The United States asserts that an upward departure to a statutory maximum fine of $500,000.00 is appropriate because, pursuant to § 5K2.0(a)(1)(A), there exists an aggravating circumstance of a kind, or to a degree, not adequately taken into consideration by the Sentencing Commission in formulating the guidelines. PURDUE does not oppose the Court ordering the statutory maximum fine of $500,000.00.

The parties agree and stipulate that determining the pecuniary gain or loss would unduly complicate or prolong the sentencing process and, in accordance with U.S.S.G. § 8C2.4(c) and 18 U.S.C. § 3571(d), should not be used for the determination of the fine.

The parties agree that if the Court refuses to accept the Plea Agreement with the agreed-upon sentence, this Plea Agreement will be null and void, and PURDUE will be free to withdraw this guilty plea. In the event the Court refuses to accept the Plea Agreement with the agreed-upon sentence and PURDUE withdraws this guilty plea, nothing in this Plea Agreement shall be deemed a waiver of the provisions of Federal Rule of Evidence ("Fed. R. Evid.") 410 and the United States will move to dismiss the Information without prejudice to the United States' right to indict PURDUE or any other entity or individual on any charge.

The parties have not agreed to any matters concerning the length and terms of probation. Accordingly, the Court may impose whatever length and terms of probation, if any, that it determines is appropriate.

3. FINANCIAL OBLIGATIONS

PURDUE agrees and understands that any of the money paid pursuant to this Plea Agreement will be returned if, and only if, the Court refuses to accept the Plea Agreement with the agreed-upon sentence and, as a result, PURDUE withdraws its guilty plea.

For the remaining portions of this "FINANCIAL OBLIGATIONS" section, "PURDUE" means "THE PURDUE FREDERICK COMPANY, INC. or Purdue Pharma L.P.")

a. Immediate Payments

Prior to the entry of PURDUE's guilty plea, PURDUE will make the following disbursements:

(1) $3,087,277.60 (three million eighty-seven thousand two hundred seventy-seven dollars and sixty cents) to the Federal and State Medicaid programs for improperly calculated Medicaid rebates for the years 1998 and 1999;

(2) $500,000.00 (five hundred thousand dollars) to the Clerk, U.S. District Court, Abingdon, Virginia, as payment of the maximum statutory fine;

(3) $20,000,000.00 (twenty million dollars) will be paid into an account to be held in trust ("Trust Account") solely for the operation of the Virginia Prescription Monitoring Program ("PMP") or its successors. The Trust Account funds should be prudently invested to ensure an adequate return. Money may be drawn from the Trust Account solely for the purpose of funding the PMP (including, but not limited to, operating and maintaining the PMP and providing training and educational programs concerning the use of the PMP.) The maximum amount to be drawn from the account each year shall be the lesser of (a) sufficient funds to fund Virginia's Prescription Monitoring Program or (b) the Yearly Expenditure Cap. The Yearly Expenditure Cap will be $1,000,000.00 (one million dollars) for the first year and will increase by 4% per year. If, prior to December 31, 2057, there is a calendar year during which Virginia does not have a PMP or its rough equivalent, the remaining money in the Trust Account shall be paid to the United States Treasury. The money in the Trust Account may not be used for any purpose other than funding the PMP, prior to December 31, 2057. As of December 31, 2057, if the PMP and its successors no longer exist, the money remaining in the account may be used for any purpose, for the benefit of the Commonwealth of Virginia;

(4) $5,300,000.00 (five million three hundred thousand dollars) to the Virginia Medicaid Fraud Control Unit's Program Income Fund; and

(5) $151,100,000.00 (one hundred fifty-one million one hundred thousand dollars) as directed by the United States Attorney's Office as partial payment of a total forfeiture of $276,100,000.00 (two hundred seventy six million one hundred thousand dollars).

b. Civil Settlement Payments

PURDUE will pay a total of $160,000,000.00 (one hundred sixty million dollars) to the United States and the States to settle civil governmental claims, as set forth below:

(1) PURDUE shall pay $100,615,797.25 (one hundred million six hundred fifteen thousand seven hundred ninety-seven dollars and twenty-five cents) to the United States plus interest at the rate of 4.75% per annum ($13,093.84 per day) on $100,615,797.25 from the

date of the plea by The Purdue Frederick Company, Inc. and continuing until and including the day before complete payment is made pursuant to the Civil Settlement Agreement (attached as Attachment D) between the United States and PURDUE; and $59,384,202.75 (fifty-nine million three hundred eighty-four thousand two hundred two dollars and seventy-five cents) to the States as set forth in Section 3(b)(2) below. These payments shall satisfy Purdue's obligation to make restitution under this Plea Agreement;

(2) The $59,384,202.75 paid to the States shall be placed in a dedicated interest bearing account. Each state that elects to participate in this settlement shall, upon execution of the Form State Release (attached as Attachment L) (or an alternative release agreed to by PURDUE and the state), receive its proportionate share as determined by the Medicaid Fraud Control Unit Negotiating Team, plus interest in accordance with the Form State Release, in a timely manner in accordance with the schedule as provided in the Form State Release. Any money remaining in the dedicated interest bearing account after PURDUE has fully paid all of its obligations shall be returned to PURDUE; and

(3) The parties agree and stipulate, pursuant to 18 U.S.C. § 3663(a)(1)(B)(ii), that no other restitution should be ordered.

c. Subsequent Forfeiture Payments

On or before the six month anniversary of the entry of its guilty plea, PURDUE will deposit $90,000,000.00 (ninety million dollars) as directed by the United States Attorney's Office as payment toward a total forfeiture of $276,100,000.00 (two hundred seventy six million one hundred thousand dollars).

On or before the twelve month anniversary of the entry of its guilty plea, PURDUE will deposit $35,000,000.00 (thirty-five million dollars) as directed by the United States Attorney's Office as final payment of a total forfeiture of $276,100,000.00 (two hundred seventy six million one hundred thousand dollars).

d. Compensation and Settlement

Based on the agreement in principle reached between PURDUE and the United States on October 25, 2006, PURDUE set aside a total of $130,000,000.00 (one hundred thirty million dollars), some or all of which will have been paid by the date of the entry of the guilty plea, for compensation and settlement of private civil liabilities related to OxyContin. Any of the $130,000,000.00 (one hundred thirty million dollars) remaining unpaid two years after the entry of

PURDUE's guilty plea will be paid to the United States Treasury. Two years after the entry of PURDUE's guilty plea or at the time the entire $130,000,000.00 has been appropriately expended (if the moneys have been expended in less than two years), PURDUE's attorney shall provide to the Court and the United States Attorney's Office an accounting of the moneys paid and will certify that all payments have been made to resolve PURDUE's private civil liabilities related to OxyContin.

e. Forfeiture

To accomplish the forfeiture, which will be paid as set forth above, PURDUE agrees to the filing of a civil forfeiture complaint, pursuant to 18 U.S.C. § 981(a)(1)(A), in the Western District of Virginia and agrees to forfeit $276,100,000.00 in cash in settlement of the forfeiture complaint ("settlement sum"). PURDUE agrees to sign, concurrent with the signing of this Plea Agreement, a settlement agreement acknowledging that the settlement sum represents proceeds of a violation of 18 U.S.C. § 1957 and/or are forfeitable in lieu of certain property that would be otherwise subject to forfeiture pursuant to 19 U.S.C. § 1613(c). PURDUE agrees to forfeit all interest in these funds and to take whatever steps are necessary to pass clear title of this sum to the United States. These steps include but are not limited to making the sum available to the United States, as directed by the United States. PURDUE agrees not to file a claim in any forfeiture proceeding or to contest, in any manner, the forfeiture of said assets. PURDUE understands and agrees that forfeiture of this property is proportionate to the degree and nature of the offense, and does not raise any of the concerns raised in *United States v. Austin*, 113 S.Ct. 2801 (1993). To the extent that such concerns are raised, PURDUE freely and knowingly waives any and all right it may have to raise a defense of "excessive fines" under the Eighth Amendment to this forfeiture. PURDUE further understands and agrees that this forfeiture is separate and distinct from, and is not in the nature of, or in lieu of, any monetary penalty that may be imposed by the court.

f. Monitoring Costs

PURDUE agrees to expend not less than $5,012,722.40 (five million twelve thousand seven hundred twenty-two dollars and forty cents) in monitoring costs over the next seventy-two months for the purpose of ensuring that Purdue Pharma L.P. complies with its Corporate Integrity Agreement ("CIA") with the Department of Health and Human Services Office of Inspector General ("OIG") and does not engage in any further criminal activity. On an annual basis, beginning on the first anniversary of PURDUE's guilty plea, PURDUE's attorney shall provide to the United States Attorney's Office an accounting of the moneys paid and will certify that all payments set forth therein have been paid as part of a monitoring program as set forth by the CIA between Purdue Pharma L.P. and the OIG or otherwise to prevent future criminal activity by Purdue Pharma L.P. Any of the $5,012,722.40 (five million twelve thousand seven hundred twenty-two dollars and forty cents) remaining unspent seventy-two months after the entry of PURDUE's guilty plea will be paid to the United States Treasury.

g. **Security**

Prior to pleading guilty, Purdue agrees to provide a lien to the United States against sufficient company assets to secure the $125,000,000.00 in deferred payments.

4. MANDATORY ASSESSMENT

PURDUE understands that there is a mandatory assessment of $400.00 per felony count of conviction. PURDUE agrees that it will submit to the U.S. Clerk's Office, a certified check, money order, or attorney's trust check, made payable to the "Clerk, U.S. District Court" in the amount of $400.00 within seven days of entering its plea of guilty.

5. ADDITIONAL OBLIGATIONS

Unless the Court rejects this Plea Agreement and, as a result, PURDUE withdraws its plea, PURDUE agrees to: (1) accept responsibility for its conduct; (2) fully comply with all terms of probation, if probation is imposed; (3) not attempt to withdraw its guilty plea; (4) not deny that it committed the crime to which it has pled guilty; and (5) not make or adopt any arguments or objections to the presentence investigation report that are inconsistent with this Plea Agreement (if a presentence report is ordered by the Court); and (6) comply with its obligations under the Civil Settlement Agreement (attached as Attachment D).

PURDUE consents to public disclosure of all resolution documents related to this case.

Neither PURDUE nor any of its associated entities (as set forth in Attachment A), will, through its present or future directors, officers, employees, agents, or attorneys, make any public statements, including statements or positions in litigation in which any United States department or agency is a party, contradicting any statement of fact set forth in the Agreed Statement of Facts (attached as Attachment B). Should the United States Attorney's Office for the Western District of Virginia notify PURDUE of a public statement by any such person that in whole or in part contradicts a statement of fact contained in the Agreed Statement of Facts, PURDUE may avoid noncompliance with its obligations under this Plea Agreement by publicly repudiating such statement within two business days after such notification. Notwithstanding the above, any PURDUE entity may avail itself of any legal or factual arguments available to it in defending litigation brought by a party other than the United States or in any investigation or proceeding brought by a state entity or by the United States Congress. This paragraph is not intended to apply to any statement made by any individual in the course of any actual or contemplated criminal, regulatory, administrative or civil case initiated by any governmental or private party against such individual.

6. ADMISSIBILITY OF STATEMENTS

PURDUE understands that any statements made on its behalf (including, but not limited to, this Plea Agreement and its admission of guilt) during or in preparation for any guilty plea hearing, sentencing hearing, or other hearing and any statements made, in any setting, may be used against

it in this or any other related criminal proceeding. PURDUE knowingly waives any right it may have under the Constitution, any statute, rule or other source of law to have such statements, or evidence derived from such statements, suppressed or excluded from being admitted into evidence in this or any other related criminal proceeding. With the exception of the situations set forth above, PURDUE does not waive its right to argue against admissibility under any ground permitted under federal or state rules of evidence in any other proceeding.

If the Court rejects the Plea Agreement, and, as a result, PURDUE withdraws its plea, PURDUE will not be bound by the waivers set forth in this section of the Plea Agreement.

7. WAIVER OF RIGHT TO APPEAL AND COLLATERALLY ATTACK THE JUDGMENT AND SENTENCE IMPOSED BY THE COURT

If the Court accepts this Plea Agreement, PURDUE agrees that PURDUE will not appeal the conviction or sentence imposed. PURDUE is knowingly and voluntarily waiving any right to appeal and is voluntarily willing to rely on the Court in sentencing it, pursuant to the terms of Fed. R. Crim. P. 11(c)(1)(C).

PURDUE agrees not to collaterally attack the judgment and/or sentence imposed in this case and waives its right, if any, to collaterally attack, pursuant to Title 28, United States Code, Section 2255, the judgment and any part of the sentence imposed upon it by the Court. PURDUE agrees and understands that if PURDUE, or anyone acting on PURDUE's behalf, files any court document (including but not limited to a notice of appeal) seeking to disturb, in any way, the judgment and/or sentence imposed in its case, the United States will be free to take whatever actions it wishes based on this failure of PURDUE to comply with its obligations under the Plea Agreement.

8. REMEDIES FOR FAILURE TO COMPLY WITH ANY PROVISION OF THE PLEA AGREEMENT OR OVERALL RESOLUTION

PURDUE understands that if: (1) PURDUE attempts to withdraw its plea (in the absence of the Court refusing to accept the Plea Agreement) or fails to comply with any provision of this Plea Agreement, at any time; (2) any defendant in this case does not fulfill the defendant's obligations under the defendant's plea agreement prior to the imposition of judgment; (3) PURDUE's conviction is set aside, for any reason; (4) any entity related to any defendant fails to execute all required paperwork or fails to fulfill its obligations to effectuate the resolution of this entire investigation prior to the imposition of judgment; and/or (5) PURDUE fails to comply with its obligations under the Civil Settlement Agreement (attached as Attachment D) the United States may, at its election, pursue any or all of the following remedies: (a) declare this Plea Agreement void; (b) file, by indictment or information, any charges which were filed and/or could have been filed concerning the matters involved in the instant investigation; (c) refuse to abide by any stipulations and/or recommendations contained in this Plea Agreement; (d) not be bound by any obligation of the United States set forth in this Plea Agreement, including, but not limited to, those obligations set forth in the section of this Plea Agreement entitled "COMPLETION OF PROSECUTION;" and (e) take any other action provided for under this Plea Agreement or by statute, regulation or court rule.

The remedies set forth above are cumulative and not mutually exclusive. If the United States pursues any of its permissible remedies as set forth in this Plea Agreement, PURDUE will still be bound by its obligations under this Plea Agreement. PURDUE hereby waives its right under Fed. R. Crim. P. 7 to be proceeded against by indictment and consents to the filing of an information against it concerning any charges filed pursuant to this section of the Plea Agreement. PURDUE hereby waives any statute of limitations argument as to any such charges.

9. INFORMATION ACCESS WAIVER

PURDUE and any related entity knowingly and voluntarily agrees to waive all rights, whether asserted directly or by a representative, to request or receive from any department or agency of the United States any records pertaining to the investigation or prosecution of this case, including without limitation any records that may be sought under the Freedom of Information Act, 5 U.S.C. § 552, or the Privacy Act of 1974, 5 U.S.C. § 552a.

10. DESTRUCTION OF ITEMS OBTAINED BY LAW ENFORCEMENT

By signing this Plea Agreement, PURDUE and any related entities hereby consent to the destruction of all items obtained by law enforcement agents during the course of the investigation, with the exception of the company's original files. However, PURDUE expressly agrees that, within 30 days of being informed by the United States Attorney's Office that records and/or other items obtained from PURDUE or entities/individuals who were employed by PURDUE or entities/individuals who were agents of PURDUE are available for removal, it will remove, at its cost, all such records and/or other items from the premises designated by the United States Attorney's Office.

11. COMPLETION OF PROSECUTION

PURDUE understands that except as provided for in this Plea Agreement and the Non-Prosecution Agreement (attached as Attachment C), so long as PURDUE complies with all of its obligations under the Plea Agreement, and all entities set forth in the Non-Prosecution Agreement comply with their obligations therein, there will be no further criminal prosecution or forfeiture action by the United States for any violations of law, occurring before May 10, 2007, pertaining to OxyContin that was the subject matter of the investigation by the United States Attorney's Office for the Western District of Virginia and the United States Department of Justice Office of Consumer Litigation that led to this agreement, against the following, or any property owned by any of the following: PURDUE, its current and former directors, officers, employees, co-promoters, owners (including trustees and trust beneficiaries of such owners), successors and assigns; any of PURDUE'S related and associated entities (as listed on Attachment A); and such related and associated entities' current and former directors, officers, employees, owners (including trustees and trust beneficiaries of such owners), successors and assigns, and trusts for the benefit of the families of the current and former directors of PURDUE, including the trustees and trust beneficiaries of such trusts.

Nothing in this Plea Agreement affects the administrative, civil, criminal, or other tax liability of any entity or individual and this Plea Agreement does not bind the Internal Revenue Service of the Department of Treasury, the Tax Division of the United States Department of Justice, or any other government agency with respect to the resolution of any tax issue.

PURDUE understands that nothing in this Plea Agreement precludes any private party from pursuing any civil remedy against PURDUE, and PURDUE agrees that it will not raise this Plea Agreement or its guilty plea as a defense to any such civil action.

12. LIMITATION OF AGREEMENT

This Plea Agreement is limited to the United States of America and does not bind any state or local authorities.

13. EFFECTIVE REPRESENTATION

PURDUE has discussed the terms of the foregoing Plea Agreement and all matters pertaining to the charges against it with its attorney and is fully satisfied with its attorney and its attorney's advice. At this time, PURDUE has no dissatisfaction or complaint with its attorney's representation. PURDUE agrees to make known to the Court no later than at the time of sentencing any dissatisfaction or complaint PURDUE may have with its attorney's representation.

14. EFFECT OF PURDUE'S SIGNATURE

PURDUE understands that its Authorized Corporate Officer's signature on this Plea Agreement constitutes a binding offer by it to enter into this Plea Agreement. PURDUE understands that the United States has not accepted PURDUE's offer until the authorized representative of the United States has signed the Plea Agreement.

15. GENERAL UNDERSTANDINGS

The parties jointly submit that this Plea Agreement and the Agreed Statement of Facts provide sufficient information concerning PURDUE and the crimes charged in this case to enable the meaningful exercise of sentencing authority by the Court under 18 U.S.C. § 3553. The parties agree to request that the Court impose sentence at the date of the arraignment and plea pursuant to the provisions of Fed. Rule Crim. P. 32(c)(1)(A)(ii) and U.S.S.G. § 6A1.1(a)(2), if the Court determines that a presentence report is not necessary.

If the Court orders a presentence report, PURDUE understands that a thorough presentence investigation will be conducted and sentencing recommendations independent of the United States Attorney's Office will be made by the presentence preparer.

PURDUE understands that the prosecution will be free to allocute or describe the nature of this offense and the evidence in this case.

PURDUE understands that the United States retains the right, notwithstanding any provision in this Plea Agreement, to inform the Probation Office and the Court of all relevant facts, to address

the Court with respect to the nature and seriousness of the offense(s), to respond to any questions raised by the Court, to correct any inaccuracies or inadequacies in the presentence report, if a report is prepared, and to respond to any statements made to the Court by or on behalf of the defendant.

PURDUE willingly stipulates that there is a sufficient factual basis for the Court to accept the plea.

PURDUE understands that this Plea Agreement does not apply to any crimes or charges not addressed in this Plea Agreement.

PURDUE has not been coerced, threatened, or promised anything other than the terms of this Plea Agreement, described above, in exchange for its plea of guilty. PURDUE understands that its attorney will be free to argue any mitigating factors on its behalf; to the extent they are not inconsistent with the terms of this Plea Agreement. PURDUE understands that PURDUE will have an opportunity to have a representative address the Court prior to sentence being imposed.

This writing and the Agreed Statement of Facts (attached as Attachment B), Non-Prosecution Agreement (attached as Attachment C), Civil Settlement Agreement (attached as Attachment D), Corporate Integrity Agreement (attached as Attachment E), Stipulation for Compromise Settlement (attached as Attachment G), and Agreed Order of Forfeiture (attached as Attachment H) are the complete and only agreements between the United States and PURDUE, Purdue Pharma L.P. and its related and associated entities concerning resolution of this matter. Also attached to this agreement are the Virginia Release (attached as Attachment L) and the Form State Release (attached as Attachment M). In addition, PURDUE has no objection to the filing of the Information (Attachment F), Verified Complaint for Forfeiture *In Rem* (attached as Attachment I), and the Notice of Compliance (attached as Attachment J) and the Court's entry of a Warrant of Arrest *In Rem* (attached as Attachment K). The agreements and documents listed in this paragraph set forth the entire understanding between the parties and constitutes the complete agreement between the United States Attorney for the Western District of Virginia and PURDUE, Purdue Pharma L.P. and its related and associated entities and no other additional terms or agreements shall be entered except and unless those other terms or agreements are in writing and signed by the parties. These agreements supersede all prior understandings, promises, agreements, or conditions, if any, between the United States and PURDUE, Purdue Pharma L.P. and its related and associated entities.

PURDUE has consulted with its attorney and fully understands its rights with respect to the offenses charged in the charging document(s). Further, PURDUE has consulted with its attorney and fully understands its rights. PURDUE has read this Plea Agreement and carefully reviewed every part of it with its attorney. PURDUE understands this Plea Agreement and PURDUE voluntarily agrees to it. Being aware of all of the possible consequences of its plea, PURDUE has independently decided to enter this plea of its own free will and is affirming that agreement on this date by the signature of its Authorized Corporate Officer below.

The Authorized Corporate Officer, by her signature below, hereby certifies to the following:

(1) She has read the entire Plea Agreement and documents referenced herein and discussed them with PURDUE's owners;

(2) PURDUE understands all the terms of the Plea Agreement and those terms correctly reflect the results of plea negotiations;

(3) PURDUE is fully satisfied with PURDUE's attorneys' representation during all phases of this case;

(4) PURDUE is freely and voluntarily pleading guilty in this case;.

(5) PURDUE is pleading guilty as set forth in this Plea Agreement because it is guilty of the crimes to which it is entering its plea; and

(6) PURDUE understands that it is waiving its right to appeal the judgment and conviction in this case.

PURDUE acknowledges its acceptance of this Plea Agreement by the signature of its counsel and Authorized Corporate Officer. A copy of a certification by PURDUE's Board of Directors authorizing the Authorized Corporate Officer to execute this Plea Agreement and all other documents to resolve this matter on behalf of PURDUE is attached.

Date: May 7, 2007

Robin E. Abrams, Esquire
Vice-President and Director of
The Purdue Frederick Company, Inc. and
Vice-President and Associate General Counsel
of Purdue Pharma L.P.
Authorized Corporate Officer for
The Purdue Frederick Company, Inc.

I have discussed with and fully explained to the Board of Directors of PURDUE the facts and circumstances of the case; all rights with respect to the offense charged in the Information; possible defenses to the offense charged in the Information; all rights with respect to the Sentencing Guidelines; and all of the consequences of entering into this Plea Agreement and entering a guilty plea. I have reviewed the entire Plea Agreement and documents referenced herein with my client, through its Authorized Corporate Officer. In my judgment, PURDUE understands the terms and conditions of the Plea Agreement, and I believe PURDUE's decision to enter into the Plea Agreement is knowing and voluntary. PURDUE's execution of and entry into the Plea Agreement is done with my consent.

Date: May 8, 2007

Howard M. Shapiro, Esquire
Counsel for The Purdue Frederick Company, Inc.

Date: May 9, 2007

John L. Brownlee
United States Attorney
Western District of Virginia

Rick A. Mountcastle, Assistant United States Attorney
Randy Ramseyer, Assistant United States Attorney
Sharon Burnham, Assistant United States Attorney
Barbara T. Wells, Trial Attorney, U.S. Dept. Of Justice
Elizabeth Stein, Trial Attorney, U.S. Dept. Of Justice

SCHEDULE 1

RESOLVED, that the Agreed Statement of Facts between the United States of America and the Corporation (the "Agreed Statement of Facts") in the form presented to the Director of the Corporation be and the same hereby is approved; and further

RESOLVED, that the Settlement Agreement among the United States of America, acting through the Civil Division of the Department of Justice and the United States Attorney's Office for the Western District of Virginia, the Office of the Inspector General of the United States Department of Health and Human Services, the United States Office of Personnel Management, the United States Department of Defense TRICARE Management Activity, the United States Department of Labor Office of Workers' Compensation Programs, the Corporation and Purdue Pharma L.P., a Delaware limited partnership (the "Civil Settlement Agreement"), in the form presented to the Director of the Corporation be and the same hereby is approved; and further

RESOLVED, that the Plea Agreement between the United States of America and the Corporation (the "Plea Agreement") in the form presented to the Director of the Corporation be and the same hereby is approved; and further

RESOLVED, that the Stipulation for Compromise Settlement between the United States of America and the Corporation (the "Stipulation for Compromise Settlement") in the form presented to the Director of the Corporation be and the same hereby is approved; and further

RESOLVED, that the Agreed Order of Forfeiture between the United States of America and the Corporation (the "Agreed Order of Forfeiture"; the Agreed Statement of Facts, the Civil Settlement Agreement, the Plea Agreement, the Stipulation for Compromise Settlement, and the Agreed Order of Forfeiture are hereinafter collectively referred to as the "Settlement Documents"), in the form presented to the Director of the Corporation be and the same hereby is approved; and further

RESOLVED, that Robin E. Abrams as the Vice President of the Corporation, be and she hereby is authorized and directed to execute and deliver in the name and on behalf of the Corporation the Settlement Documents, each in the form or substantially in the form presented to the Director of the Corporation, with such changes, additions and modifications thereto as she shall approve, such approval to be conclusively evidenced by her execution and delivery thereof; and further

RESOLVED, that Robin E. Abrams as the Vice President of the Corporation, be and she hereby is authorized and directed to make, execute and deliver, or cause to be made, executed and delivered, all such agreements, documents, instruments and other papers, and to do or cause to be done on behalf of the Corporation all such acts, as she may deem necessary or appropriate to carry out the purposes and intent of the foregoing resolutions, including, but not limited to, appearing on behalf of the Corporation in the United States District Court for the Western district of Virginia, Abingdon Division, in order to make any statement or statements on behalf of the Corporation she deems appropriate in connection with the judgment to be pronounced against the Corporation in accordance with the Settlement Documents.

THE PURDUE FREDERICK COMPANY INC.

Vice President's Certificate

The undersigned, Robin E. Abrams, the Vice President of The Purdue Frederick Company Inc., a New York corporation (the "Corporation"), DOES HEREBY CERTIFY that attached hereto as Schedule 1 is a true, correct and complete copy of the resolutions approved by the Written Consent of the Sole Director of the Corporation dated May 4, 2007 authorizing the Corporation to execute and deliver on behalf of the Corporation that certain Plea Agreement between the United States of America and the Corporation, together with other documents listed therein with respect to settling that certain investigation by the United States Attorney's Office for the Western District of Virginia, which resolutions have not been amended or rescinded as of the date hereof.

IN WITNESS WHEREOF, the undersigned has executed this Certificate this May 4, 2007.

Robin E. Abrams
Vice President

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
ABINGDON DIVISION

UNITED STATES OF AMERICA	)	
	)	
v.	)	**Case No.** _____
	)	
MICHAEL FRIEDMAN	)	

PLEA AGREEMENT

My counsel and I have entered into a Plea Agreement with the United States of America, by counsel, pursuant to Rule 11(c)(1)(C) of the Federal Rules of Criminal Procedure ("Fed. R. Crim. P.)" The terms and conditions of this agreement are as follows:

1. CHARGE(S) TO WHICH I AM PLEADING GUILTY AND WAIVER OF RIGHTS

I will enter a plea of guilty to Count Two of the attached Information, charging me with the strict liability misdemeanor offense of misbranding a drug in violation of Title 21, United States Code, Sections 331(a) and 333(a)(1). The maximum statutory penalty for Count Two is a fine of $100,000.00, pursuant to 18 U.S.C. § 3571(b)(5), and/or imprisonment for a term of one year, plus a period of supervised release. I understand that fees may be imposed to pay for incarceration or supervised release and that there will be a $25 special assessment, pursuant to 18 U.S.C. § 3013(a)(1)(A)(iii). I further understand that any term of probation may be revoked if I violate its terms and conditions.

My attorney has informed me of the nature of the charge(s) and the elements of the charge(s) that must be proved by the United States beyond a reasonable doubt before I could be found guilty as charged.

I acknowledge that I have had all of my rights explained to me and I expressly recognize that I have the following constitutional rights and, that by voluntarily pleading guilty, I knowingly waive and give up these valuable constitutional rights:

The right to plead not guilty and persist in that plea.
The right to a speedy and public jury trial.
The right to assistance of counsel at that trial and in any subsequent appeal.
The right to remain silent at trial.
The right to testify at trial.
The right to confront and cross-examine witnesses.
The right to present evidence and witnesses in my own behalf.
The right to compulsory process of the court.
The right to compel the attendance of witnesses at trial.
The right to be presumed innocent.
The right to a unanimous guilty verdict.
The right to appeal a guilty verdict.

Defendant's Initials: _____

I am pleading guilty as described above because I am in fact guilty and because I believe it is in my best interest to do so and not because of any threats or promises, other than the terms of this Plea Agreement, described herein, in exchange for my plea of guilty. I agree that the Court can accept the Agreed Statement of Facts as the factual basis for my guilty plea.

I understand that the plea is being entered in accordance with Fed. R. Crim. P. 11(c)(1)(C).

2. SENTENCING PROVISIONS

The parties agree and stipulate that the following Guidelines' section should apply, exclusively, to my conduct:

2N2.1	6	Base Offense Level

Pursuant to Fed. R. Crim. P. 11(c)(1)(C), the parties agree to ask the Court to impose a non-incarcerative sentence. The parties agree that if the Court refuses to accept the Plea Agreement with the agreed-upon sentence I will be free to withdraw this guilty plea. In that event, this Agreement will be null and void and nothing in this Plea Agreement shall be deemed a waiver of the provisions of Federal Rule of Evidence ("Fed. R. Evid.") 410 and the United States will move to dismiss the Information without prejudice to the United States' right to indict me or any other entity or individual on any charge.

The parties agree and stipulate that restitution is not applicable to my conviction.

If the Court were to impose a sentence that includes probation, I do not believe that any non-standard conditions of probation are appropriate. The United States agrees to take no position as to any non-standard conditions of probation.

3. DISGORGEMENT

Prior to the entry of my guilty plea, I will transfer $19,000,000.00 (nineteen million dollars) to the Virginia Medicaid Fraud Control Unit's Program Income Fund. If the Court rejects this Plea Agreement and, as a result, I withdraw my plea, the $19,000,000.00 (nineteen million dollars) will be returned to me.

4. MANDATORY ASSESSMENT AND FINE

I understand that there is a mandatory assessment of $25.00 per misdemeanor count of conviction. The parties agree and stipulate that a fine of $5,000.00, at the upper end of the guidelines' range, is appropriate for this case. I agree that I will submit to the U.S. Clerk's Office, a certified check, money order, or attorney's trust check, made payable to the "Clerk, U.S. District Court" in the amount of $5,025.00 within seven days of entering my plea of guilty.

5. ADDITIONAL OBLIGATIONS

Unless the Court rejects this Plea Agreement and, as a result, I withdraw my plea, I agree to: (1) accept responsibility for my conduct; (2) fully comply with all terms of probation, if a term of probation is imposed; (3) not attempt to withdraw my guilty plea; (4) not deny that I committed the crime to which I have pled guilty; and (5) not make or adopt any arguments or objections to the presentence investigation report that are inconsistent with this agreement (if a presentence report is ordered by the Court).

I consent to public disclosure of all resolution documents related to this case.

I will not make any public statements, including statements or positions in litigation in which any United States department or agency is a party, contradicting any statement of fact set forth in the Agreed Statement of Facts. Should the United States Attorney's Office for the Western District of Virginia notify me of a public statement that contradicts a statement of fact contained in the Agreed Statement of Facts, I may avoid noncompliance with my obligations under this Plea Agreement by publicly repudiating such statement within two business days after such notification. Notwithstanding the above, I may avail myself of any legal or factual arguments available to me in defending litigation brought by a party other than the United States or in any investigation or proceeding brought by a state entity or by the United States Congress. This paragraph is not intended to apply to any statement made by any individual in the course of any actual or contemplated criminal, regulatory, administrative or civil case initiated by any governmental or private party against such individual.

6. ADMISSIBILITY OF STATEMENTS

I understand that any statements I make or made on my behalf (including, but not limited to, this Plea Agreement and its admission of guilt) during or in preparation for any guilty plea hearing, sentencing hearing, or other hearing and any statements made, in any setting, may be used against me in this or any other related criminal proceeding. I knowingly waive any right I may have under the Constitution, any statute, rule or other source of law to have such statements, or evidence derived from such statements, suppressed or excluded from being admitted into evidence in this or any other related criminal proceeding. With the exception of the situations set forth above, I do not waive my right to argue against admissibility under any ground permitted under federal or state rules of evidence in any other proceeding.

If the Court rejects the Plea Agreement, and, as a result, I withdraw my plea, I will not be bound by the waivers set forth in this section of the Plea Agreement.

7. WAIVER OF RIGHT TO APPEAL AND COLLATERALLY ATTACK THE JUDGMENT AND SENTENCE IMPOSED BY THE COURT

If the Court accepts this Plea Agreement, I agree that I will not appeal the conviction or sentence imposed. I am knowingly and voluntarily waiving any right to appeal and am voluntarily willing to rely on the Court in sentencing me pursuant to the terms of Fed. R. Crim. P. 11(c)(1)(C). I agree not to collaterally attack the judgment and/or sentence imposed in this case and waive my right to collaterally attack, pursuant to Title 28, United States Code, Section 2255, the judgment and

any part of the sentence imposed upon me by the Court. I agree and understand that if I file any court document (including but not limited to a notice of appeal) seeking to disturb, in any way, the judgment and/or sentence imposed in my case, the United States will be free to take whatever actions it wishes based on this failure to comply with my obligations under the Plea Agreement.

8. REMEDIES FOR FAILURE TO COMPLY WITH ANY PROVISION OF THE PLEA AGREEMENT OR OVERALL RESOLUTION

I understand that if: (1) I attempt to withdraw my plea (in the absence of the Court refusing to accept the Plea Agreement) or fail to comply with any provision of this agreement, at any time; (2) any defendant in this case does not fulfill the defendant's obligations under the defendant's Plea Agreement prior to the imposition of judgment; (3) my conviction is set aside, for any reason; and/or (4) any entity related to any defendant fails to execute all required paperwork or fails to fulfill its obligations to effectuate the resolution of this entire investigation prior to the imposition of judgment, the United States may, at its election, pursue any or all of the following remedies: (a) declare this Plea Agreement void; (b) file, by indictment or information, any charges which were filed and/or could have been filed concerning the matters involved in the instant investigation; (c) refuse to abide by any stipulations and/or recommendations contained in this Plea Agreement; (d) not be bound by any obligation of the United States set forth in this agreement, including, but not limited to, those obligations set forth in the section of this agreement entitled "COMPLETION OF PROSECUTION;" and (e) take any other action provided for under this agreement or by statute, regulation or court rule.

The remedies set forth above are cumulative and not mutually exclusive. If the United States pursues any of its permissible remedies as set forth in this agreement, I will still be bound by my obligations under this agreement. I hereby waive my right under Fed. R. Crim. P. 7 to be proceeded against by indictment and consent to the filing of an information against me concerning any charges filed pursuant to this section of the Plea Agreement. I hereby waive any statute of limitations argument as to any such charges.

9. INFORMATION ACCESS WAIVER

I knowingly and voluntarily agree to waive all rights, whether asserted directly or by a representative, to request or receive from any department or agency of the United States any records pertaining to the investigation or prosecution of this case, including without limitation any records that may be sought under the Freedom of Information Act, 5 U.S.C. §552, or the Privacy Act of 1974, 5 U.S.C. §552a.

10. DESTRUCTION OF ITEMS OBTAINED BY LAW ENFORCEMENT

The United States Attorney's Office will inform me when my personal financial records and/or other records or items obtained from my accountant or any documents otherwise relating to my personal finances are available for removal. I expressly agree that, within 30 days of being informed by the United States Attorney's Office that such records are available for removal, I will remove, at my cost, all such records from the premises designated by the United States Attorney's

Office. In addition, by signing this Plea Agreement, I hereby consent to the destruction of all items obtained by law enforcement agents during the course of the investigation (other than those described above), and will execute any documents necessary to comply with this provision.

11. COMPLETION OF PROSECUTION

I understand that except as provided for in this agreement, so long as I comply with all of my obligations under the agreement, there will be no further criminal prosecution or forfeiture action by the United States against me, for any violations of law, occurring before May 10, 2007, pertaining to OxyContin that was the subject matter of the investigation by the United States Attorney's Office for the Western District of Virginia and the United States Department of Justice Office of Consumer Litigation that led to this agreement.

Nothing in this Plea Agreement affects the administrative, civil, criminal, or other tax liability of any entity or individual and this Plea Agreement does not bind the Internal Revenue Service of the Department of Treasury, the Tax Division of the United States Department of Justice, or any other government agency with respect to the resolution of any tax issue.

I understand that nothing in this Plea Agreement precludes any private party from pursuing any civil remedy against me, and I agree that I will not raise this Plea Agreement or my guilty plea as a defense to any such civil action.

12. LIMITATION OF AGREEMENT

This Plea Agreement is limited to the United States of America and does not bind any state or local authorities.

13. EFFECTIVE REPRESENTATION

I have discussed the terms of the foregoing Plea Agreement and all matters pertaining to the charges against me with my attorney and am fully satisfied with my attorney and my attorney's advice. At this time, I have no dissatisfaction or complaint with my attorney's representation. I agree to make known to the Court no later than at the time of sentencing any dissatisfaction or complaint I may have with my attorney's representation.

14. WAIVER OF CERTAIN DEFENSES

By signing this Plea Agreement, I waive any defenses regarding pre-indictment delay, statute of limitations, or Speedy Trial Act with respect to any and all criminal charges that could have been timely brought or pursued as of March 29, 2006. This waiver is binding on me only as to charges brought by the United States. This waiver expires once judgment is entered, except as set forth in the section of the Plea Agreement entitled "REMEDIES FOR FAILURE TO COMPLY WITH ANY PROVISION OF THE PLEA AGREEMENT OR OVERALL RESOLUTION."

15. EFFECT OF MY SIGNATURE

I understand that my signature on this Plea Agreement constitutes a binding offer by me to enter into this Plea Agreement. I understand that the United States has not accepted my offer until it signs the Plea Agreement.

16. GENERAL UNDERSTANDINGS

The parties jointly submit that this Plea Agreement and the attached Agreed Statement of Facts provide sufficient information concerning PURDUE and the crimes charged in this case to enable the meaningful exercise of sentencing authority by the Court under 18 U.S.C. § 3553. The parties agree to request that the Court impose sentence at the date of the arraignment and plea pursuant to the provisions of Fed. Rule Crim. P. 32(c)(1)(A)(ii) and U.S.S.G. § 6A1.1(a)(2), if the Court determines that a presentence report is not necessary.

If the Court accepts this Plea Agreement and sentences me to a non-incarcerative sentence, I understand that I will have no right to withdraw my guilty plea. In addition, I understand that I will not have any right to withdraw my plea if I violate my conditions of probation (if any term of probation is imposed) and, as a result, I am sentenced to incarceration.

If the Court orders a presentence report, I understand that a thorough presentence investigation will be conducted and sentencing recommendations independent of the United States Attorney's Office will be made by the presentence preparer.

I understand that the prosecution will be free to allocute or describe the nature of this offense and the evidence in this case. I understand that the United States retains the right, notwithstanding any provision in this Plea Agreement, to inform the Probation Office and the Court of all relevant facts, to address the Court with respect to the nature and seriousness of the offense(s), to respond to any questions raised by the Court, to correct any inaccuracies or inadequacies in the presentence report, if a report is prepared, and to respond to any statements made to the Court by or on behalf of the defendant.

I willingly stipulate that the Agreed Statement of Facts provides the Court with a sufficient factual basis to support my plea of guilty.

I understand that this Plea Agreement does not apply to any crimes or charges not addressed in this agreement. I understand that if I should testify falsely in this or in a related proceeding I may be prosecuted for perjury and statements I may have given authorities pursuant to this Plea Agreement may be used against me in such a proceeding.

I have not been coerced, threatened, or promised anything other than the terms of this Plea Agreement, described above, in exchange for my plea of guilty. I understand that my attorney will be free to argue any mitigating factors on my behalf; to the extent that they are not inconsistent with the terms of this Plea Agreement. I understand that I will have an opportunity to personally address the Court prior to sentence being imposed.

This writing sets forth the entire understanding between the parties and constitutes the complete Plea Agreement between the United States of America and me, and no other additional terms or agreements shall be entered except and unless those other terms or agreements are in writing and signed by the parties. This Plea Agreement supersedes all prior understandings, promises, agreements, or conditions, if any, between the United States and me.

I have consulted with my attorney and fully understand all my rights with respect to the offenses charged in the Information. I have read this Plea Agreement and carefully reviewed every part of it with my attorney. I understand this Plea Agreement and I voluntarily agree to it. Being aware of all of the possible consequences of my plea, I have independently decided to enter this plea of my own free will, and am affirming that agreement on this date and by my signature below.

Date: 5/7/07

Michael Friedman, Defendant

I have fully explained to my client all rights available to my client with respect to the offenses charged in the Information. I have carefully reviewed every part of this Plea Agreement and attached Agreed Statement of Facts with my client. To my knowledge, my client's decision to enter into this Plea Agreement is an informed and voluntary one.

Date: 5/8/07

Mark F. Pomerantz
Counsel for Defendant

Date: May 9, 2007

John L. Brownlee
United States Attorney
Western District of Virginia

Rick A. Mountcastle, Assistant United States Attorney
Randy Ramseyer, Assistant United States Attorney
Sharon Burnham, Assistant United States Attorney
Barbara T. Wells, Trial Attorney, U.S. Dept. Of Justice
Elizabeth Stein, Trial Attorney, U.S. Dept. Of Justice

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
ABINGDON DIVISION

UNITED STATES OF AMERICA	)	
	)	
v.	)	**Case No.** _____
	)	
HOWARD R. UDELL	)	

PLEA AGREEMENT

My counsel and I have entered into a Plea Agreement with the United States of America, by counsel, pursuant to Rule 11(c)(1)(C) of the Federal Rules of Criminal Procedure ("Fed. R. Crim. P.)" The terms and conditions of this agreement are as follows:

1. CHARGE(S) TO WHICH I AM PLEADING GUILTY AND WAIVER OF RIGHTS

I will enter a plea of guilty to Count Two of the attached Information, charging me with the strict liability misdemeanor offense of misbranding a drug in violation of Title 21, United States Code, Sections 331(a) and 333(a)(1). The maximum statutory penalty for Count Two is a fine of $100,000.00, pursuant to 18 U.S.C. § 3571(b)(5), and/or imprisonment for a term of one year, plus a period of supervised release. I understand that fees may be imposed to pay for incarceration or supervised release and that there will be a $25 special assessment, pursuant to 18 U.S.C. § 3013(a)(1)(A)(iii). I further understand that any term of probation may be revoked if I violate its terms and conditions.

My attorney has informed me of the nature of the charge(s) and the elements of the charge(s) that must be proved by the United States beyond a reasonable doubt before I could be found guilty as charged.

I acknowledge that I have had all of my rights explained to me and I expressly recognize that I have the following constitutional rights and, that by voluntarily pleading guilty, I knowingly waive and give up these valuable constitutional rights:

The right to plead not guilty and persist in that plea.
The right to a speedy and public jury trial.
The right to assistance of counsel at that trial and in any subsequent appeal.
The right to remain silent at trial.
The right to testify at trial.
The right to confront and cross-examine witnesses.
The right to present evidence and witnesses in my own behalf.
The right to compulsory process of the court.
The right to compel the attendance of witnesses at trial.
The right to be presumed innocent.
The right to a unanimous guilty verdict.
The right to appeal a guilty verdict.

I am pleading guilty as described above because I am in fact guilty and because I believe it is in my best interest to do so and not because of any threats or promises, other than the terms of this Plea Agreement, described herein, in exchange for my plea of guilty. I agree that the Court can accept the Agreed Statement of Facts as the factual basis for my guilty plea.

I understand that the plea is being entered in accordance with Fed. R. Crim. P. 11(c)(1)(C).

2. SENTENCING PROVISIONS

The parties agree and stipulate that the following Guidelines' section should apply, exclusively, to my conduct:

2N2.1	6	Base Offense Level

Pursuant to Fed. R. Crim. P. 11(c)(1)(C), the parties agree to ask the Court to impose a non-incarcerative sentence. The parties agree that if the Court refuses to accept the Plea Agreement with the agreed-upon sentence I will be free to withdraw this guilty plea. In that event, this Agreement will be null and void and nothing in this Plea Agreement shall be deemed a waiver of the provisions of Federal Rule of Evidence ("Fed. R. Evid.") 410 and the United States will move to dismiss the Information without prejudice to the United States' right to indict me or any other entity or individual on any charge.

The parties agree and stipulate that restitution is not applicable to my conviction.

If the Court were to impose a sentence that includes probation, I do not believe that any non-standard conditions of probation are appropriate. The United States agrees to take no position as to any non-standard conditions of probation.

3. DISGORGEMENT

Prior to the entry of my guilty plea, I will transfer $8,000,000.00 (eight million dollars) to the Virginia Medicaid Fraud Control Unit's Program Income Fund. If the Court rejects this Plea Agreement and, as a result, I withdraw my plea, the $8,000,000.00 (eight million dollars) will be returned to me.

4. MANDATORY ASSESSMENT AND FINE

I understand that there is a mandatory assessment of $25.00 per misdemeanor count of conviction. The parties agree and stipulate that a fine of $5,000.00, at the upper end of the guidelines' range, is appropriate for this case. I agree that I will submit to the U.S. Clerk's Office, a certified check, money order, or attorney's trust check, made payable to the "Clerk, U.S. District Court" in the amount of $5,025.00 within seven days of entering my plea of guilty.

5. ADDITIONAL OBLIGATIONS

Unless the Court rejects this Plea Agreement and, as a result, I withdraw my plea, I agree to: (1) accept responsibility for my conduct; (2) fully comply with all terms of probation, if a term of probation is imposed; (3) not attempt to withdraw my guilty plea; (4) not deny that I committed the crime to which I have pled guilty; and (5) not make or adopt any arguments or objections to the presentence investigation report that are inconsistent with this agreement (if a presentence report is ordered by the Court).

I consent to public disclosure of all resolution documents related to this case.

I will not make any public statements, including statements or positions in litigation in which any United States department or agency is a party, contradicting any statement of fact set forth in the Agreed Statement of Facts. Should the United States Attorney's Office for the Western District of Virginia notify me of a public statement that contradicts a statement of fact contained in the Agreed Statement of Facts, I may avoid noncompliance with my obligations under this Plea Agreement by publicly repudiating such statement within two business days after such notification. Notwithstanding the above, I may avail myself of any legal or factual arguments available to me in defending litigation brought by a party other than the United States or in any investigation or proceeding brought by a state entity or by the United States Congress. This paragraph is not intended to apply to any statement made by any individual in the course of any actual or contemplated criminal, regulatory, administrative or civil case initiated by any governmental or private party against such individual.

6. ADMISSIBILITY OF STATEMENTS

I understand that any statements I make or made on my behalf (including, but not limited to, this Plea Agreement and its admission of guilt) during or in preparation for any guilty plea hearing, sentencing hearing, or other hearing and any statements made, in any setting, may be used against me in this or any other related criminal proceeding. I knowingly waive any right I may have under the Constitution, any statute, rule or other source of law to have such statements, or evidence derived from such statements, suppressed or excluded from being admitted into evidence in this or any other related criminal proceeding. With the exception of the situations set forth above, I do not waive my right to argue against admissibility under any ground permitted under federal or state rules of evidence in any other proceeding.

If the Court rejects the Plea Agreement, and, as a result, I withdraw my plea, I will not be bound by the waivers set forth in this section of the Plea Agreement.

7. WAIVER OF RIGHT TO APPEAL AND COLLATERALLY ATTACK THE JUDGMENT AND SENTENCE IMPOSED BY THE COURT

If the Court accepts this Plea Agreement, I agree that I will not appeal the conviction or sentence imposed. I am knowingly and voluntarily waiving any right to appeal and am voluntarily willing to rely on the Court in sentencing me pursuant to the terms of Fed. R. Crim. P. 11(c)(1)(C). I agree not to collaterally attack the judgment and/or sentence imposed in this case and waive my right to collaterally attack, pursuant to Title 28, United States Code, Section 2255, the judgment and

any part of the sentence imposed upon me by the Court. I agree and understand that if I file any court document (including but not limited to a notice of appeal) seeking to disturb, in any way, the judgment and/or sentence imposed in my case, the United States will be free to take whatever actions it wishes based on this failure to comply with my obligations under the Plea Agreement.

8. REMEDIES FOR FAILURE TO COMPLY WITH ANY PROVISION OF THE PLEA AGREEMENT OR OVERALL RESOLUTION

I understand that if: (1) I attempt to withdraw my plea (in the absence of the Court refusing to accept the Plea Agreement) or fail to comply with any provision of this agreement, at any time; (2) any defendant in this case does not fulfill the defendant's obligations under the defendant's Plea Agreement prior to the imposition of judgment; (3) my conviction is set aside, for any reason; and/or (4) any entity related to any defendant fails to execute all required paperwork or fails to fulfill its obligations to effectuate the resolution of this entire investigation prior to the imposition of judgment, the United States may, at its election, pursue any or all of the following remedies: (a) declare this Plea Agreement void; (b) file, by indictment or information, any charges which were filed and/or could have been filed concerning the matters involved in the instant investigation; (c) refuse to abide by any stipulations and/or recommendations contained in this Plea Agreement; (d) not be bound by any obligation of the United States set forth in this agreement, including, but not limited to, those obligations set forth in the section of this agreement entitled "COMPLETION OF PROSECUTION;" and (e) take any other action provided for under this agreement or by statute, regulation or court rule.

The remedies set forth above are cumulative and not mutually exclusive. If the United States pursues any of its permissible remedies as set forth in this agreement, I will still be bound by my obligations under this agreement. I hereby waive my right under Fed. R. Crim. P. 7 to be proceeded against by indictment and consent to the filing of an information against me concerning any charges filed pursuant to this section of the Plea Agreement. I hereby waive any statute of limitations argument as to any such charges.

9. INFORMATION ACCESS WAIVER

I knowingly and voluntarily agree to waive all rights, whether asserted directly or by a representative, to request or receive from any department or agency of the United States any records pertaining to the investigation or prosecution of this case, including without limitation any records that may be sought under the Freedom of Information Act, 5 U.S.C. §552, or the Privacy Act of 1974, 5 U.S.C. §552a.

10. DESTRUCTION OF ITEMS OBTAINED BY LAW ENFORCEMENT

The United States Attorney's Office will inform me when my personal financial records and/or other records or items obtained from my accountant or any documents otherwise relating to my personal finances are available for removal. I expressly agree that, within 30 days of being informed by the United States Attorney's Office that such records are available for removal, I will remove, at my cost, all such records from the premises designated by the United States Attorney's

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I understand that my signature on this Plea Agreement constitutes a binding offer by me to

enter into this Plea Agreement. I understand that the United States has not accepted my offer until it signs the Plea Agreement.

16. GENERAL UNDERSTANDINGS

The parties jointly submit that this Plea Agreement and the attached Agreed Statement of Facts provide sufficient information concerning PURDUE and the crimes charged in this case to enable the meaningful exercise of sentencing authority by the Court under 18 U.S.C. § 3553. The parties agree to request that the Court impose sentence at the date of the arraignment and plea pursuant to the provisions of Fed. Rule Crim. P. 32(c)(1)(A)(ii) and U.S.S.G. § 6A1.1(a)(2), if the Court determines that a presentence report is not necessary.

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I willingly stipulate that the Agreed Statement of Facts provides the Court with a sufficient factual basis to support my plea of guilty.

I understand that this Plea Agreement does not apply to any crimes or charges not addressed in this agreement. I understand that if I should testify falsely in this or in a related proceeding I may be prosecuted for perjury and statements I may have given authorities pursuant to this Plea Agreement may be used against me in such a proceeding.

I have not been coerced, threatened, or promised anything other than the terms of this Plea Agreement, described above, in exchange for my plea of guilty. I understand that my attorney will be free to argue any mitigating factors on my behalf; to the extent that they are not inconsistent with the terms of this Plea Agreement. I understand that I will have an opportunity to personally address the Court prior to sentence being imposed.

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I have consulted with my attorney and fully understand all my rights with respect to the offenses charged in the Information. I have read this Plea Agreement and carefully reviewed every part of it with my attorney. I understand this Plea Agreement and I voluntarily agree to it. Being

aware of all of the possible consequences of my plea, I have independently decided to enter this plea of my own free will, and am affirming that agreement on this date and by my signature below.

Date: 5/7/07

Howard R. Udell, Defendant

I have fully explained to my client all rights available to my client with respect to the offenses charged in the Information. I have carefully reviewed every part of this Plea Agreement and attached Agreed Statement of Facts with my client. To my knowledge, my client's decision to enter into this Plea Agreement is an informed and voluntary one.

Date: 5/8/07

Mary Jo White
Counsel for Defendant

Date: May 9, 2007

John L. Brownlee
United States Attorney
Western District of Virginia

Rick A. Mountcastle, Assistant United States Attorney
Randy Ramseyer, Assistant United States Attorney
Sharon Burnham, Assistant United States Attorney
Barbara T. Wells, Trial Attorney, U.S. Dept. Of Justice
Elizabeth Stein, Trial Attorney, U.S. Dept. Of Justice

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
ABINGDON DIVISION

UNITED STATES OF AMERICA	)	
	)	
v.	)	**Case No.** _____
	)	
PAUL D. GOLDENHEIM	)	

PLEA AGREEMENT

My counsel and I have entered into a Plea Agreement with the United States of America, by counsel, pursuant to Rule 11(c)(1)(C) of the Federal Rules of Criminal Procedure ("Fed. R. Crim. P.)" The terms and conditions of this agreement are as follows:

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My attorney has informed me of the nature of the charge(s) and the elements of the charge(s) that must be proved by the United States beyond a reasonable doubt before I could be found guilty as charged.

I acknowledge that I have had all of my rights explained to me and I expressly recognize that I have the following constitutional rights and, that by voluntarily pleading guilty, I knowingly waive and give up these valuable constitutional rights:

The right to plead not guilty and persist in that plea.
The right to a speedy and public jury trial.
The right to assistance of counsel at that trial and in any subsequent appeal.
The right to remain silent at trial.
The right to testify at trial.
The right to confront and cross-examine witnesses.
The right to present evidence and witnesses in my own behalf.
The right to compulsory process of the court.
The right to compel the attendance of witnesses at trial.
The right to be presumed innocent.
The right to a unanimous guilty verdict.
The right to appeal a guilty verdict.

I am pleading guilty as described above because I am in fact guilty and because I believe it is in my best interest to do so and not because of any threats or promises, other than the terms of this Plea Agreement, described herein, in exchange for my plea of guilty. I agree that the Court can accept the Agreed Statement of Facts as the factual basis for my guilty plea.

I understand that the plea is being entered in accordance with Fed. R. Crim. P. 11(c)(1)(C).

2. SENTENCING PROVISIONS

The parties agree and stipulate that the following Guidelines' section should apply, exclusively, to my conduct:

2N2.1	6	Base Offense Level

Pursuant to Fed. R. Crim. P. 11(c)(1)(C), the parties agree to ask the Court to impose a non-incarcerative sentence. The parties agree that if the Court refuses to accept the Plea Agreement with the agreed-upon sentence I will be free to withdraw this guilty plea. In that event, this Agreement will be null and void and nothing in this Plea Agreement shall be deemed a waiver of the provisions of Federal Rule of Evidence ("Fed. R. Evid.") 410 and the United States will move to dismiss the Information without prejudice to the United States' right to indict me or any other entity or individual on any charge.

The parties agree and stipulate that restitution is not applicable to my conviction.

If the Court were to impose a sentence that includes probation, I do not believe that any non-standard conditions of probation are appropriate. The United States agrees to take no position as to any non-standard conditions of probation.

3. DISGORGEMENT

Prior to the entry of my guilty plea, I will transfer $7,500,000.00 (seven million five hundred thousand dollars) to the Virginia Medicaid Fraud Control Unit's Program Income Fund. If the Court rejects this Plea Agreement and, as a result, I withdraw my plea, the $7,500,000.00 (seven million five hundred thousand dollars) will be returned to me.

4. MANDATORY ASSESSMENT AND FINE

I understand that there is a mandatory assessment of $25.00 per misdemeanor count of conviction. The parties agree and stipulate that a fine of $5,000.00, at the upper end of the guidelines' range, is appropriate for this case. I agree that I will submit to the U.S. Clerk's Office, a certified check, money order, or attorney's trust check, made payable to the "Clerk, U.S. District Court" in the amount of $5,025.00 within seven days of entering my plea of guilty.

5. ADDITIONAL OBLIGATIONS

Unless the Court rejects this Plea Agreement and, as a result, I withdraw my plea, I agree to: (1) accept responsibility for my conduct; (2) fully comply with all terms of probation, if a term of probation is imposed; (3) not attempt to withdraw my guilty plea; (4) not deny that I committed the crime to which I have pled guilty; and (5) not make or adopt any arguments or objections to the presentence investigation report that are inconsistent with this agreement (if a presentence report is ordered by the Court).

I consent to public disclosure of all resolution documents related to this case.

I will not make any public statements, including statements or positions in litigation in which any United States department or agency is a party, contradicting any statement of fact set forth in the Agreed Statement of Facts. Should the United States Attorney's Office for the Western District of Virginia notify me of a public statement that contradicts a statement of fact contained in the Agreed Statement of Facts, I may avoid noncompliance with my obligations under this Plea Agreement by publicly repudiating such statement within two business days after such notification. Notwithstanding the above, I may avail myself of any legal or factual arguments available to me in defending litigation brought by a party other than the United States or in any investigation or proceeding brought by a state entity or by the United States Congress. This paragraph is not intended to apply to any statement made by any individual in the course of any actual or contemplated criminal, regulatory, administrative or civil case initiated by any governmental or private party against such individual.

6. ADMISSIBILITY OF STATEMENTS

I understand that any statements I make or made on my behalf (including, but not limited to, this Plea Agreement and its admission of guilt) during or in preparation for any guilty plea hearing, sentencing hearing, or other hearing and any statements made, in any setting, may be used against me in this or any other related criminal proceeding. I knowingly waive any right I may have under the Constitution, any statute, rule or other source of law to have such statements, or evidence derived from such statements, suppressed or excluded from being admitted into evidence in this or any other related criminal proceeding. With the exception of the situations set forth above, I do not waive my right to argue against admissibility under any ground permitted under federal or state rules of evidence in any other proceeding.

If the Court rejects the Plea Agreement, and, as a result, I withdraw my plea, I will not be bound by the waivers set forth in this section of the Plea Agreement.

7. WAIVER OF RIGHT TO APPEAL AND COLLATERALLY ATTACK THE JUDGMENT AND SENTENCE IMPOSED BY THE COURT

If the Court accepts this Plea Agreement, I agree that I will not appeal the conviction or sentence imposed. I am knowingly and voluntarily waiving any right to appeal and am voluntarily willing to rely on the Court in sentencing me pursuant to the terms of Fed. R. Crim. P. 11(c)(1)(C). I agree not to collaterally attack the judgment and/or sentence imposed in this case and waive my right to collaterally attack, pursuant to Title 28, United States Code, Section 2255, the judgment and

any part of the sentence imposed upon me by the Court. I agree and understand that if I file any court document (including but not limited to a notice of appeal) seeking to disturb, in any way, the judgment and/or sentence imposed in my case, the United States will be free to take whatever actions it wishes based on this failure to comply with my obligations under the Plea Agreement.

8. REMEDIES FOR FAILURE TO COMPLY WITH ANY PROVISION OF THE PLEA AGREEMENT OR OVERALL RESOLUTION

I understand that if: (1) I attempt to withdraw my plea (in the absence of the Court refusing to accept the Plea Agreement) or fail to comply with any provision of this agreement, at any time; (2) any defendant in this case does not fulfill the defendant's obligations under the defendant's Plea Agreement prior to the imposition of judgment; (3) my conviction is set aside, for any reason; and/or (4) any entity related to any defendant fails to execute all required paperwork or fails to fulfill its obligations to effectuate the resolution of this entire investigation prior to the imposition of judgment, the United States may, at its election, pursue any or all of the following remedies: (a) declare this Plea Agreement void; (b) file, by indictment or information, any charges which were filed and/or could have been filed concerning the matters involved in the instant investigation; (c) refuse to abide by any stipulations and/or recommendations contained in this Plea Agreement; (d) not be bound by any obligation of the United States set forth in this agreement, including, but not limited to, those obligations set forth in the section of this agreement entitled "COMPLETION OF PROSECUTION;" and (e) take any other action provided for under this agreement or by statute, regulation or court rule.

The remedies set forth above are cumulative and not mutually exclusive. If the United States pursues any of its permissible remedies as set forth in this agreement, I will still be bound by my obligations under this agreement. I hereby waive my right under Fed. R. Crim. P. 7 to be proceeded against by indictment and consent to the filing of an information against me concerning any charges filed pursuant to this section of the Plea Agreement. I hereby waive any statute of limitations argument as to any such charges.

9. INFORMATION ACCESS WAIVER

I knowingly and voluntarily agree to waive all rights, whether asserted directly or by a representative, to request or receive from any department or agency of the United States any records pertaining to the investigation or prosecution of this case, including without limitation any records that may be sought under the Freedom of Information Act, 5 U.S.C. §552, or the Privacy Act of 1974, 5 U.S.C. §552a.

10. DESTRUCTION OF ITEMS OBTAINED BY LAW ENFORCEMENT

The United States Attorney's Office will inform me when my personal financial records and/or other records or items obtained from my accountant or any documents otherwise relating to my personal finances are available for removal. I expressly agree that, within 30 days of being informed by the United States Attorney's Office that such records are available for removal, I will remove, at my cost, all such records from the premises designated by the United States Attorney's

Office. In addition, by signing this Plea Agreement, I hereby consent to the destruction of all items obtained by law enforcement agents during the course of the investigation (other than those described above), and will execute any documents necessary to comply with this provision.

11. COMPLETION OF PROSECUTION

I understand that except as provided for in this agreement, so long as I comply with all of my obligations under the agreement, there will be no further criminal prosecution or forfeiture action by the United States against me, for any violations of law, occurring before May 10, 2007, pertaining to OxyContin that was the subject matter of the investigation by the United States Attorney's Office for the Western District of Virginia and the United States Department of Justice Office of Consumer Litigation that led to this agreement.

Nothing in this Plea Agreement affects the administrative, civil, criminal, or other tax liability of any entity or individual and this Plea Agreement does not bind the Internal Revenue Service of the Department of Treasury, the Tax Division of the United States Department of Justice, or any other government agency with respect to the resolution of any tax issue.

I understand that nothing in this Plea Agreement precludes any private party from pursuing any civil remedy against me, and I agree that I will not raise this Plea Agreement or my guilty plea as a defense to any such civil action.

12. LIMITATION OF AGREEMENT

This Plea Agreement is limited to the United States of America and does not bind any state or local authorities.

13. EFFECTIVE REPRESENTATION

I have discussed the terms of the foregoing Plea Agreement and all matters pertaining to the charges against me with my attorney and am fully satisfied with my attorney and my attorney's advice. At this time, I have no dissatisfaction or complaint with my attorney's representation. I agree to make known to the Court no later than at the time of sentencing any dissatisfaction or complaint I may have with my attorney's representation.

14. WAIVER OF CERTAIN DEFENSES

By signing this Plea Agreement, I waive any defenses regarding pre-indictment delay, statute of limitations, or Speedy Trial Act with respect to any and all criminal charges that could have been timely brought or pursued as of March 29, 2006. This waiver is binding on me only as to charges brought by the United States. This waiver expires once judgment is entered, except as set forth in the section of the Plea Agreement entitled "REMEDIES FOR FAILURE TO COMPLY WITH ANY PROVISION OF THE PLEA AGREEMENT OR OVERALL RESOLUTION."

15. EFFECT OF MY SIGNATURE

I understand that my signature on this Plea Agreement constitutes a binding offer by me to

enter into this Plea Agreement. I understand that the United States has not accepted my offer until it signs the Plea Agreement.

16. GENERAL UNDERSTANDINGS

The parties jointly submit that this Plea Agreement and the attached Agreed Statement of Facts provide sufficient information concerning PURDUE and the crimes charged in this case to enable the meaningful exercise of sentencing authority by the Court under 18 U.S.C. § 3553. The parties agree to request that the Court impose sentence at the date of the arraignment and plea pursuant to the provisions of Fed. Rule Crim. P. 32(c)(1)(A)(ii) and U.S.S.G. § 6A1.1(a)(2), if the Court determines that a presentence report is not necessary.

If the Court accepts this Plea Agreement and sentences me to a non-incarcerative sentence, I understand that I will have no right to withdraw my guilty plea. In addition, I understand that I will not have any right to withdraw my plea if I violate my conditions of probation (if any term of probation is imposed) and, as a result, I am sentenced to incarceration.

If the Court orders a presentence report, I understand that a thorough presentence investigation will be conducted and sentencing recommendations independent of the United States Attorney's Office will be made by the presentence preparer.

I understand that the prosecution will be free to allocute or describe the nature of this offense and the evidence in this case. I understand that the United States retains the right, notwithstanding any provision in this Plea Agreement, to inform the Probation Office and the Court of all relevant facts, to address the Court with respect to the nature and seriousness of the offense(s), to respond to any questions raised by the Court, to correct any inaccuracies or inadequacies in the presentence report, if a report is prepared, and to respond to any statements made to the Court by or on behalf of the defendant.

I willingly stipulate that the Agreed Statement of Facts provides the Court with a sufficient factual basis to support my plea of guilty.

I understand that this Plea Agreement does not apply to any crimes or charges not addressed in this agreement. I understand that if I should testify falsely in this or in a related proceeding I may be prosecuted for perjury and statements I may have given authorities pursuant to this Plea Agreement may be used against me in such a proceeding.

I have not been coerced, threatened, or promised anything other than the terms of this Plea Agreement, described above, in exchange for my plea of guilty. I understand that my attorney will be free to argue any mitigating factors on my behalf; to the extent that they are not inconsistent with the terms of this Plea Agreement. I understand that I will have an opportunity to personally address the Court prior to sentence being imposed.

This writing sets forth the entire understanding between the parties and constitutes the complete Plea Agreement between the United States of America and me, and no other additional terms or agreements shall be entered except and unless those other terms or agreements are in writing and signed by the parties. This Plea Agreement supersedes all prior understandings, promises, agreements, or conditions, if any, between the United States and me.

I have consulted with my attorney and fully understand all my rights with respect to the offenses charged in the Information. I have read this Plea Agreement and carefully reviewed every part of it with my attorney. I understand this Plea Agreement and I voluntarily agree to it. Being

aware of all of the possible consequences of my plea, I have independently decided to enter this plea of my own free will, and am affirming that agreement on this date and by my signature below.

Date: May 8, 2007

Paul D. Goldenheim, Defendant

I have fully explained to my client all rights available to my client with respect to the offenses charged in the Information. I have carefully reviewed every part of this Plea Agreement and attached Agreed Statement of Facts with my client. To my knowledge, my client's decision to enter into this Plea Agreement is an informed and voluntary one.

Date: May 8, 2007

Andrew Good
Counsel for Defendant

Date: May 10, 2007

John L. Brownlee
United States Attorney
Western District of Virginia

Rick A. Mountcastle, Assistant United States Attorney
Randy Ramseyer, Assistant United States Attorney
Sharon Burnham, Assistant United States Attorney
Barbara T. Wells, Trial Attorney, U.S. Dept. Of Justice
Elizabeth Stein, Trial Attorney, U.S. Dept. Of Justice

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
ABINGDON DIVISION

UNITED STATES OF AMERICA	)	
	)	
Plaintiff,	)	
	)	
v.	)	**Case No. _____**
	)	
THE PURDUE FREDERICK COMPANY, INC.	)	
	)	
Defendant.	)	

VERIFIED COMPLAINT FOR FORFEITURE *IN REM*

Now comes the plaintiff, United States of America, by and through its attorney, Sharon Burnham, Assistant United States Attorney, and brings this complaint and alleges as follows in accordance with Supplemental Rule G(2) of the Federal Rules of Civil Procedure:

NATURE OF THE ACTION

1. This is an action to forfeit and condemn to the use and benefit of the United States of America, pursuant to18 U.S.C. § 981(a)(1)(A), the following property: THE PURDUE FREDERICK COMPANY, INC. ("defendant property"), for violations of 18 U.S.C. § 1957.

THE DEFENDANT *IN REM*

2. The defendant property consists of the corporation known as THE PURDUE FREDERICK COMPANY, INC., and its assets. The defendant property has not been seized and is not located within this district, but jurisdiction is proper pursuant to 28 U.S.C. §§1355 and 1395.

JURISDICTION AND VENUE

3. Plaintiff brings this action in rem in its own right to forfeit and condemn the defendant property. This Court has jurisdiction over an action commenced by the United States

under 28 U.S.C. § 1345, and over an action for forfeiture under 28 U.S.C. § 1355(a).

4. This Court has in rem jurisdiction over the defendant property under 28 U.S.C. § 1355(b). Upon the filing of this complaint, the plaintiff requests that the Court issue an arrest warrant *in rem* pursuant to Supplemental Rule G(3)(b), which the plaintiff will execute upon the property pursuant to 28 U.S.C. § 1355(d) and Supplemental Rule G(3)(c).

5. Venue is proper in this district pursuant to 28 U.S.C. §1355(b)(1), because a criminal prosecution of the owner of the property could be brought in this district.

BASIS FOR FORFEITURE

6. The defendant property is subject to forfeiture pursuant to 18 U.S.C. § 981(a)(1)(A), because it constitutes property involved in transactions and attempted transactions in violation of 18 U.S.C. § 1957, or is property traceable to such property.

FACTS

7. The attached Agreed Statement of Facts and Declaration of Special Agent Philip Barnett are incorporated by reference.

WHEREFORE, the United States of America respectfully requests that the Clerk of Court issue an arrest warrant *in rem* pursuant to Supplemental Rule G(3)(b); that due notice be given to all parties to appear and show cause why the forfeiture should not be decreed; that judgment be entered declaring the defendant property to be condemned and forfeited to the United States of America for disposition according to law; and that the United States of America be granted such other and further relief as this Court may deem just and proper, together with the costs and disbursements of this action.

Respectfully submitted,

JOHN L. BROWNLEE
United States Attorney
Western District of Virginia

Sharon Burnham
Assistant United States Attorney

DATE: May 9, 2007

DECLARATION

I am a Special Agent of the Internal Revenue Service, United States Department of Treasury, and one of the agents assigned the responsibility for this case. I have read the contents of the foregoing complaint for forfeiture, and the exhibits thereto, and the statements contained therein are true to the best of my knowledge and belief.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on this ____ day of _____, 2007.

_____

Phillip A. Barnett
Special Agent, IRS-CID

DECLARATION OF PHILLIP A. BARNETT
IN SUPPORT OF A COMPLAINT FOR FORFEITURE

I, Phillip A. Barnett, upon my oath make the following statements under penalty of perjury:

I am a Special Agent of the Internal Revenue Service, United States Department of Treasury, and one of the agents assigned the responsibility for this case. Unless otherwise stated, the information in this affidavit is either personally known to me, or was provided to me by other law enforcement officers.

This affidavit is made in support of the filing of a complaint for forfeiture against The Purdue Frederick Company, Inc., and incorporates by reference the attached Agreed Statement of Facts. Your affiant has been involved in the investigation of The Purdue Frederick Company, Inc., since January 2003. The Purdue Frederick Company, Purdue Pharma L.P., and The Purdue Pharma Company ("Purdue") were part of a group of entities involved in the manufacture, marketing, promotion, sale, and distribution of pharmaceutical products, including OxyContin.

The Purdue Frederick Company, Inc., d/b/a The Purdue Frederick Company, was a New York corporation, headquartered in Connecticut. Purdue Pharma L.P. was a Delaware limited partnership, with the same headquarters and facilities as The Purdue Frederick Company. The Purdue Pharma Company was a Delaware general partnership owned by and co-located with The Purdue Frederick Company and Purdue Pharma L.P. The Purdue Pharma Company was also used to conduct pharmaceutical business until September 30, 2004, when the partnership was terminated. After The Purdue Pharma Company was terminated, The Purdue Frederick Company, Inc. became an owner of Purdue Pharma L.P.

On December 12, 1995, the United States Food and Drug Administration (FDA) approved OxyContin for marketing and distribution in the United States for moderate to severe pain lasting more than a few days. From approximately January 1996 until September 30, 2004, OxyContin sales were recorded by The Purdue Pharma Company. After The Purdue Pharma Company was terminated, OxyContin sales were recorded by Purdue Pharma L.P.

From approximately January 1996 to approximately June 2006, proceeds from the sale of OxyContin were deposited and flowed into various Purdue checking accounts, including an account at JP Morgan Chase. The JP Morgan Chase account served to aggregate the receipts of all products sold by the related Purdue companies, including OxyContin.

From 1995 to June 2006, Purdue had OxyContin gross sales of approximately $10.2 billion, with sales net of rebates and discounts totaling approximately $8.4 billion. Federal and state health care programs were among the purchasers of OxyContin and paid for OxyContin prescriptions filled at pharmacies, including pharmacies in the Western District of Virginia. The pharmacies received the monies via mail and/or wire. The pharmacies paid the wholesalers for their supplies of OxyContin via mail and/or wire. The wholesalers paid Purdue via mail and/or wire payments.

From 1995 to September 30, 2004, The Purdue Pharma Company made distributions of approximately $2,854,760,301 (two billion, eight hundred fifty four million, seven hundred sixty thousand, three hundred and one dollars) in profits, including OxyContin proceeds, via wire transfers between Purdue-owned accounts at JP Morgan Chase to The Purdue Frederick Company and Purdue Pharma L.P. All transfers of funds relied upon by the government exceeded $10,000. Although OxyContin sales receipts were co-mingled with other funds, OxyContin receipts comprised up to 90% of the total receipts.

Based upon the preceding facts, information and evidence gathered as a result of the investigation, your affiant contends there is sufficient probable cause to believe that violations under 18 U.S.C. § 1957 have been committed by The Purdue Frederick Company, Inc., supporting the complaint for forfeiture pursuant to 18 U.S.C. § 981(a)(1)(A).

I declare under penalty of perjury that the foregoing is true and correct.

Executed on this ____ day of _____, 2007.

_____
Phillip A. Barnett
Special Agent, IRS-CID

EXHIBIT 59

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 30 2000

TRANSMITTED VIA FACSIMILE

Cynthia Chianese
Assistant Director
Regulatory Affairs
Janssen Pharmacuetica
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

RE: NDA 19-813
Duragesic (fentanyl transdermal system)
MACMIS ID #8664

Dear Ms. Chianese:

Reference is made to Janssen Pharmaceutica's (Janssen) letter, dated February 29, 2000, in response to a letter from the Division of Drug Marketing, Advertising, and Communications (DDMAC), dated February 15, 2000. Our letter concerned the alleged dissemination of "homemade" promotional pieces that promoted Duragesic (fentanyl transdermal system) capsules in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. We requested that you investigate the extent that these "homemade" pieces were used to promote Duragesic, the number of health care professionals who received these pieces, and that you provide the complete promotional pieces as they were allegedly disseminated.

In your letter, you described the circumstances in which the violative promotional materials were disseminated. Additionally, your letter commented on your policy for prohibiting dissemination of homemade materials by your sales force, and specified the corrective actions taken to ensure that this activity will not continue.

We have reviewed the "homemade" promotional pieces and have determined that they are false or misleading because they contain misrepresentations of safety information, broaden Duragesic's indication, contain unsubstantiated claims, and lack fair balance. Specific examples include, but are not limited to, the following "homemade" promotional pieces:

December 9, 1999 Mailing – "The #1 Reason to convert your patients to the Duragesic Patch"

Misrepresentation of Safety Information

Promotional materials are false or misleading if they contain representations or suggestions that a drug's safety or effectiveness is comparable or superior to another drug when such has not been demonstrated by substantial evidence. Examples of your claims that misrepresent the safety profile for Duragesic include:

- You present the claim, "Significantly LESS constipation!" This claim suggests that Duragesic is associated with significantly less constipation than other available opioids. However, this claim has not been demonstrated by substantial evidence. Therefore, without supporting substantial evidence, this claim is false or misleading. Furthermore, this claim misrepresents the safety profile for Duragesic because it minimizes the risk of constipation that is associated with Duragesic therapy. Please refer to our untitled letter to Janssen, dated March 5, 1998, addressing this issue.

- You present the claim, "Low abuse potential!" This claim suggests that Duragesic has less potential for abuse than other currently available opioids. However, this claim has not been demonstrated by substantial evidence. Furthermore, this claim is contradictory to information in the approved product labeling (PI) that states, "Fentanyl is a Schedule II controlled substance and can produce drug dependence similar to that produced by morphine." Therefore, this claim is false or misleading.

Broadening of indication

Promotional materials are misleading if they contain a representation or suggestion that a drug is more useful in a broader range of conditions or patients than has been demonstrated by substantial evidence.

- You present the claim, "It's not just for end stage cancer anymore!" This claim suggests that Duragesic can be used for any type of pain management. However, the PI for Duragesic states, "Duragesic (fentanyl transdermal system) is indicated in the management of chronic pain in patients who require continuous opiod analgesia for pain that cannot be managed by lesser means…." Therefore, the suggestion that Duragesic can be used for any type of pain management promotes Duragesic's for a much broader use than is recommended in the PI, and thus, is misleading. In addition, the suggestion that Duragesic can be used to treat any kind of pain is contradictory to the boxed warning in the PI. Specifically the PI sates,

  BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, DURAGESIC® (FENTANYL TRANSDERMAL SYSTEM) IS CONTRAINDICATED:

- In the management of acute or post-operative pain, including use in out-patient surgeries....

Unsubstantiated Claims

You present several unsubstantiated claims for Duragesic throughout this "homemade" promotional piece. Examples of your unsubstantiated claims include:

- You present the claim, "Preferred regimen: 2 x per week versus 2 x per day!" This claim suggests that patients prefer Duragesic to other available oral opioids that are taken twice daily. However, this patient preference claim is not supported by substantial evidence. Therefore, we consider this claim false or misleading.

- You present the claim, "Easy for Patient Compliance." This claim suggests that Duragesic may enhance patient compliance when compared to other opioids. However, this claim is not supported by specific compliance data, and therefore, is false or misleading.

- You present quality of life claims, including but not limited to, "And the #1 reason to convert your patients to the Duragesic patch: QUALITY OF LIFE," and "...without pain, patient's sleep better, increase daily activities, and spend more quality time with their families." Health related quality of life claims such as these require substantial supporting evidence in the form of adequate and well-controlled studies designed to specifically assess these outcomes. Therefore, without substantiation from adequate studies, the claims presented in this "homemade" promotional piece are misleading,

Fair Balance

Promotional materials must present information relating to the contraindications, warnings, precautions, and side effects with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the product. This "homemade" promotional piece is lacking in fair balance with respect to the content and presentation of risk information related to the use of Duragesic.

- Although this piece contains numerous claims for the efficacy and safety of Duragesic, **you have not presented any risk information** concerning the boxed warnings, contraindications, warnings, precautions, or side effects associated with Duragesic's use (emphasis added). Therefore, this promotional piece is lacking in fair balance, or otherwise misleading, because it fails to address important risks and restrictions associated with Duragesic therapy.

Monthly Cost of Therapy (30 Days)

Misrepresentation of Safety Information

- Your present the claim, "Duragesic results in **much less Constipation** compared to Oxycontin (Senokot $1.00/day). However, this comparative claim to Oxycontin is not supported by substantial evidence. Therefore, this unsubstantiated superiority claim is false or misleading. Furthermore, this claim minimizes the risk of constipation that is associated with Duragesic therapy.

Cost Comparison

- You present a table that compares the price of different strengths of Duragesic and Oxycontin from eight retail pharmacies. This table is followed by the claim that "Duragesic is marginally less expensive." However, this comparison is misleading because it implies that Duragesic is equally safe, effective, and interchangeable with Oxycontin for the doses compared. Furthermore, this cost information lacks substantiation and does not provide a reference as to the source of the cost information presented.

Failure to Submit

- Promotional materials must be submitted to the FDA under Form FDA 2253 at the time of initial dissemination. However, our records indicate these promotional materials were not submitted at the time of initial use.

We have reviewed your response and actions taken in response to the dissemination of this violative promotional piece. We do not wish to comment on your internal processes, however we do acknowledge your investigation and the corrective actions taken to prevent reoccurrence of this type of violative promotional activity. At this time we have no further questions and consider the matter regarding the "homemade" promotional pieces described in this letter to be closed.

However, you should immediately cease distribution of all other promotional materials for Duragesic that contain the same or similar claims or presentations. You should submit a written response to us on or before April 13, 2000, describing your intent and plans to comply with the above. Your letter should include a list of materials discontinued and the date on which these materials were discontinued.

If you have any further questions or comments, please contact me by facsimile at (301) 594-6771, or by writing at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this matter, please refer to the MACMIS # 8664 and the NDA number.

Sincerely,

/S/

Spencer Salis, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

DURAGESIC

entanyl Transdermal System

Top 10 List

Reasons to Switch Your Patients to the Duragesic Patch:

#10	It's not just for end stage cancer anymore!
#9	DURAGESIC - the LONGEST acting opioid!
#8	Significantly LESS constipation!
#7	EASY to Titrate - Remember the 6-30-60 rule!
#6	Cost Effective
#5	No clock watching as with oral opioids!
#4	Preferred regimen: 2 x per week versus 2 x per day!
#3	Low abuse potential!
#2	EASY for Patient Compliance

And the #1 reason to convert your patients to the Duragesic patch:

#1 QUALITY OF LIFE

Duragesic gives patients the FREEDOM to enjoy their lives without focus on their pain. And without pain, patients sleep better, increase daily activities, and spend more quality time with their families. They may even find time to stop and smell the flowers!

Our Top 10 List is complete, and now you know just how much your patients with chronic non-malignant pain can benefit from Duragesic. With these seeds, enjoy the blooms of your newly planted habit of writing Duragesic.

The New Standard in the New Millennium
For Chronic Non-Malignant Pain

Monthly Cost of Therapy (30 Days)

	Duragesic 25mcg	Oxycontin 20mg	Duragesic 50mcg	Oxycontin 40mg	Duragesic 75mcg	Oxycontin 80mg	Duragesic 100mcg
Target	119.38	155.39	181.38	256.69	281.98	402.99	347.98
Publix	127.78	139.39	183.78	246.99	287.98	450.99	357.98
Walmart	133.92	141.88	213.24	247.63	331.08	461.21	407.68
Perkins	139.14	156.88	209.86	266.24	326.8	486.82	403.28
Medicine Shoppe	125.78	136.89	191.78	238.89	299.78	590.89	371.78
Eckerds	162.58	149.59	217.38	254.69	347.98	485.19	399.78
Walgreens	135.98	132.95	209.98	235.97	323.98	447.95	405.98
Pill Box	128.00	137.40	198.00	237.00	308.00	450.00	360.00
Avg Cost	134	144	201	248	313	472	382

Duragesic results in ***much less Constipation*** compared to Oxycontin (Senokot $1.00/day)
Duragesic is marginally less expensive.

EXHIBIT 60

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

94934d

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Ajit Shetty, M.D.
CEO
Janssen Pharmaceutica, Inc.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

RE: NDA # 19-813
Duragesic® (fentanyl transdermal system) CII
MACMIS # 12386

WARNING LETTER

Dear Dr. Shetty,

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional file card (DR-850) for Duragesic® (fentanyl transdermal system) submitted by Janssen Pharmaceutica, Inc. (Janssen) under cover of Form FDA 2253. The file card makes false or misleading claims about the abuse potential and other risks of the drug, and includes unsubstantiated effectiveness claims for Duragesic. The file card thus misbrands the drug under Section 502(a) of the Federal Food, Drug, and Cosmetic Act (Act) 21 U.S.C. 352(a). By suggesting that Duragesic has a lower potential for abuse compared to other opioid products, the file card could encourage the unsafe use of the drug, potentially resulting in serious or life-threatening hypoventilation.

Background

According to the approved product labeling (PI), Duragesic is a transdermal system providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. Duragesic is indicated in the management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids. The Indications and Usage section of the PI states: "Duragesic should not be used in the management of acute or postoperative pain because serious or life-threatening hypoventilation could result (see BOX WARNING and CONTRAINDICATIONS)." The boxed warning and contraindications sections further discuss the risk of serious or life-threatening hypoventilation. This risk is also addressed in the warnings and precautions sections of the PI.

Duragesic has the potential for abuse. The Drug Abuse and Dependence section of the PI states, in pertinent part:

> Fentanyl is a Schedule II controlled substance and can produce drug dependence similar to that produced by morphine. DURAGESIC® (fentanyl transdermal system) therefore has the

potential for abuse. Tolerance, physical and psychological dependence may develop upon repeated administration of opioids.

False or Misleading Safety Claims

The file card presents the prominent claim, "Low reported rate of mentions in DAWN data," along with Drug Abuse Warning Network (DAWN) data comparing the number of mentions for Fentanyl/combinations (710 mentions) to other listed opioid products, including Hydrocodone/combinations (21,567 mentions), Oxycodone/combinations (18,409 mentions), and Methadone (10,725 mentions). The file card thus suggests that Duragesic is less abused than other opioid drugs.

This is false or misleading for two reasons. First, we are not aware of substantial evidence or substantial clinical experience to support this comparative claim. The DAWN data cannot provide the basis for a valid comparison among these products. As you know, DAWN is not a clinical trial database. Instead, it is a national public health surveillance system that monitors drug-related emergency department visits and deaths. If you have other data demonstrating that Duragesic is less abused, please submit them.

Second, Duragesic is not as widely prescribed as other opioid products. As a result, the relatively lower number of mentions could be attributed to the lower frequency of use, and not to a lower incidence of abuse. The file card fails to disclose this information.

The information from the Drug Abuse and Dependence section of the PI, which appears in a footnote on the opposite page of the spread (entitled "Favorable side-effect profile") is not sufficient to make the claim truthful and non-misleading. The footnote does not substantiate the claim. Nor does it set forth qualifying information about the frequency of prescribing of the compared opioids.

In addition, on the page entitled "Favorable side-effect profile," the file card presents the claim, "Minimizes the potential for local GI side effects by avoiding GI absorption," along with a table entitled, "Adverse experiences in patients with cancer," that shows a 14 percent rate of constipation with Duragesic and a 0 percent discontinuation rate because of constipation. This combination of text and graphics is false or misleading, in that it suggests that Duragesic is associated with less constipation, nausea, and vomiting than oral opioids, which are absorbed by the GI tract. We are not aware of substantial evidence or substantial clinical experience to support this comparative claim.

Unsubstantiated Effectiveness Claims

The file card states, on page four, "Demonstrated effectiveness in chronic back pain with additional patient benefits." The referenced study,[1] conducted by Simpson et al., is inadequate to support this claim, because it was an open-label, single-arm trial with no control group. We are not aware of substantial evidence or substantial clinical experience to support this claim.

On pages 4 and 5, the file card includes the claims, "86% of patients experienced overall benefit in a clinical study based on: pain control, disability in ADLs, quality of sleep," "All patients who experienced overall benefit from DURAGESIC would recommend it to others with chronic low back

[1] Simpson RK Jr, Edmondson EA, Constant CF, Collier C. Transdermal fentanyl as treatment for chronic low back pain. J Pain Symptom Manage. 1997; 14:218-224.

pain," "Significantly reduced nighttime awakenings," and "Significant improvement in disability scores as measured by the Oswestry Disability Questionnaire and Pain Disability Index." To support these claims, the file card again cites the Simpson et al. trial. For the reasons noted above, this uncontrolled study is inadequate to support such claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.

On pages 6 and 7, the file card includes the claims, "Long-term effects: 12-month open-label study," "Significant improvement in physical functioning summary score," and "Significant improvement in social functioning," along with figures illustrating these claims. To support these claims, the file card cites a study[2] conducted by Milligan et al. This open-label, uncontrolled study is not adequate in design to show an analgesic effect. The data from this study are not substantial evidence or substantial clinical experience to support such outcomes claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.

On pages 8 and 9, the file card includes the claims, "Improved patient outcomes: Open-label, crossover comparison study," "Significant improvement in physical functioning summary score," and "Significant improvement in social functioning," along with figures comparing data for Duragesic and sustained release oral morphine. To support these claims, the file card cites the study[3] conducted by Allan et al.. An open-label study cannot minimize bias in the reporting of subjective response in the SF-36, a general healthcare questionnaire. It is therefore not sufficient to support the cited claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.

Finally, the file card prominently presents the claims, "1,360 loaves…and counting," "Work, uninterrupted," "Life, uninterrupted," "Game, uninterrupted," "Chronic pain relief that supports functionality," "Helps patients think less about their pain," and "Improvements in physical and social functioning." These outcome claims are misleading because they imply that patients will experience improved social or physical functioning or improved work productivity when using Duragesic. Janssen has not provided references to support these outcome claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.

Conclusions and Requested Actions

The file card makes false or misleading safety claims and unsubstantiated effectiveness claims for Duragesic. The file card thus misbrands Duragesic in violation of the Act. 21 U.S.C. § 352(a).

DDMAC requests that Janssen immediately cease the dissemination of promotional materials for Duragesic the same as or similar to those described above. Please submit a written response to this letter on or before September 17, 2004, describing your intent to comply with this request, listing all promotional materials for Duragesic the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug

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[2] Milligan K, Lanteri-Minet M, Borchert K, et al. Evaluation of long-term efficacy and safety of transdermal fentanyl in the treatment of chronic noncancer pain. J Pain. 2001;2:197-204.

[3] Allan L, Hays H, Jensen N-H, et al. Radomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain BMJ. 2001;322:1154-1158

Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS # 12386 in addition to the NDA numbers. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Duragesic comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Abrams
9/2/04 04:32:52 PM

EXHIBIT 61

PAIN

Finding Relief

Pain Management for Older Adults

DVD Inside

Featuring
KATHY BAKER

Complaints of pain are the #1 reason older adults go to the doctor!

PHYSICIANS DEDICATED TO RELIEVING PAIN
the AMERICAN ACADEMY of PAIN MEDICINE
the voice of pain medicine

AMERICAN GERIATRICS SOCIETY A·G·S MCMXLII

THE AGS FOUNDATION FOR HEALTH IN AGING

PriCara
Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Manufactured in the United States of America

PAIN

Finding Relief

Pain Management for Older Adults

Contents

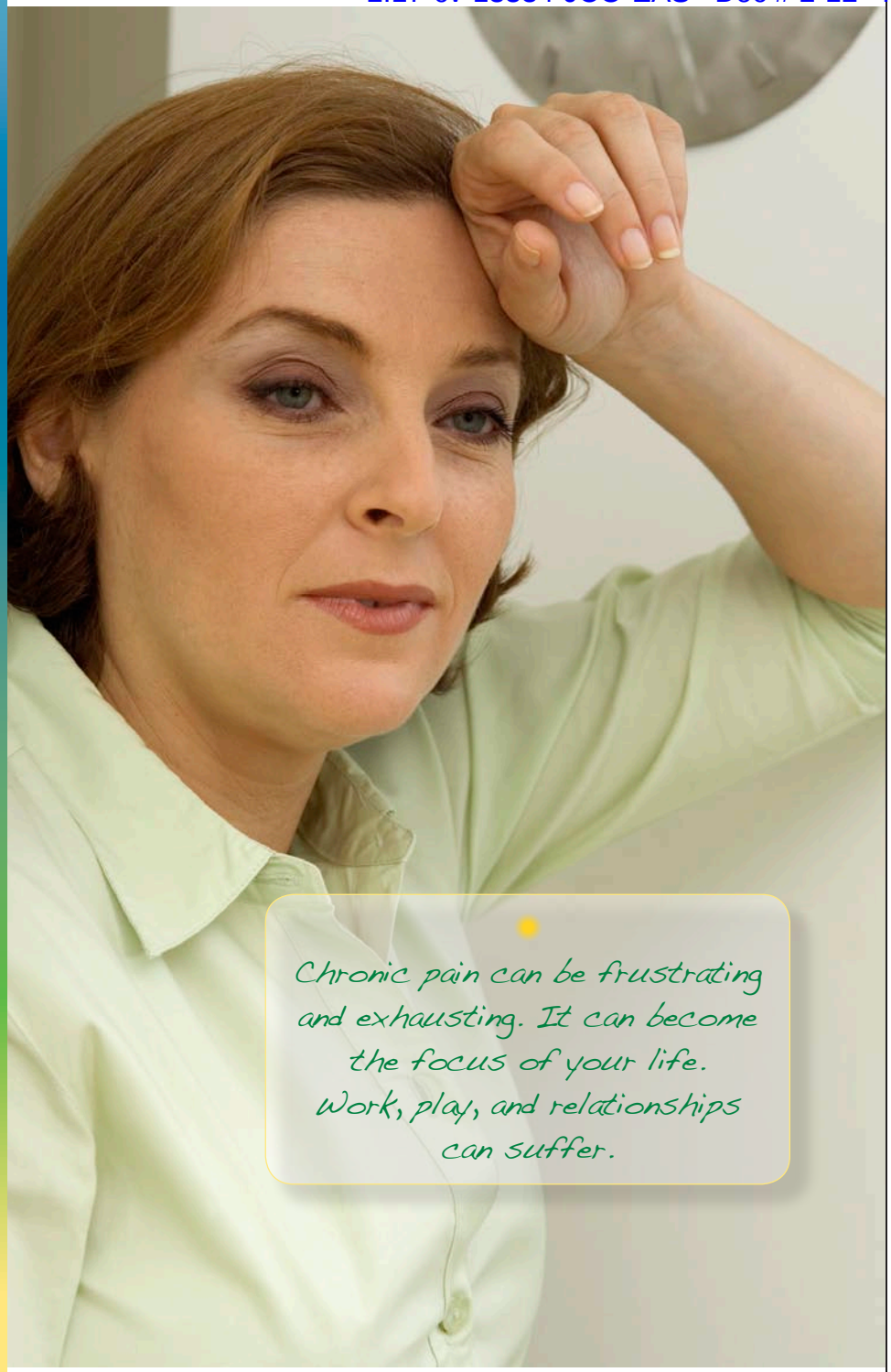
Introduction

Complaints of pain are the #1 reason people go to the doctor, and painful conditions, such as arthritis, tend to increase with age. Pain affects more Americans than diabetes, heart disease, and cancer combined.

These days, most pain can be very effectively treated. But, unfortunately, many older adults don't get the relief they deserve. Untreated pain not only causes needless suffering, but it can also lead to many other problems. If pain is not treated quickly, it may become worse or become more difficult to treat. And long-term pain can lead to loss of function at home and work, lost income, and personal-relationship problems.

This program is aimed specifically at older adults and what they need to know to get effective pain relief. You will learn that there are many pathways to this relief.

You will learn about your options for pain management and how to find the treatment that's right for you. By learning more about pain and the many ways it can be treated, you are taking solid steps toward reducing the pain you or a loved one may be feeling.



Pain Basics

Pain is the body's alarm system. It tells us when something is wrong. Pain caused by an injury such as a cut, broken bone, or infection can be intense, but it doesn't usually last very long. This is called *acute* pain.

If pain remains even after an injury has healed, or if it continues for longer than expected, it is called *chronic* pain. About 70 million people suffer from chronic pain in the U.S. alone. Chronic pain can be frustrating and exhausting. It can become the focus of your life. Work, play, and relationships can suffer.

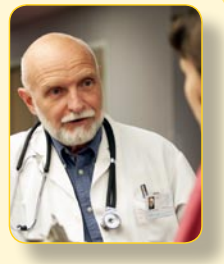
One difficult thing about pain is that it can't be measured. No test or device can measure how much you hurt. That's why most doctors say that "pain is what the patient says it is." In addition, sometimes a physical cause of pain cannot be found. Some people worry that a doctor will think their pain is "all in their head." Most doctors know better. They will take your pain seriously and work hard to find a solution.

This booklet focuses on treatments for the most common causes of acute and chronic pain. It does not address the special situations of pain caused by cancer or nerve damage, or pain occurring at the end of life.

Finding Out What's Wrong

When you visit your doctor, he or she will ask you questions about your pain.

The questions will help him or her understand the pain.



You may be asked:

- Where does it hurt?
- Does the pain move from place to place?
- Do you have pain in more than one place?
- When does the pain happen?
- How long does it last?
- Does the pain come and go?
- Have you had this pain before?
- Does the pain keep you from doing all you want to do?
- Does the pain disrupt your sleep?
- Has your mood changed because of the pain?
- Are your relationships being affected by the pain?
- What do you think is causing the pain?
- What makes the pain better?
- What makes it worse?

The answers to these questions will help your doctor find possible causes.

You may also be asked to rate your pain on a scale of some kind. Some scales use faces showing different expressions:

Other scales use numbers, from 0 to 10:

0	1	2	3	4	5	6	7	8	9	10
No pain					Moderate pain					Worst pain possible

In most cases, additional tests, such as x-rays, are not needed. A thorough patient history and physical exam are usually enough to guide effective pain treatment.

But even if a specific physical cause cannot be found, your pain is real! And even when the source is unknown, the pain can almost always be managed.

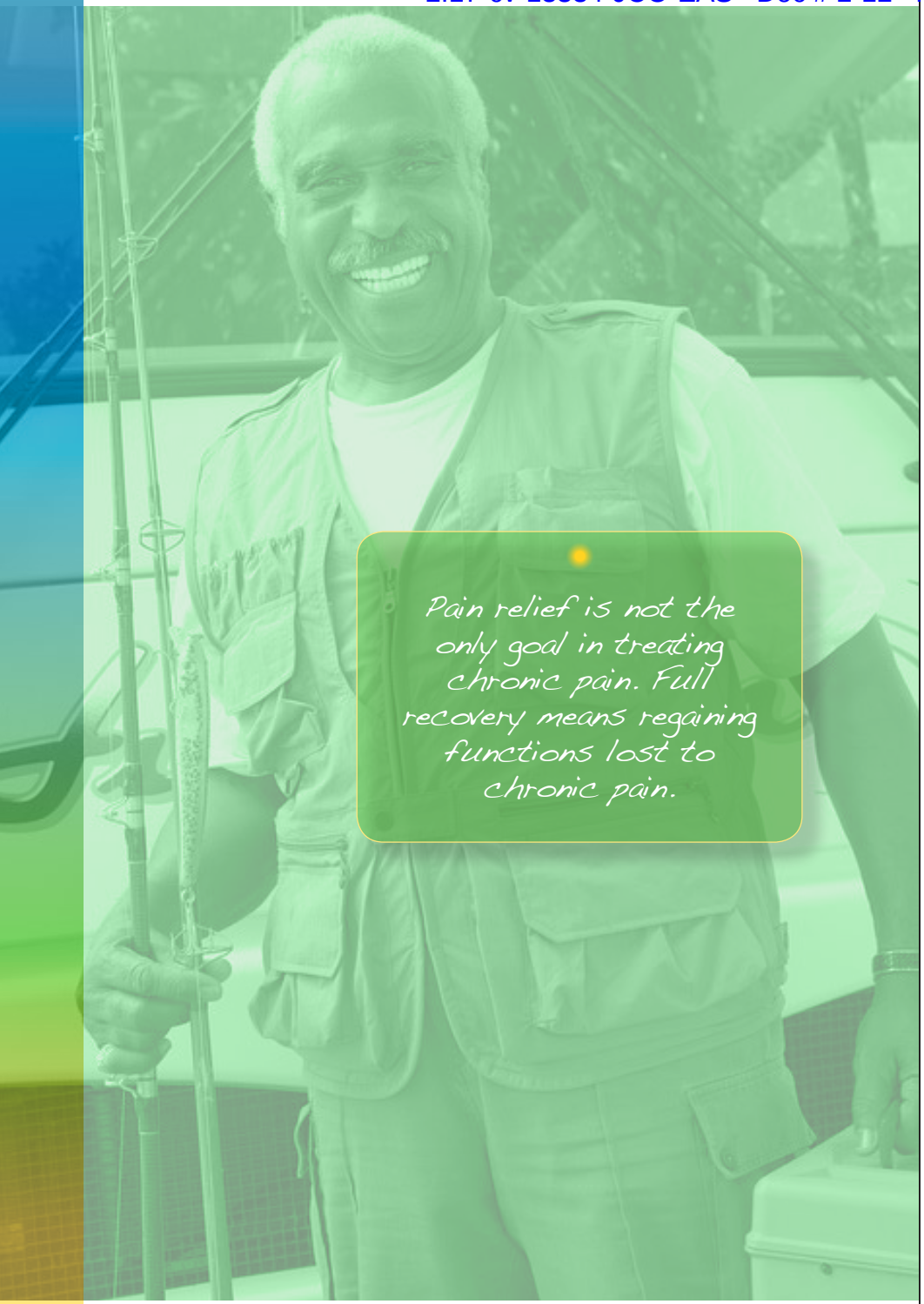
Pain-Medicine Specialists

Your doctor may suggest that you see a pain specialist. Pain specialists are physicians with extra training in pain medicine. They try to treat the whole person, not just the pain. They look for a balance of different treatments that are tailored to each person's needs.

Special centers for treating pain are in many parts of the country. (You can find a physician who is expert in treating pain by using the "Physician Finder" on the website of the American Academy of Pain Medicine, www.painmed.org, or by calling 847-375-4731.)

Many people with chronic pain rely on a team that may include:

- Their doctor
- A pain specialist
- A physical therapist
- A mental-health worker
- Specialists in other disorders , such as diabetes or heart disease



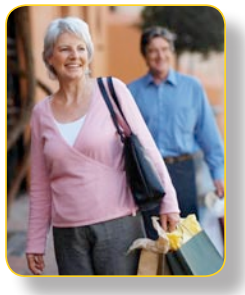
Pain relief is not the only goal in treating chronic pain. Full recovery means regaining functions lost to chronic pain.

Treatment Goals—It's Not Just About Pain Relief!

If you are in pain, you want it to stop. That's certainly understandable! But pain relief is not the *only* goal in treating chronic pain. Sometimes people stop doing things because of pain. They stop exercising, working, walking, or even just sleeping in their own bed. Full recovery means regaining functions lost to chronic pain. Reducing pain is often just the first step.

Your recovery will be measured by how well you reach functional goals, such as:

- Sleeping without waking from pain
- Sleeping in your own bed
- Returning to work
- Enjoying recreational activities
- Having sex
- Walking without help
- Climbing stairs



You and your doctor will work together to set goals that are right for you. The key to success is finding the right balance between your goals and the treatments needed to achieve those goals.

Treating chronic pain is a marathon, not a sprint!

Medications for Pain Relief

Medications that relieve pain are called *analgesics*. Analgesics are the mainstay of pain management. But many non-drug treatments, such as exercise or acupuncture, can also be used, either alone or with medications. Combining such treatments may reduce the intensity of your pain, boost your ability to cope, enhance your comfort and improve your quality of life.

There are many types of analgesics. You can buy some in stores; others require a prescription. This section describes the common types of analgesics.

Aspirin

Aspirin was discovered and first used more than a century ago. It remains one of the most widely used pain relievers in the world.

Advantages

- Relieves minor to moderate pain, fever, headaches, and swelling
- Inexpensive
- No prescription needed

Disadvantages

- Can cause stomach upset or bleeding in the stomach or intestines
- Can cause kidney damage if taken at high doses or for a long time

Acetaminophen

Acetaminophen is a non-aspirin pain reliever. It is used alone for mild to moderate pain. It is also combined with other types of pain medications to treat more serious pain.

Advantages

- Relieves minor to moderate pain, headaches, and fever
- Little or no stomach upset or bleeding
- Inexpensive
- No prescription needed

Disadvantages

- Does not reduce swelling
- Can cause liver and kidney damage if taken in excessive doses

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are a large family of medicines that work in a similar way to aspirin by relieving both pain and swelling. This class includes drugs such as ibuprofen, naproxen, and celecoxib. Some are available without a prescription.

Advantages

- Relieve mild to moderate pain, fever, headaches, and swelling

Disadvantages

- Can cause stomach upset or bleeding in stomach or intestines
- Can cause kidney or liver damage if taken at high doses or for a long time
- May cause adverse reactions in people with asthma
- Can increase the risk of heart attack and stroke

Topical anesthetics

Topical anesthetics are used to numb the surface of a body part. They can be used to numb the front of the eye, the inside of the nose, the throat, the skin, the ear, the anus, and the genital area. Topical anesthetics are available in creams, ointments, aerosols, sprays, lotions, and jellies. They are used to relieve many types of pain and itching, such as that caused by sunburn, minor burns, insect bites or stings, nerve damage, or conditions such as hemorrhoids.

Opioid medications

Medicines containing opioids have been used for centuries. *Opioids* are strong pain medicines for moderate to severe pain. Today, opioids come in many forms and strengths. Some work very quickly but don't last very long. Some give long-lasting pain relief. And some are less likely to be addictive.

All opioids require a prescription. Talk to your doctor about what type of opioid would be best for you.

Opioids usually produce side effects. At first, the drugs can cause upset stomach or sleepiness. These side effects often go away as you get used to the drugs. Some other side effects, such as constipation, don't lessen with time. Constipation can be prevented or lessened by taking a laxative on a regular basis.

Used properly, opioid medications can make it possible for people with chronic pain to "return to normal"—get back to work, walk or run, play sports, and participate in other activities.

Opioid myths

Myth: Opioid medications are always addictive.

Fact: Many studies show that opioids are *rarely* addictive when used properly for the management of chronic pain.

Myth: Opioids make it harder to function normally.

Fact: When used correctly for appropriate conditions, opioids may make it *easier* for people to live normally.

Myth: Opioid doses have to get bigger over time because the body gets used to them.

Fact: Unless the underlying cause of your pain gets worse (such as with cancer or arthritis), you will probably remain on the same dose or need only small increases over time.

Other types of medications

Many other types of drugs can relieve pain. Some have special effects that can be very helpful for some people. For example, some medicines can improve your mood and relieve pain. This can be good for people who are both depressed and in pain.

Here are three types of drugs your health care professional might suggest:

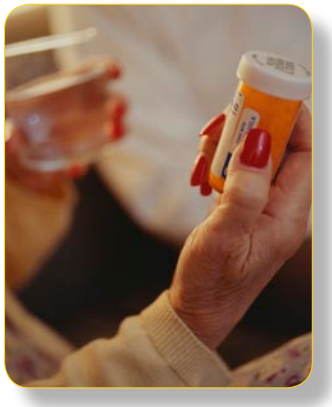
- Drugs that improve your mood (antidepressants)
- Drugs that give you more energy (stimulants)
- Drugs that relieve anxiety (anxiolytics)

These drugs may be combined with other pain medications. Sometimes a combination of drugs works better than a single drug.

Responsible Prescription Use

Some people today use prescription medicines to get "high" or to relieve stress. They may steal these medicines from parents, friends, or relatives. If you are taking an opioid medication for pain, you must be careful. Follow this advice:

- Store medications in a safe, secure place
- Take note if any pills appear to be missing
- Never share your medication with others
- Don't take your medication more often—or in a larger dose—than prescribed



Being responsible also means knowing yourself. Be aware of how you react to your medication. Are you having any unusual side effects? Is the medication working as well as you think it should? Your goal should always be to balance the benefits of a drug with the side effects the drug might cause. If you have any questions, call your doctor or other health care professional.

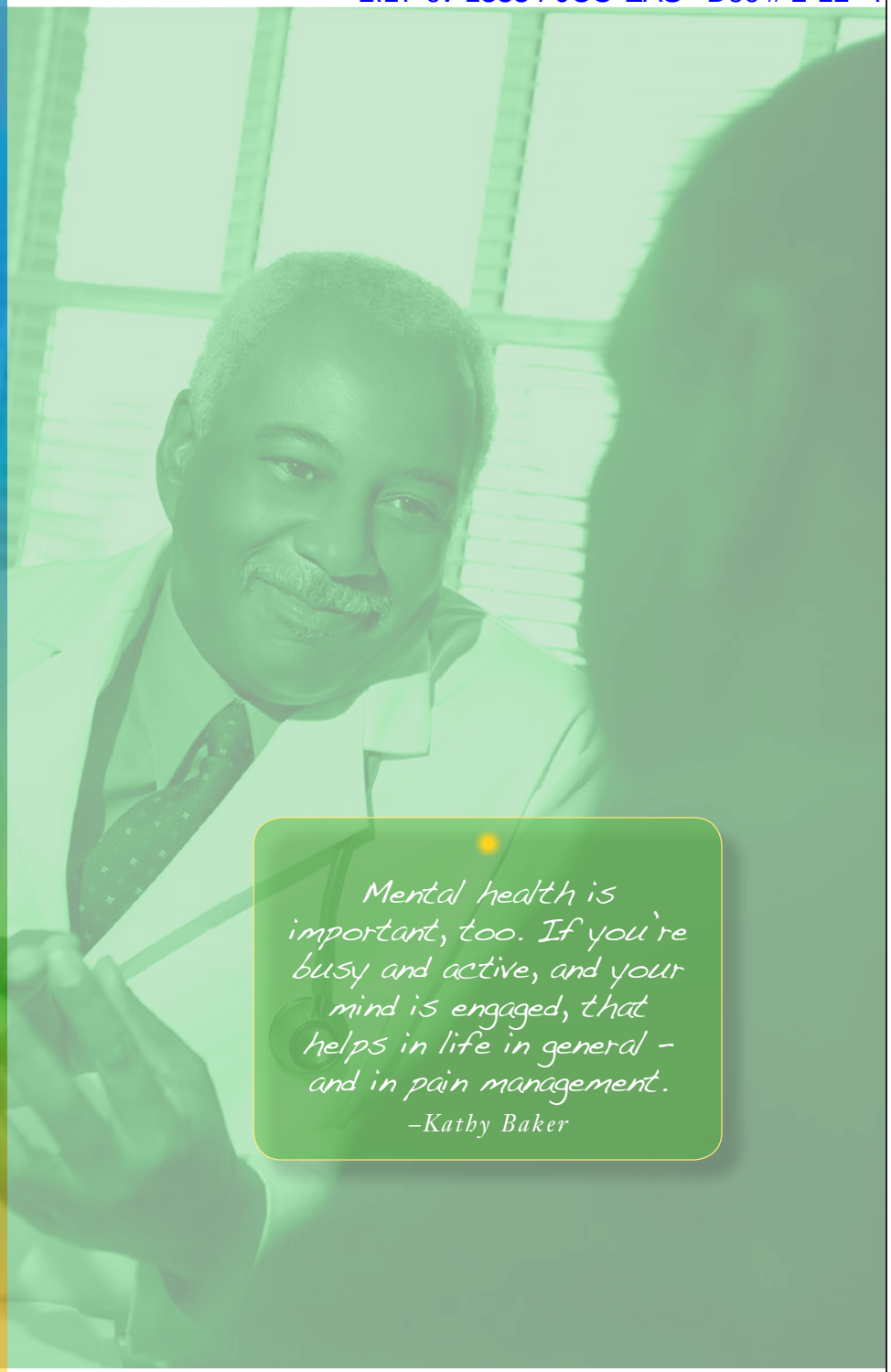
Injection Therapies

Injection therapies (sometimes called "nerve blocks") may be used to treat painful conditions in many areas of the body. These procedures involve placing a needle into a muscle, joint, the spine, or around a specific group of nerves. Then medication is injected or some other treatment is used, such as electricity, heat or cold. Injection therapies can be used for both acute and chronic pain.

Physical Therapy

Physical therapy can help restore function, improve mobility, and relieve pain. In addition to teaching patients how to exercise, physical therapists may also use such treatments as electrical stimulation, hot packs, cold compresses, traction, deep-tissue massage, and ultrasound. Physical therapists may also teach patients to use assistive or adaptive devices, such as crutches, prostheses, and wheelchairs.

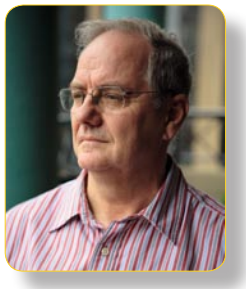
The most important part of physical therapy is exercise training. Once taught, exercises can be performed at home to help relieve pain flare-ups, improve flexibility, and increase strength and/or endurance. Physical therapy can help you function better even if your pain doesn't completely go away.



Mental health is important, too. If you're busy and active, and your mind is engaged, that helps in life in general – and in pain management.
–Kathy Baker

Counseling and Emotional Support

Living with pain often causes a ripple effect that touches many parts of your life. You may feel a range of emotions, such as fear, anger, hopelessness, confusion, and isolation. Those around you may have similar feelings. Individual counseling—and in some cases, counseling with your family—can help. Many people find great benefit from individual or group counseling specifically focused on pain and related worries. Trained professionals can teach useful skills and provide needed emotional support and guidance.



One form of therapy that can help people in chronic pain is *cognitive behavioral therapy* (CBT). This is a short-term, focused form of psychotherapy. You and the therapist identify goals and problem-solve to find ways of reaching them. With any type of therapy, it's important to take an active role in the process. Patients who are assertive and fully engaged in their own health care cope better than those who are more passive.

Alternative and Complementary Approaches

Many Americans have tried alternative methods of controlling their pain, such as acupuncture or hypnosis. Some of these methods have been shown to work for some patients. Most alternative treatments rely on the power of the mind to control pain. These methods can be used alone or combined with medications and other "traditional" treatments. The most important thing older adults with chronic pain can do is work with their doctor to create a treatment plan that is right for them.

Acupuncture

Acupuncture uses very fine needles inserted into the skin. Needles may be placed according to theories developed in China more than 2000 years ago or using techniques developed more recently. Some scientific studies show that acupuncture can relieve chronic pain. The evidence is strongest for relief of back, neck, and arthritis pain.

Hypnosis

Hypnosis is a range of techniques that can alter people's awareness of themselves or their surroundings. It was first used more than 100 years ago to help patients in pain. The scientific study of hypnosis as a treatment for pain is ongoing, but early research has shown promise. When a patient is hypnotized, his or her mind is focused and aware. For reasons that are not yet understood, this state can relieve many types of pain.

Meditation

Meditation is any method of focusing and calming the mind. It need not have a religious or spiritual component. Several medical centers now use meditation to help patients manage chronic pain. The techniques vary, but all involve calming the body, being aware of oneself, and focusing attention. Some scientific studies have shown that patients who meditate regularly may function better and have less pain.

Massage

There are many techniques and approaches to *massage*, but most can help relieve pain. Massage acts directly on the muscles and nerves to promote relaxation. It can ease tight, painful muscles and reduce spasms.

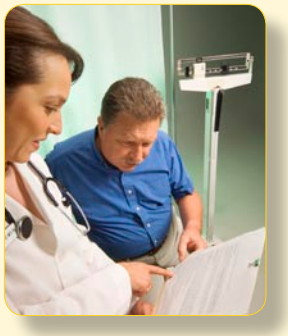
Tips for Managing Pain

Older adults in pain can almost always be helped these days. With the right treatments and a good health care team, most people can return to the activities they enjoy. There are many things you can do to secure your progress and manage your pain. The choices you make can make a big difference!

Keep the following tips in mind:

Exercise regularly. Keeping your muscles strong will help prevent future injury. Start slow and easy. Work up gradually to more distance, time, or weight. The type of exercise is not as important as exercising on a regular basis. Always talk to your doctor before trying a new exercise.

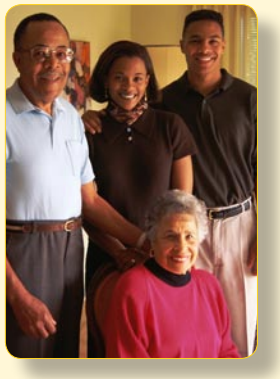
Stay flexible. Yoga or stretching exercises can be a great way to become more flexible. Just be careful to stretch gently. If it hurts, you're going too far!

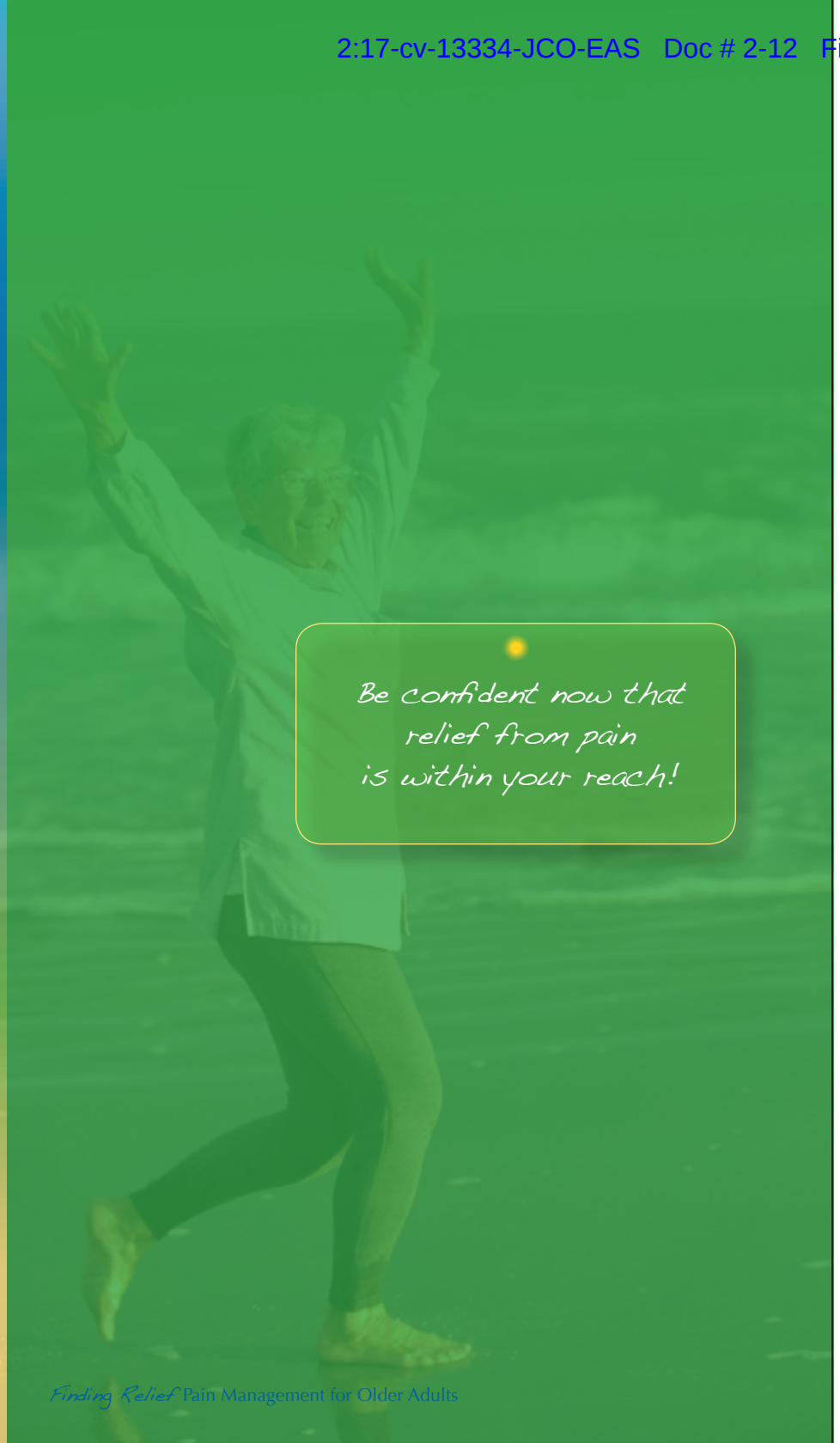


Lose weight if you need to. Extra body weight strains joints, muscles, and your back. Even losing just 10 pounds can make a difference!

Learn how to lift, sit, and stand. Keep your back straight when lifting. Use your legs, not your back! Keep your back straight when sitting and standing as well. If you use a computer, be sure to position your arms and hands so they are relaxed and well-supported.

Connect with others. It can be hard for others to understand what it feels like to be in chronic pain. That's why it can be so helpful to find people who can "share your pain." Chronic-pain support groups can be found in almost every city. You can also find online support groups. People can share their feelings and swap tips that have helped them manage their pain. (You can find support groups through the organizations listed at the back of this booklet.)





Reasons for Hope

The key messages of this booklet are; Be educated, be responsible, and be confident. Acute and chronic pain can almost always be managed! It may take some time to find the best balance between your goals and a treatment program. But if you stick with it, you can overcome your pain.

Remember that you have a right to adequate and effective pain relief. Nobody should suffer with needless pain today. Work closely with your doctor. Determine whether you should see a pain specialist. Use a team of health care professionals who can give you what you need. By reading this booklet, you have begun learning about your condition. You can be confident now that relief from pain is within your reach!

Resources

American Academy of Pain Medicine
The AAPM site provides educational materials and a search feature to help you find a board-certified pain physician in your region.
www.painmed.org

American Chronic Pain Association
Support for those suffering with chronic pain through education and self-help group activities.
www.theacpa.org
800-533-3231

American Geriatrics Society
A nonprofit organization devoted to improving the health, independence and quality of life of all older people.
www.americangeriatrics.org
212-308-1414

AGS Foundation for Health in Aging
www.healthinaging.org
800-563-4916

American Pain Foundation
www.painfoundation.org
888-615-7246

Arthritis Foundation
www.arthritis.org
800-283-7800

The National Pain Foundation
An online education and support community for pain patients and their families.
www.painconnection.org

Sponsor

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American Academy of Pain Medicine

The American Academy of Pain Medicine is the medical specialty society representing physicians practicing in the field of pain medicine. The Academy is involved in education, training, advocacy, and research in the specialty of pain medicine. The practice of pain medicine is multidisciplinary in approach, incorporating modalities from various specialties to ensure the comprehensive evaluation and treatment of the pain patient. AAPM represents the diverse scope of the field through membership from a variety of origins, including such specialties as anesthesiology, internal medicine, neurology, neurological surgery, orthopedic surgery, physiatry, and psychiatry.

PHYSICIANS DEDICATED TO RELIEVING PAIN
the AMERICAN ACADEMY of PAIN MEDICINE
the voice of pain medicine

American Geriatrics Society

The American Geriatrics Society is a not-for-profit organization of more than 6,700 health professionals devoted to improving the health, independence and quality of life of all older people. The Society provides leadership to health care professionals, policymakers and the public by implementing and advocating for programs in patient care, research, professional and public education, and public policy. Our mission is to improve the health, independence and quality of life of all older people.

AMERICAN GERIATRICS SOCIETY · A·G·S · MCMXLII

AGS Foundation for Health in Aging

The AGS Foundation for Health in Aging champions initiatives in public education, clinical research, and public policy that advance the principles and practice of geriatrics medicine; educate policymakers and the public on the health care needs and concerns of older adults; support research on aging that reduces disability and frailty, and improves quality of life and health outcomes; encourage older adults to be effective advocates for their own health care; and help family members and caregivers take better care of their older loved ones and themselves.

THE AGS FOUNDATION FOR HEALTH IN AGING

Credits

Finding Relief: Pain Management for Older Adults has been made possible through the expertise, time, and efforts of many individuals who are committed to the health and wellness of older Americans. Special gratitude to:

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American Academy of Pain Medicine

American Geriatrics Society

American Geriatrics Society Foundation for Health in Aging

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Special Thanks to:

KATHY BAKER

Photograph by Gregory Schwartz

Actress Kathy Baker has played critically acclaimed roles in more than two dozen movies and several television series since she entered the film business 1983. Her credits include *Edward Scissorhands*, *The Cider House Rules*, and *Cold Mountain*. Her performance in *Street Smart* earned her Best Supporting Actress awards from the Boston Society of Film Critics and the National Society of Film Critics.

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DVD Inside

Finding Relief

Pain Management for Older Adults

Older adults suffer pain more often than younger people. Complaints of pain are the #1 reason older people go to the doctor.

These days, most pain can be very effectively treated. But, unfortunately, many older adults don't get the relief they deserve. Untreated pain not only causes needless suffering, but it can also lead to many other problems. If pain is not treated quickly, it may become worse or become more difficult to treat. And long-term pain may lead to loss of function at home or work, lost income, or harm to personal relationships.

This program is focused specifically on older adults and what they need to know to get effective pain relief. You will learn that there are many pathways to this relief. You can return to doing the things you did before the pain began!

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- ***Find ways to minimize the side effects of some treatments and maximize their effectiveness***
- ***Be confident that you can find relief and manage your pain***

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KATHY BAKER

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EXHIBIT 62

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EXHIBIT 63

Use of Opioid Analgesics in Pain Management

by **Keith Candiotti, MD**

Expert authors received compensation from Janssen Pharmaceuticals, Inc. for their contributions to PrescribeResponsibly.com

History

Opioid analgesics have been used as medicinal agents, especially for the treatment of acute and chronic pain, for thousands of years. Ancient Greeks first identified and used these medicines, which were originally derived from opium — the latex of immature seed capsules of the poppy flower (Papaver somniferum).[5,6] From these simple beginnings, opioid analgesics have become a mainstay of medical therapy used by millions of patients each year.[7] While numerous drugs have been developed for the treatment of different types of pain, no single class of agent has replaced or reached the same level of usefulness for the treatment of moderate to severe pain as have opioid analgesics.[8]

Use of Opioid Analgesics in Pain Management

Opioid analgesics are often the first line of treatment for many painful conditions and may offer advantages over nonsteroidal anti-inflammatory drugs (NSAIDs). Opioid analgesics, for example, have no true "ceiling dose" for analgesia and do not cause direct organ damage; however, they do have several possible side effects, including constipation, nausea, vomiting, a decrease in sexual interest, drowsiness, and respiratory depression. With the exception of constipation, many patients often develop tolerance to most of the opioid analgesic-related side effects.[8]

While practitioners often express concern about the use of opioid analgesics for acute and chronic pain conditions, they are often the only suitable agent to control significant pain. This is especially true in the postoperative period.[60] Morphine is the most commonly used opioid analgesic in the postoperative period, but some practitioners prefer other agents, such as hydromorphone.[9] There is some debate as to whether hydromorphone is better tolerated than morphine in terms of side effects. Some recent studies, however, do not support this concept and adverse reactions to either drug are possible.[9]

Another area of debate concerning opioid analgesics is their use in the treatment of neuropathic pain. This area is still being explored and remains somewhat controversial. Most studies related to this question have been small, demonstrated equivocal results, and have failed to clearly establish the long-term risk/benefit ratio of these agents.[10] A recent Cochrane Review found that the results were somewhat mixed; short-term trials had contradictory results, while intermediate trials demonstrated opioid analgesic efficacy for spontaneous neuropathic pain. Across trials, the side effects were nausea, constipation, dizziness, and drowsiness.[10]

Mechanism of Action of Opioid Analgesics

Opioid analgesics bind to a number of different receptors throughout the body—mu, delta, and kappa.[8] The binding to these different receptors results in both the therapeutic and adverse effects of opioid analgesics. Genetic variations in the structure of these receptors can partially explain interindividual responses, including some adverse reactions to these agents.[11]

Adverse Reactions to Opioid Analgesics

Adverse reactions to opioid analgesics can be a limiting factor in the effective use of these drugs. In a study of patients taking opioid analgesics for prolonged periods of time, 80 percent of patients reported at least 1 adverse event, and 24 percent of patients discontinued therapy due to an adverse event.[12] Evaluation of the discontinuations due to adverse events demonstrated that constipation (41 percent), nausea (32 percent), vomiting (15 percent), and somnolence (29 percent) were the most common reasons cited for cessation of therapy.[12]

Early cessation or limitation of pain treatment due to adverse reactions can result in the inadequate treatment of pain. While more than just an inconvenience, the consequences of inadequate pain control can be far reaching and often are overlooked. Patients experiencing significant pain will have an increase in autonomic and sympathetic activity.[3] Older patients, in particular, may develop delirium and cognitive dysfunction.[13] The intensity of pain in the preoperative, interaoperative and early postoperative periods have been shown to be strong predictors for the development of chronic, persistent postoperative pain.[14] While there are reports that excessive use of opioid analgesics may lead to a state of hyperalgesia,[5] thus prompting some physicians to be concerned about using opioid analgesics for pain control, the lack of sufficient pain control may itself promote a hyperalgesic state in the form of persistent pain.[3]

Other Opioid Analgesic Concerns

Aside from medical issues related to opioid analgesics, there are nonmedical issues that may have an impact on prescribing patterns and patient use of these drugs. Practitioners are often concerned about prescribing opioid analgesics due to potential legal issues and questions of addiction.[15,16] By the same token, patients report similar concerns about developing an addiction to opioid analgesics.[17] While these concerns are not without some merit, it would appear that they are often overestimated. According to clinical opinion polls, true addiction occurs only in a small percentage of patients with chronic pain who receive chronic opioid analgesics analgesic therapy.[18]

Conclusion

To date, no agents have fully replaced opioid analgesics for the treatment of moderate to severe pain. While many patients and physicians have concerns about the use of opioid analgesics, which often prevent their use, it would appear that, with appropriate dosing and titration, they can be effective and safe medications for the treatment of painful conditions. In spite of how long these agents have been in clinical use, there still remains much to be learned, and ongoing research will no doubt help clarify some of these questions.

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EXHIBIT 64

What a Prescriber Should Know Before Writing the First Prescription

by **Howard A. Heit, MD, FACP, FASAM**
& **Douglas L. Gourlay, MD, MSc, FRCPC, FASAM**

Expert authors received compensation from Janssen Pharmaceuticals, Inc. for their contributions to PrescribeResponsibly.com

The Importance of Definitions

Knowing the precise definitions that are listed in Table 1 will allow healthcare professionals to improve their understanding of the interface of pain and addiction and their clinical practice.[19] Confusion between physical dependence and addiction may contribute to the undertreatment of chronic pain.[19]

Physical dependence and addiction can coincide, but physical dependence is neither necessary nor sufficient to make a diagnosis of addiction.[20] Physical dependence is an expected, neuropharmacological adaptation that occurs as a result of chronic exposure to an agonist class of drug.[21] Addiction is a much more complex biobehavioral phenomenon.[19]

Physical dependence is a natural, expected neuroadaptive response that can occur with opioids, alcohol, benzodiazepines, corticosteroids, antidepressants, diabetic agents, cardiac medications, and many other medications used in clinical medicine. Abrupt cessation of these medications can produce a withdrawal syndrome that can include, but is not limited to, nausea, vomiting, diaphoresis, diarrhea, abdominal cramps, seizures, anhedonia, dysphoria, and in some cases, death.[20]

Tolerance is also a natural, expected physiologic response that can occur with exposure to certain classes of drugs, especially alcohol and opioids. The key to this definition is that all other factors remain stable so that only the physiologic response to the drug can be evaluated.[19] In fact, tolerance is neither good nor bad. It occurs at different rates, to different effects in different patients, over time. So while there is relatively rapid tolerance to the cognitive blunting effects of the opioid class of drug, tolerance to the constipating effects of opioids rarely occurs.[21]

Concurrent diagnoses such as addiction or pseudoaddiction can be confirmed only by careful evaluation and rational pharmacotherapeutic management of the pain. While a diagnosis of addiction is made prospectively over time, a diagnosis of pseudoaddiction is usually made retrospectively. When reasonable limits and boundaries are placed on a patient, and yet he or she continues to step out of bounds, addiction or pseudoaddiction should be considered.[20]

Healthcare professionals with improved understanding of the definitions on the basic scientific and clinical levels will be better able to evaluate and treat patients with chronic pain, with or without the disease of addiction.

Disease of Addiction

The healthcare professional must recognize addiction as a treatable, albeit irreversible, brain disease — that is, a distinct medical condition that may or may not be associated with the patient's pain syndrome.[20] One can treat acute pain in the face of an active addiction; however, the treatment of chronic pain in a patient with an active addiction seldom is successful. The patient must be willing to work a program for both diagnoses. The pain specialist must have a rudimentary knowledge of addiction medicine, and the addiction specialist must understand the basics of pain management.

Drugs of misuse act at local cellular and membrane sites that are within a neurochemical system called the reward and withdrawal pathway.[22] This pathway is in the mesolimbic dopamine system of the primitive brain, and addiction causes a disruption of this pathway. This disruption is mediated via receptor sites and neurotransmitters. Central to this reward and withdrawal pathway is the neurotransmitter dopamine, which has been shown to be relevant not only to drug reward, but to food, drink, sex, and social reward.[23]

One of the most common reasons for relapse of patients with addiction is stress.[22] It stands to reason that if a patient with chronic pain is in recovery from drug or alcohol use, and his or her pain is inadequately treated, the patient may turn to licit or illicit drugs and/or alcohol to anesthetize the pain.

Opioid Agreements

Informed consent is part of an initial evaluation. Healthcare professionals must discuss with, and answer any questions about, the proposed treatment plan, including anticipated benefits and foreseeable risks. Written opioid agreements (OA) facilitate the documentation of informed consent, patient education, and compliance in the management of chronic pain.[24]

A well-written agreement establishes the responsibilities of a healthcare professional to the patient and vice versa. It outlines the treatment plan and documents informed consent. The OA establishes boundaries and consequences for drug misuse or diversion. Noncompliance with the agreement can aid in the diagnosis of the disease of addiction or substance misuse, which would often require a change in the treatment plan. Table 2 delineates the salient points of an OA.[25]

The agreement, whether written and signed or informal, must be part of an environment of care that emphasizes honest and open communication. A practice policy for all patients prescribed opioids to sign a medication management agreement is often a simple and effective way to approach this often uncomfortable issue. The agreement should be reasonable, readable, and flexible.[25]

Conclusion

Before writing the first prescription, the healthcare professional should know the basic definitions and principles common to pain and addiction medicine and establish the boundaries through an opioid agreement.[20,26] Risk can never be eliminated, but it can usually be managed. By approaching these patients within a biopsychosocial framework, the healthcare professional can give the patient the best quality of life possible, given the reality of his or her clinical situation.

TABLE 1: Definitions

1. **Aberrant behavior** is when the patient steps outside the boundaries of the agreed upon treatment plan, which is established as early as possible in the healthcare professional-patient relationship.[20]
2. **Abuse** is any use of an illicit drug with the intentional self-administration of a medication for nonmedical purpose such as altering one's state of consciousness (eg, getting high). A licit substance such as alcohol also can be abused.[27]
3. **Addiction** is a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. Addiction is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm and craving.[21]
4. **Diversion** is the intentional removal of a medication from legitimate distribution and dispensing channels for illicit sale or distribution.[27]

5. **Iatrogenic addiction** occurs when a patient with a personal or family history of alcohol, drug addiction, or abuse is appropriately prescribed a controlled substance and subsequently in the therapeutic course, meets the diagnostic criteria for addiction to that substance.[25]
6. **Misuse** is use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not.[27]
7. **Physical dependence** is a state of adaptation that is manifested by a drug-class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.[21]
8. **Pseudoaddiction** is a syndrome that causes patients to seek additional medications due to inadequate pharmacotherapy being prescribed. Typically when the pain is treated appropriately, the inappropriate behavior ceases.[25]
9. **Pseudotolerance** is the need to increase medication such as opioids for pain when other factor(s) are present such as disease progression, new disease, increased physical activity, lack of compliance, change in medication, drug interaction, addiction, and/or deviant behavior.[25]
10. **Tolerance** is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.[21]

TABLE 2: Treatment Agreement for Opioid Analgesic Maintenance Therapy for Noncancer/Cancer Pain[25]

- Goals of therapy
- Single prescriber, if possible
- Informed consent on all opioid analgesic risks
- Definition of addiction, tolerance, and physical dependence
- Need for patient disclosure of substance abuse history; psychiatric history including history of sexual, physical, or verbal abuse; and medications currently prescribed
- Need for complete, honest self-report of pain relief, side effects, and function at each medical visit
- Establishment of regular medical visits
- Requirement for prescription renewal only during regular office hours
- Conditions of noncompliance (eg, evidence of drug hoarding or use of any illegal drug may cause termination of the healthcare professional–patient relationship)
- Use of the word *may* instead of *will* in the agreement, so clinical judgment can be used in each situation
- Patient consent to random urine drug tests and pill counts
- Permission for the practice to contact appropriate sources to obtain or provide information about the patient's care or actions
- Recovery program for substance misuse or addiction (patients must agree to concurrent assessment and treatment of their substance use disorder)

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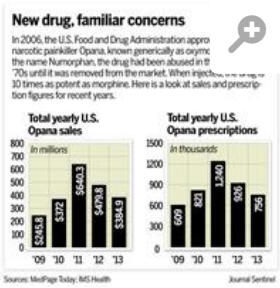
EXHIBIT 65

WATCHDOG REPORTS | SIDE EFFECTS | WATCHDOG REPORT

Opana gets FDA approval despite history of abuse, limited effectiveness in trials

Records show regulators, drug company had cozy relationship



By John Fauber and Kristina Fiore of the Journal Sentinel

May 09, 2015

In 2006, in the midst of a growing national opioid epidemic, the U.S. Food and Drug Administration approved the new narcotic painkiller Opana.

It was a familiar drug.

Known generically as oxymorphone, the drug is 10 times as potent as morphine when injected. Under the name Numorphan, it had been abused in the 1960s and '70s until it was removed from the market.

And now there is a familiar problem.

After initially approving Opana as both an immediate-release and extended-release product, the FDA in December 2011 approved a formulation designed to prevent abuse by making the drug tough to crush or dissolve.

But users have been able to foil the anti-injection mechanism and have continued to shoot up Opana.

Related Coverage

More blood-clotting disorders reported after abuse-deterrent Opana introduced

problem that didn't occur with the earlier version.

And it has been tied to a recent outbreak of HIV in rural Indiana as well as a surge in hepatitis C infections in Kentucky, Tennessee, West Virginia and Virginia.

When the FDA approved Opana, manufactured by Endo Pharmaceuticals, the drug joined more than a dozen other narcotic painkillers on the market.

"There certainly didn't seem to be a need for it," said James Roberts, a professor of emergency medicine at Drexel University College of Medicine in Philadelphia. "There are plenty of narcotics around for pain relief."

As Numorphan, the drug's popularity among addicts was due to its quick and sustained effect, according to the 1974 report "Drugs and Addict Lifestyle" by the National Institute on Drug Abuse.

The report said the drug — which carried the street name "blues" — was used primarily by white males. The report focused on 309 Philadelphia-area Numorphan addicts who were interviewed in 1970, with many saying they preferred the drug over heroin. The drug was taken off the market in 1979.

Asked about the basis for approving Opana, FDA spokesman Eric Pahon said opioids are important medications for the treatment of pain, when used properly.

"The FDA is concerned about the misuse and abuse of prescription opioids, which is a serious public health challenge, and is working in many ways to help prescribers and patients make the best possible choices about how to use these powerful drugs," he wrote in an email. "We must balance this effort, however, with ensuring prescribers and patients maintain access to these medications and a variety of treatment options are available."

The extended release version of Opana alone generated 756,000 prescriptions and sales of $385 million in 2013, according to data supplied by IMS Health, a drug market research firm. Since 2009, its annual sales have ranged from $246 million to $640 million.

effectiveness in clinical trials and its successful submission of an application for approval."

Drug's Reappearance

A Milwaukee Journal Sentinel/MedPage Today examination found oxymorphone's reappearance on the market followed a pattern identified in past investigations, including cozy relationships between regulators and drug company executives and the use of questionable clinical testing methods allowed by the FDA.

Endo Pharmaceuticals was a frequent participant at meetings of an organization funded by pain drug companies that brought together pharmaceutical executives and federal regulators during the 2000s, records show.

The group, known as IMMPACT, was the subject of a 2013 Journal Sentinel/MedPage Today investigation.

That investigation examined how federal health industry officials, members of academia and executives of companies that make pain drugs held private meetings at expensive hotels at least once a year beginning in 2002, according to emails obtained through a public records request.

Each year, a handful of drug companies paid up to $35,000 each to send a representative to the meetings, where they could discuss clinical trial design with FDA officials.

In 2014, two U.S. senators wrote to the medical school dean at the University of Rochester demanding financial records related to the IMMPACT meetings. A researcher at the school was a co-founder of the group.

Sens. Joe Manchin (D-W.Va.) and David Vitter (R-La.) wrote that they were "deeply troubled by allegations that the FDA gave manufacturers of prescription drugs the opportunity to pay thousands of dollars to the University of Rochester Medical Center for the privilege to attend private meetings with FDA officials."

the meetings were invitation only, he said, they were attended by a variety of government officials, academics and pain advocates.

"These were large scientific meetings at which the outside experts almost always outnumbered the attending companies," he said. "We are not aware of any separate, private meetings between FDA and pharmaceutical companies during or as a result of IMMPACT meetings."

He said the meetings had no bearing on the approval of Opana and did not include the discussion of any particular product or the standards for FDA approval of pain products.

'Enriched Enrollment'

Those meetings did help lead to a new approach to winning approval of drugs known as "enriched enrollment."

The approach, which is faster and less expensive for drug-makers, allows companies to weed out people who don't respond well to a drug or who can't tolerate taking it before an actual clinical trial for the drug begins.

Independent doctors say that approach makes it much more likely a drug will be found effective and win FDA approval. More importantly, experts say, drugs tested that way are not likely to reflect what will happen when a medication gets on the market and is prescribed for large numbers of people.

When Endo first tried to get Opana approved in 2003, the FDA said the drug didn't appear effective enough in clinical trials. It also raised safety concerns after several postoperative pain patients overdosed on the drug.

So Endo conducted new clinical trials using enriched enrollment.

In those trials, only the patients who initially responded to the drug were entered into the trial, where they were given either Opana or a placebo. The idea was that the drug's effects can be clearly demonstrated in comparison to a placebo, because it is already known to work for these patients.

He would not say whether the FDA encouraged Endo to use the enriched enrollment approach for Opana.

When the drug was approved in 2006, the FDA's own medical review acknowledged that, given the enriched study design, "one could argue that the results may not be generalizable to the wider chronic pain population."

Opana is not the only opioid approved using enriched enrollment. In 2013, drug-maker Zogenix used the strategy to win approval for Zohydro, a high-dose, hydrocodone-only drug that was originally approved without any abuse-deterrent mechanisms.

The FDA approved that drug despite its own advisory committee voting 11-2 against it.

"The FDA should be in the business of requiring high-quality evidence and not shortcut evidence," said Lewis Nelson, a medical toxicologist at NYU Langone Medical Center. "Unfortunately, they're under pressure to make pharmaceuticals available to the general public."

John Fauber is a reporter with the Journal Sentinel. Kristina Fiore is a reporter with MedPage Today. This story was reported as a joint project of the Journal Sentinel and MedPage Today, which provides a clinical perspective for physicians on breaking medical news at medpagetoday.com.

Read Past Investigations

For past investigations into prescription painkillers, and related examinations of medical conflicts of interest, go to jsonline.com/sideeffects

About John Fauber

John Fauber is an investigative medical reporter who focuses on conflicts of interest in medicine and how drug and medical device companies and the FDA influence the practice of medicine. He has won more than two dozen national journalism awards.

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EXHIBIT 66

shots

EMBEDDED

How A Painkiller Designed To Deter Abuse Helped Spark An HIV Outbreak

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April 1, 2016 · 2:04 PM ET
Heard on All Things Considered

TOM DREISBACH

Opana pills, seen in 2010, before Endo Pharmaceuticals changed the formula in a move intended to deter abuse.

Tom Walker/Flickr

When Kevin Polly first started abusing Opana ER, a potent prescription opioid painkiller, he took pills — or fractions of pills — and crushed them into a fine powder, then snorted it.

When Opana pills are swallowed, they release their painkilling ingredient over 12 hours. If the pills were crushed and snorted, though, the drug was released in a single dose.

"Just think about it," Polly says, "12 hours of medicine, and, 'BAM!' you're getting it all at once."

But the drug's manufacturer, Endo Pharmaceuticals, reformulated Opana in 2012. The new pills featured a coating that was intended to make them more difficult to abuse by crushing them into powder or dissolving them.

SHOTS - HEALTH NEWS

Inside A Small Brick House At The Heart Of Indiana's Opioid Crisis

Polly discovered he could no longer snort the medicine in the pill, to which he had become addicted. But he and other Opana users soon found a way to remove the drug's hard coating and receive Opana's powerful dose all at once: injection.

Polly says he used to inject Opana as many as five times a day. He often shared needles with other people.

He says he never anticipated what would happen next. In early 2015, Polly tested positive for HIV. "It was devastating news," he says.

Kevin Polly is among the 190 people in Indiana's Scott County who have tested positive for HIV since early 2015, in the largest HIV outbreak in Indiana history.

The Change To Opana That Was Intended To Prevent Abuse

For its part, Endo has said that its decision to reformulate Opana was a well-intended attempt to prevent abuse. As the company told the Food and Drug Administration in

2012, Endo reformulated the drug "to provide a crush-resistant product, equally as effective as Opana ER, which would discourage abuse, misuse and diversion." Endo declined repeated requests from NPR for an interview.

According to study data, as well as interviews with Indiana residents addicted to Opana, the reformulation effectively deterred many people from snorting the drug. But the change also led a significant number of people to abuse the drug by injection. When needles are shared, the injection route can transmit HIV, hepatitis C or other infections.

And interviews with experts, court filings, documents from the FDA, as well as Endo's own statements, suggest the company's decision to reformulate Opana was also motivated in large part by financial interests.

Public health experts say "abuse deterrent" drugs may serve a role in reducing what the Centers for Disease Control and Prevention calls a national epidemic of prescription opioid abuse. The FDA and members of Congress have also supported their development. But the experience with Opana's reformulation may serve as a cautionary tale for the potential effects of "abuse deterrent" drugs.

Experiences In Austin, Ind.

While NPR's Kelly McEvers and I were reporting in Austin, Ind., people who abused Opana and were familiar with changes to the drug's formula told us similar stories.

"The pharmaceutical company, they changed it so you can't crush them and snort them," said Devin, a 26-year old. "Whenever they done that, that's when everybody started shooting them."

Jeff, a veteran of the Army National Guard, said he became addicted to Opana after being prescribed opioid painkillers for a back injury he sustained in Iraq.

At some point, Jeff said, he began crushing and snorting pills. Then, he said, the company "reformulated them, and the only way you could do them is to inject them."

Joy, a former registered nurse who got addicted to opioids after a back injury, said that she initially stopped using Opana after the reformulation. But that didn't last long. "Some genius figured out, 'Hey we can cook this down and turn [it] into a liquid and shoot it up,' " Joy said. "And then it took off like wildfire after that."

(NPR is withholding Devin's, Jeff's and Joy's last names to protect their privacy.)

Because of the coating added to Opana, the process of preparing it for injection does take a little work. But in the end, it's not that difficult.

My colleague Kelly watched people prepare Opana for injection, using just the bottom of a soda can, a small lighter, a cigarette filter and tap water.

Behind The Reformulation, Public Health And Business Considerations

So why did Endo Pharmaceuticals reformulate the drug in the first place?

Volunteers search for used needles near Rural Street in Austin, Ind. Scott County, in southeastern Indiana, experienced the worst outbreak of HIV in the state's history after people began injecting the prescription painkiller Opana.

Seth Herald/NurPhoto/Corbis

The answer involves both public health concerns and business considerations.

Endo Pharmaceuticals released Opana in 2006. Taken orally, Opana is about twice as powerful as OxyContin, and the company says it is "indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment."

Soon afterward, though, communities around the country began reporting abuse of Opana and even overdose deaths.

Endo said those concerns over public health and abuse were key motivations to reformulate the drug. Opana also was a major moneymaker for the company.

In 2011, for example, Opana generated $384 million in net sales for Endo, accounting for 14 percent of the company's total revenue that year.

But the company also faced the threat of generic competition.

So Endo developed a strategy that would block its competitors and maintain Opana's share of the market.

The company reformulated the drug, this time with features designed to prevent abuse, a move that could potentially protect Endo at a time it faced the loss of patent protection.

The FDA approved Endo's reformulated Opana, and in 2012 the company began replacing the old versions of Opana on pharmacy shelves.

In August of that year, Endo took another step. The company filed a petition with the FDA, arguing that it had removed the old, crushable version of Opana from the market "for reasons of safety or effectiveness." It also asked the agency to "refuse to approve" and "suspend and withdraw the approval" of generic, noncrush-resistant versions of Opana.

If the FDA agreed with Endo, the agency would effectively eliminate the company's generic competition.

"We see this again and again in the pharmaceutical industry," says Dr. Anna Lembke, an assistant professor of psychiatry at Stanford University Medical Center. "They come up with some new fancy formulation of basically the same old drug ... and then that way they have a new drug that they can charge a lot of money for."

Endo Pharmaceuticals Inc Citizen Petition

To print the document, click the "Original Document" link to open the original PDF. At this time it is not possible to print the document with annotations.

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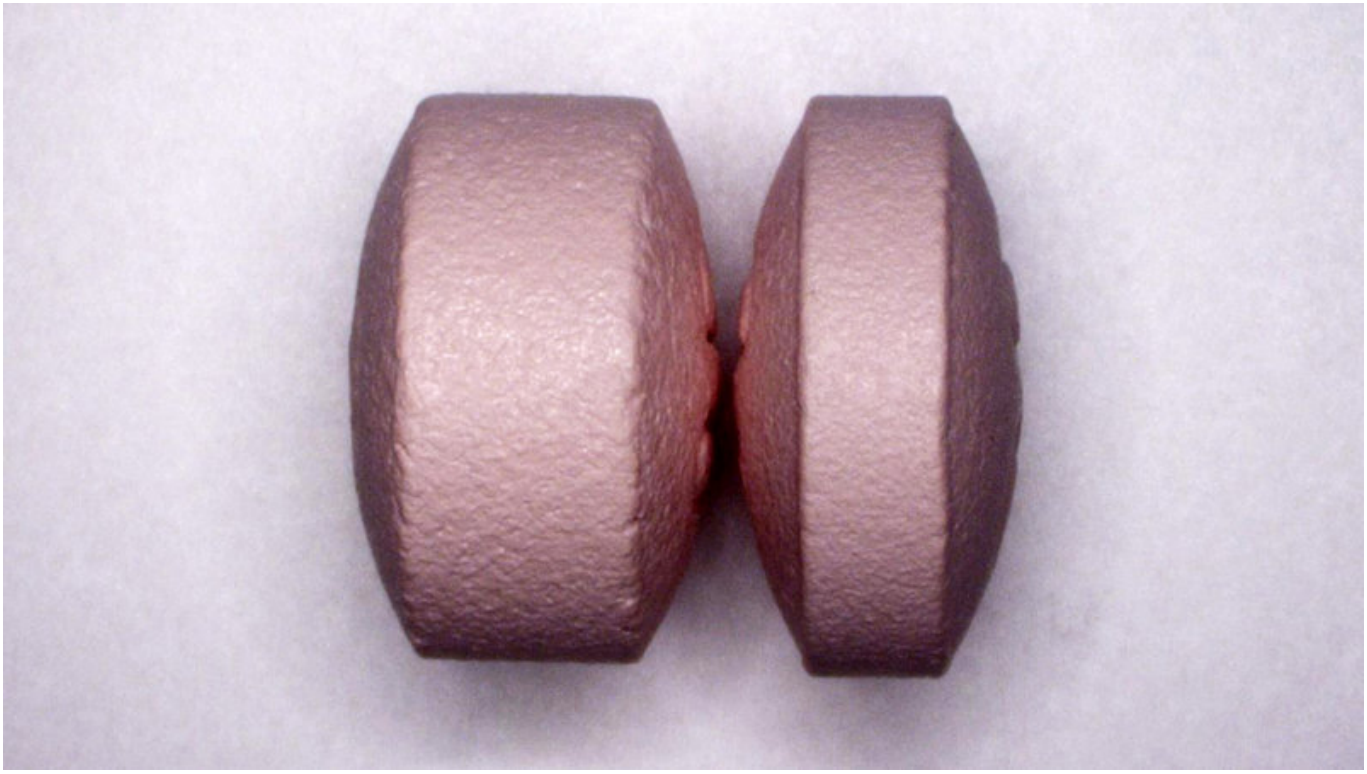
For example, in 2010, Purdue Pharma reformulated its popular opioid painkiller OxyContin to make the drug crush-resistant. The FDA later determined that the reformulated version of OxyContin was significantly safer and that "the benefits of original OxyContin no longer outweigh its risks."

The agency then blocked generic, noncrush-resistant versions of OxyContin. Dr. Andrew Kolodny, executive director of Physicians for Responsible Opioid Prescribing and a prominent critic of the drug industry, says this type of decision "is worth billions to a pharmaceutical company."

Business Concerns Versus Public Health

Endo's financial motivations for reformulating Opana were suggested in court filings.



A reformulated OxyContin pill (left) releases its active ingredient over time, but an added polymer makes it difficult to crush, melt or prepare for injection. When heated, the polymer forms a viscous gel that binds the active ingredient.
Science Source

In 2012, while Endo's petition was pending FDA's decision, the company filed a lawsuit in U.S. District Court for the District of Columbia to compel the agency to speed up the review.

Endo's lawyers predicted a "spike of misuse and abuse" if generic — and noncrush-resistant — versions of Opana hit the market.

But the company also acknowledged its business interests.

In a signed declaration, Julie H. McHugh, then the chief operating officer at Endo, said that if a generic version of Opana entered the market, "annualized net sales will decrease by an amount up to $135 million."

The loss in sales, McHugh stated, "could result in the termination of up to 150 employees and contractors employed by Endo."

The FDA said that profits — not public health – were behind Endo's impatience.

"Endo's true interest in expedited FDA consideration stems from business concerns rather than protection of the public health," lawyers for the agency stated in a legal filing.

FDA Finds Opana Reformulation Not Significantly Safer

On May 10, 2013, the FDA rendered its decision, concluding that reformulated Opana didn't effectively deter abuse. The decision opened the door to Opana's generic competitors, and that day the price of shares in the company dropped more than 5 percent.

FDA Response to Endo Lawsuit

To print the document, click the "Original Document" link to open the original PDF. At this time it is not possible to print the document with annotations.

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Opana was still safe and effective when appropriately prescribed, the FDA said.

But the agency said, "study data show that the reformulated version's extended-release features can be compromised when subjected to ... cutting, grinding, or chewing." The FDA also determined that "reformulated Opana ER can be readily prepared for injection."

Significantly, the agency warned that preliminary data about how the drug was being abused suggested "the troubling possibility that a higher percentage of reformulated Opana ER abuse is via injection than was the case with the original formulation."

Unintended Consequences

By the time the FDA concluded that reformulated Opana didn't effectively deter abuse, warning signs had already appeared.

In October 2012, the CDC issued a health alert, saying a "cluster of at least 12 patients" in Tennessee had contracted thrombotic thrombocytopenic purpura, a rare blood-clotting disorder, after injecting reformulated Opana. (The number of patients later rose to 15.)

In a conference call with investors on Feb. 28, 2013, Endo officials were asked about the reports of injection abuse. "We've designed the Opana crush-resistant formulation to be crush-resistant, to avoid primarily the nasal root of abuse," said Ivan P. Gergel, who served as Endo's chief scientific officer at the time. Gergel didn't say whether intravenous abuse was considered in developing the drug's reformulation.

"Clearly, we are looking into this data," Gergel went on to say, "but it's in a very, very distinct area of the country."

Subsequent analyses of drug abuse data appear to contradict Gergel's claim and support the FDA's concerns about injection abuse.

One study from 2014, co-authored by an Endo medical director, drew from data collected at drug treatment centers around the U.S. Overall abuse of Opana had

dropped following reformulation, the authors found. But injection had become the preferred way of abusing the drug.

According to the study, 64 percent of people abusing reformulated Opana were injecting the drug, between October 2012 and March 2014. By comparison, 36 percent of people abusing the noncrush-resistant versions of Opana did so by injection.

"With the reformulation, snorting appears to be much, much lower, whereas injection appears to be the more preferred route," Theresa Cassidy, the study's lead author, told NPR in a phone interview. Still, Cassidy, a vice president of analytics at a company called Inflexxion, warns that it's not possible to draw a causal link between the reformulation and injection abuse based simply on these data.

(Inflexxion is paid by pharmaceutical companies, including Endo, to conduct research into drug abuse patterns but says it maintains independence.)

A separate study also looked at abuse data before and after Opana's reformulation. Though the sample size was small, the study found "a trend toward increases in IV [intravenous] use after the reformulation."

Endo's Response

NPR asked Endo for an interview related to abuse issues of Opana and the company's decision to reformulate the drug.

"Patient safety is a top priority for Endo and we are committed to providing patients with approved products that are safe and effective when used as prescribed," the company said in a statement in response. "We are dedicated to providing quality medications for the treatment of patients diagnosed with chronic pain as well as to addressing opioid misuse and abuse."

While declining an interview, Endo directed NPR to contact the Center for Lawful Access and Abuse Deterrence, a nonprofit organization that advocates for the development of prescription drugs with abuse-deterrent technology. "I think that you've got a problem where the product isn't able to deter all forms of abuse," says

Mike Barnes, the executive director of CLAAD. "But to the extent that it's possible to avoid inhalation, for example, the snorting, that has a benefit."

CLAAD receives support from major pharmaceutical companies, including Endo, but the organization says its policymaking process is independent.

Re-evaluating Abuse-Deterrent Technology

The FDA has called the development of abuse-deterrent drugs a "high public health priority." In response to this story, agency spokeswoman Sarah Peddicord tells NPR in an email, "The FDA is very concerned about potential unintended consequences of abuse-deterrent opioids (and purportedly abuse-deterrent opioids) and it is something we are actively looking at."

The Food and Drug Administration has encouraged drugmakers to take steps to deter abuse of opioid medicines. But the agency hasn't agreed that all the changes are effective.

Andrew Harnik/AP

Peddicord reiterated the FDA's decision not to approve abuse-deterrent labeling for Opana, and says it is continuing to monitor the five drugs the agency has approved as abuse-deterrent.

"FDA is requiring all sponsors of opioids with approved abuse-deterrent labeling to conduct long-term epidemiological studies to assess their effectiveness in reducing abuse in the real world," says Peddicord. "Abuse-deterrent does not mean abuse-proof."

The idea of deterrence could give doctors and patients a false sense of security, since the underlying opioid is just as addictive, some experts warn.

"The two most important things that we can do to address the opioid epidemic are to prescribe fewer opioids, and to get patients with opioid addiction into treatment," says Dr. Caleb Alexander, co-director of the Johns Hopkins Center for Drug Safety and Effectiveness. "And there's no evidence to suggest that abuse-deterrent formulations are going to fundamentally change the shape of the opioid epidemic."

Endo Continues To Seek Abuse-Deterrent Status For Opana

Despite the well-publicized accounts of abuse in Indiana and Tennessee, Endo continues to push for FDA labeling that would call reformulated Opana ER "abuse-deterrent," because of its apparent effect on abuse by snorting.

In a call with investors on Feb. 29, 2016, President and CEO Rajiv De Silva said that, for the most part, "If we are successful in getting that relabeling, it will certainly serve to help remove all the generics from the market."

Endo's push for relabeling may face additional scrutiny because of ongoing legal inquiries. In February, the New York attorney general said Endo engaged in "deceptive and unlawful conduct" in its marketing of Opana and imposed a $200,000 penalty on the company.

The company's statement to NPR said, "The settlement does not include any agreement or confirmation by Endo that its marketing practices were inappropriate."

On Thursday, the Federal Trade Commission also announced a lawsuit filed in U.S. District Court for the Eastern District of Pennsylvania against Endo alleging that the company violated antitrust laws and illegally blocked access to generic versions of Opana. Endo says in a statement, "We believe the FTC's case is without merit and Endo intends to vigorously defend itself in the litigation."

Back in Austin, Ind., local, state and federal law enforcement have struggled to eliminate Opana from the town's illegal-drug market.

A recent drug bust helped reduce the amount of Opana available on the street.

But drug users there still describe Opana as the most desirable drug around.

A single Opana pill, they say, now costs about $200, up from around $140 when we started reporting this story.

Side Effects Public Media health reporter Jake Harper and NPR's Kelly McEvers contributed to this story.

opana drug abuse opioids addiction indiana pharmaceuticals

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EXHIBIT 67

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Outbreak of Recent HIV and HCV Infections among Persons Who Inject Drugs

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH ADVISORY

This information is *for historic and reference purposes only*. Content has not been updated since the last updated date at the bottom of this page.

Distributed via the CDC Health Alert Network
April 24, 2015, 11:00 ET (11:00 AM ET)
CDCHAN-00377

Summary

The Indiana State Department of Health (ISDH) and the Centers for Disease Control and Prevention (CDC) are investigating a large outbreak of recent human immunodeficiency virus (HIV) infections among persons who inject drugs (PWID). Many of the HIV-infected individuals in this outbreak are co-infected with hepatitis C virus (HCV). The purpose of this HAN Advisory is to alert public health departments and healthcare providers of the possibility of HIV outbreaks among PWID and to provide guidance to assist in the identification and prevention of such outbreaks.

Background

From November 2014 to January 2015, ISDH identified 11 new HIV infections in a rural southeastern county where fewer than 5 infections have been identified annually in the past. As of April 21, 2015, an on-going investigation by ISDH with assistance from CDC has identified 135 persons with newly diagnosed HIV infections in a community of 4,200 people; 84% were also HCV infected. Among 112 persons interviewed thus far, 108 (96%) injected drugs; all reported dissolving and injecting tablets of the prescription-type opioid oxymorphone (OPANA® ER) using shared drug preparation and injection equipment.[1]

This HIV outbreak was first recognized by a local disease intervention specialist. In late 2014, interviews conducted with three persons newly diagnosed with HIV infections in three separate venues (i.e., an outpatient clinic, a drug rehabilitation program, during a hospitalization) indicated that two of these persons had recently injected drugs and had numerous syringe-sharing and sexual partners. Contact tracing identified eight additional HIV infections leading to the current outbreak investigation, which has demonstrated that HIV had spread recently and rapidly through the local network of PWID. Without an attentive health department, active case finding, and additional testing provided as part of this investigation, this cluster may not have been identified.

Urgent action is needed to prevent further HIV and HCV transmission in this area and to investigate and control any similar outbreaks in other communities.

Injection drug use accounts for an estimated 8%[2] of the approximate 50,000 annual new HIV infections in the United States.[3] HCV infection is the most common blood-borne infection in the United States and percutaneous exposure via drug-injecting equipment contaminated with HCV-infected blood is the most frequent mode of transmission. Nationally, acute HCV infections have increased 150% from 2010 to 2013,[4] and over 70% of long-term PWID may be infected with HCV.[5] Abuse of prescription-type opioids is increasing nationally[6] and opioid-analgesic poisoning deaths have nearly quadrupled from 1999 through 2011.[7] Rates of acute HCV infection are increasing, especially among young nonurban PWID, often in association with abuse of injected prescription-type opioids. These increases have been most substantial in nonurban counties east of the Mississippi River.[8]

Recommendations for Health Departments

- Review the most recent sources of data on HIV diagnoses, HCV diagnoses (acute as well as past or present), overdose deaths, admissions for drug treatment, and drug arrests. Attributes of communities at risk for unrecognized clusters of HIV and HCV infection include the following:
  - Recent increases in the:
    - Number of HIV infections attributed to injection drug use,
    - Number of HCV infections, particularly among persons aged ≤ 35 years;
  - High rates of injection drug use and especially prescription-type opioid abuse, drug-related overdose, drug treatment admission, or drug arrests.
- Ensure complete contact tracing for all new HIV diagnoses and testing of all contacts for HIV and HCV infection.
- Ensure persons actively injecting drugs or at high-risk of drug injection (e.g., participating in drug substitution programs, receiving substance abuse counseling or treatment, recently or currently incarcerated) have access to integrated prevention services,[9] and specifically:
  - Are tested regularly for HIV and HCV infection (consider more frequent testing based on frequency of injection drug usage or sharing of injection equipment);
  - If diagnosed with HIV or HCV infection:

    - Are rapidly linked to care and treatment services.
  - If actively injecting drugs:
    - Have access to medication-assisted therapy (e.g., opioid substitution therapy) as well as other substance abuse services, if not already engaged,
    - Are counseled not to share needles and syringes or drug preparation equipment (e.g., cookers, water, filters),
    - Have access to sterile injection equipment from a reliable source.
  - If not HIV infected but actively injecting drugs:
    - Are referred for consideration of HIV pre-exposure prophylaxis[10] and if potentially exposed within the past 72 hours (e.g., shared drug preparation or injection equipment with a known or potentially HIV-infected person) HIV post-exposure prophylaxis[11,12]
- Remind venues that may encounter unrecognized infections, such as emergency departments and community-based clinical practices (e.g., family medicine, general medicine, prenatal care) of the importance of routine opt-out HIV testing as well as HCV testing per current recommendations[13-15]
- Local health departments should notify their state health department and CDC of any suspected clusters of recent HIV or HCV infection.

Recommendations for Healthcare Providers

- Ensure all persons diagnosed with HCV infection are tested for HIV infection,[16] and that all persons diagnosed with HIV infection are tested for HCV infection.[17]
- Ensure persons receiving treatment for HIV and/or HCV infection adhere to prescribed therapy and are engaged in ongoing care.
- Encourage HIV and HCV testing of syringe-sharing and sexual partners of persons diagnosed with either infection.
- Report all newly diagnosed HIV and HCV infections to the health department.
- For all persons with substance abuse problems:
  - Refer them for medication-assisted treatment (e.g., opioid substitution therapy) and counseling services,
  - Use effective treatments (e.g., methadone, buprenorphine), as appropriately indicated.
- For any persons for whom opioids are under consideration for pain management:
  - Discuss the risks and benefits of all pain treatment options, including ones that do not involve prescription analgesics.
  - Note that long-term opioid therapy has not been demonstrated to reduce chronic pain.[18]
- Contact the state or local health department to report suspected clusters of recent HIV or HCV infection.

For more information:

- Centers for Disease Control and Prevention. Integrated Prevention Services for HIV Infection, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis for Persons Who Use Drugs Illicitly: Summary Guidance from CDC and the U.S. Department of Health and Human Services. 2012: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6105a1.htm?s_cid=rr6105a1_w (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6105a1.htm?s_cid=rr6105a1_w).
- Centers for Disease Control and Prevention. HIV and Injection Drug Use fact sheet. (http://www.cdc.gov/hiv/pdf/g-l/cdc-hiv-idu-fact-sheet.pdf (http://www.cdc.gov/hiv/pdf/g-l/cdc-hiv-idu-fact-sheet.pdf))
- Centers for Disease Control and Prevention. Hepatitis C and Injection Drug Use fact sheet. http://www.cdc.gov/hepatitis/HCV/PDFs/FactSheet-PWID.pdf (http://www.cdc.gov/hepatitis/HCV/PDFs/FactSheet-PWID.pdf)
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- AASLD/IDSA/IAS–USA. HCV testing and linkage to care. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org/full-report/hcv-testing-and-linkage-care (http://www.hcvguidelines.org/full-report/hcv-testing-and-linkage-care)

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The Centers for Disease Control and Prevention (CDC) protects people's health and safety by preventing and controlling diseases and injuries; enhances health decisions by providing credible information on critical health issues; and promotes healthy living through strong partnerships with local, national and international organizations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

HAN Message Types

- **Health Alert:** Conveys the highest level of importance; warrants immediate action or attention. Example: HAN00001
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- **Health Update:** Provides updated information regarding an incident or situation; unlikely to require immediate action. Example: HAN00342
- **Info Service:** Provides general information that is not necessarily considered to be of an emergent nature. Example: HAN00345

###

This message was distributed to state and local health officers, state and local epidemiologists, state and local laboratory directors, public information officers, HAN coordinators, and clinician organizations.

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EXHIBIT 68

A.G. Schneiderman Announces Settlement With Endo Health Solutions Inc. & Endo Pharmaceuticals Inc. Over Marketing Of Prescription Opioid Drugs

Endo Will Cease Making False And Misleading Claims About The Narcotic Painkiller Opana ER

Endo Will Create A Program To Prevent Marketing Opioids To Health Care Providers Engaged In Abuse And Diversion

Schneiderman: My Office Is Committed To Preventing Opioid Abuse, Holding Drug Companies Accountable

NEW YORK - Attorney General Eric T. Schneiderman today announced an agreement with Endo Health Solutions Inc. and Endo Pharmaceuticals Inc. ("Endo"), which make and sell the long-acting opioid, Opana ER. The agreement requires Endo to cease all misrepresentations regarding the properties of Opana ER, to describe accurately the risk of addiction to Opana ER, and to summarize studies regarding Opana ER on its website. Endo must also create a program that will prevent its sales staff from promoting this powerful narcotic painkiller to health care providers who may be involved in the abuse and illegal diversion of opioids.

"The public health crisis created by improper opioid prescribing in New York remains pervasive and extremely dangerous," said **Attorney General Schneiderman**. "My office is committed to ensuring that prescription drugs are marketed and prescribed responsibly – and that consumers get the information they need about the serious risks associated with painkillers, such as addiction."

The use of prescription opioids to manage chronic non-cancer pain has increased ten-fold over the past 20 years in the United States, with a concomitant increase in opioid-related health problems. According to the New York City Department of Health and Mental Hygiene, between 2008 and 2011, the number of opioid painkiller prescriptions filled by New York City residents increased by 31%, from approximately 1.6 million to approximately 2.2 million. The resulting increase in the prescribing of opioids is associated with a sharp increase in the prevalence of opioid addiction, which in turn has been associated with a rise in overdose deaths and heroin use. According to the federal Centers for Disease Control and Prevention, in New York State, from 2003 to 2012, deaths involving opioid analgesics increased five-fold, from 179 in 2003 to 883 in 2012.

Endo, an Irish company with U.S. headquarters in Pennsylvania, makes a variety of prescription drugs. Endo's opioid drug Opana ER has been widely abused in New York State. In May 2011, after a spike in opioid prescribing and abuse, Nassau County issued a Public Health Alert on the increasing abuse of Opana ER, warning the public and law enforcement of the dangers of associated with the drug. In July 2012, USA Today reported that Opana ER had become the drug of choice for people seeking narcotics,

and that in Nassau County, hundreds of people each month were seeking treatment for addiction to Opana ER.

As a result of concerns regarding the role of Opana ER in the larger opioid abuse epidemic and Endo's marketing practices, the Office of the Attorney General launched an investigation of Endo, focusing on Opana ER. The Attorney General found that Endo improperly marketed Opana ER as designed to be crush resistant, when Endo's own studies showed that the pill could be crushed and ground. This may have bolstered Opana ER sales, but provided a false sense of security to health care providers and their patients. The Attorney General also found that Endo improperly instructed its sales representatives to diminish and distort risks associated with Opana ER, including serious dangers involving addiction.

The Attorney General's investigation also revealed that Endo had no meaningful program in place to ensure that its sales representatives were not encouraging health care providers engaged in abuse and diversion to write more prescriptions for Opana ER. Numerous New York health care providers who were heavily "detailed" by Endo were subsequently convicted of illegal prescribing of prescription opioids. The Attorney General also found that Endo made unsupported claims comparing Opana ER to other opioids, and failed to disclose accurate information regarding studies addressing the effects of Opana ER.

In light of Endo's deceptive and unlawful conduct, the Office of the Attorney General compelled Endo to change its practices. Endo has agreed to the following measures:

- Provide truthful and complete information regarding addiction risks associated with Opana ER.
- Stop improperly marketing Opana ER as being crush resistant.
- Create an Abuse and Diversion Detection Program that requires Endo's sales representatives to report to the company health care providers it suspects of engaging in abuse and illegal diversion of opioids, and for Endo to cease marketing opioids to problem prescribers.
- Post results of clinical studies on Endo's website.
- Encourage health care providers to seek training on appropriate opioid prescribing practices.
- Provide health care providers with information about addiction treatment resources for their patients.

Furthermore, the Attorney General has also imposed a $200,000 penalty on Endo for its unlawful conduct.

The Attorney General's Office has taken a multi-pronged approach to combatting New York's prescription drug abuse epidemic. Attorney General Schneiderman's ground-breaking law, "Internet System for Tracking Over-Prescribing Act," or "I-STOP," which became effective in August 2013, has reduced "doctor-shopping" by 75%. The Attorney General's Office has prosecuted many health care providers who illegally prescribed and diverted opioids. The Attorney General's Office has also aggressively enforced laws that require parity in health plan coverage of mental health and addiction treatment. The Attorney General's Community Overdose Prevention ("COP") Program, which equips New York law enforcement agencies with a life-saving heroin overdose antidote, has saved more than 100 lives.

The investigation of this matter was conducted by Assistant Attorneys General Michael D. Reisman and Carol Hunt, of the Attorney General's Health Care Bureau, which is led by Bureau Chief Lisa Landau. The Health Care Bureau is a part of the Social Justice Division, led by Executive Deputy Attorney General for Social Justice Alvin Bragg.

A copy of the settlement can be read **here.**

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The People of the State of New York v. Maurice R. Greenberg & Howard I. Smith

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EXHIBIT 69

ATTORNEY GENERAL OF THE STATE OF NEW YORK

In the Matter of

Endo Health Solutions Inc.
and
Endo Pharmaceuticals Inc.

Assurance No.: 15-228

ASSURANCE OF DISCONTINUANCE
UNDER EXECUTIVE LAW
SECTION 63, SUBDIVISION 15

Pursuant to the provisions of Section 63(12) of the Executive Law and Article 22-A of the General Business Law, Eric T. Schneiderman, Attorney General of the State of New York, caused an inquiry to be made into certain business practices of Endo Health Solutions Inc. and Endo Pharmaceuticals Inc. Based upon that inquiry, the Office of the Attorney General ("the OAG") has made the following findings, and Endo has agreed to modify its business practices and comply with the following provisions of this Assurance of Discontinuance ("Assurance").

I. BACKGROUND

1. Endo Health Solutions Inc. and Endo Pharmaceuticals Inc. (collectively, "Endo," or the "Company") are Delaware corporations with their principal place of business at 1400 Atwater Drive, Malvern, PA 19355. Endo is engaged in the manufacture, marketing and sale of prescription drugs, in particular the extended-release, long-acting opioid Opana ER, which is a branded version of the drug oxymorphone. The U.S. Food and Drug Administration (the "FDA") approved Opana ER in 2006 for the management of moderate or severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time ("Original Opana ER"). In 2012, the FDA approved a reformulated version of Opana ER containing the

same active drug but a different formulation ("Reformulated Opana ER"), the purported purpose of which was to make the pill harder to manipulate.[1]

2. Opana ER is a narcotic painkiller and its label contains "black box" warnings of serious risks from taking the drug, such as addiction and respiratory depression, which can lead to death.

3. In 2014, Endo had U.S. sales of Opana ER totaling $198 million.

4. To market Opana ER, among other things, Endo employs sales representatives who visit health care providers ("HCPs"), which include medical doctors, doctors of osteopathy, nurse practitioners, and physicians' assistants. The Endo sales representatives "detail" HCPs' offices, where they provide informational resources on Opana ER, with the objective of encouraging these HCPs to prescribe Opana ER under appropriate circumstances.

5. In addition to a yearly salary, Endo's sales representatives may receive a bonus that is based in part on the number of Opana ER prescriptions written by HCPs upon whom they are permitted to call, which can create an incentive to encourage more Opana ER prescribing.

6. The use of prescription opioids to manage chronic non-cancer pain has increased ten-fold over the past 20 years in the United States, with a concomitant increase in opioid-related health problems. According to the New York City Department of Health and Mental Hygiene, between 2008 and 2011, the number of opioid painkiller prescriptions filled by New York City residents increased by 31%, from approximately 1.6 million to approximately 2.2 million.

7. The resulting increase in prescribing of opioids is associated with a sharp increase in the prevalence of opioid addiction, which in turn has been associated with a rise in overdose

[1] Endo discontinued Original Opana ER in 2012, but as a result of certain patent litigation settlements, it provided licenses for patents related to Opana ER to certain generic drug manufacturers, some of which subsequently sold generic versions of Opana ER.

deaths and heroin use.[2] According to the federal Centers for Disease Control and Prevention, in New York State, from 2003 to 2012, deaths involving opioid analgesics increased five-fold, from 179 in 2003 to 883 in 2012.[3]

8. In May 2011, after a spike in opioid prescribing and abuse, Nassau County issued a Public Health Alert on the increasing abuse of Opana, warning the public and law enforcement of the dangers of Original Opana ER.[4] The Public Health Alert noted that methods of Original Opana ER abuse included dissolving or removing the coating and then crushing or snorting the pill. According to the FDA, oral ingestion is the most common route of abuse of prescription opioids, followed by snorting and injection.

9. In July 2012, USA Today reported that Original Opana ER had become the drug of choice for people seeking narcotics, and that in Nassau County, hundreds of people each month were seeking treatment for addiction to Opana.[5]

II. THE OAG'S INVESTIGATIONS AND FINDINGS

10. In 2013, the OAG commenced an investigation of Endo regarding its marketing of Opana ER, and after obtaining documents and testimony via subpoena, and in this Section II makes the following findings (the "Covered Conduct"):

A. Endo's Statements About Opana ER

i. The "Crush Resistance" Of Reformulated Opana ER

11. In 2009 and 2010, Endo conducted a series of studies that assessed whether Reformulated Opana ER was "crush resistant." One such study ("Study 108") showed that Reformulated Opana ER could be ground with a coffee grinder. Another study ("Study 109")

[2] *See* http://www.annualreviews.org/doi/pdf/10.1146/annurev-publhealth-031914-122957.
[3] *See* http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6414a2.htm.
[4] *See* http://archive.nassaucountyny.gov/agencies/CountyExecutive/NewsRelease/2010/5-9-2011.htm; http://archive.nassaucountyny.gov/agencies/CountyExecutive/NewsRelease/2010/8-26-2011.htm.
[5] *See* http://usatoday30.usatoday.com/news/nation/story/2012-07-10/opana-painkiller-addiction/56137086/1.

showed that Reformulated Opana ER could be chewed and that chewing "was associated with positive effects indicative of increased abuse potential." To the extent that "crush" means "to press or squeeze [something] so hard that it breaks or loses its shape," or "to break [something] into a powder or very small pieces by pressing, pounding, or grinding it,"[6] some of Endo's studies showed that Reformulated Opana ER can be crushed.

12. Endo conducted two other studies to test its claims for crush-resistance. In one study ("Study 901"), which assessed whether opioid abusers could convert Reformulated Opana ER into a form amenable to intravenous administration and whether they would be willing to inject the tampered product, two of the hypotheses – that Reformulated Opana ER would be less extractable than Original Opana ER and that it would take less time to extract the drug from Original Opana ER than Reformulated Opana ER – were not met. Both formulations behaved similarly under the study conditions with respect to manipulation time, and produced equivalent yields. Although the Results of Study 901 met the third hypothesis – that a majority of subjects would not want to inject what they extracted after tampering – a similar number of subjects said they would have injected tampered Reformulated Opana ER as would have done so with tampered Original Opana ER. In the other study ("Study 902"), which tested whether subjects could manipulate Reformulated Opana ER into snortable form using various tools, only two of 25 subjects chose to use a coffee grinder, which was a method by which Reformulated Opana ER could be crushed. Twenty-four of the 25 study subjects considered Original Opana ER suitable for snorting after tampering. Three study subjects considered Reformulated Opana ER suitable for snorting after tampering.

[6] *See* http://www.merriam-webster.com/dictionary/crush.

13. In January 2011, after reviewing the results of the above-mentioned studies, the FDA concluded that the label for Reformulated Opana ER could not include claims about crush resistance, stating: "[t]he product label should not include language asserting that [Reformulated Opana ER] provides resistance to crushing, because it may provide ***a false sense of security*** since the product may be chewed and ground for subsequent abuse" (emphasis added).

14. In October 2011, Endo's Director of Project Management wrote in an email to Grunenthal, the company that developed the formulation technology for Reformulated Opana ER, that

> [w]e already demonstrated that there was little difference between [the original and new formulations of Opana] in Study 108 when both products were ground. FDA deemed that there was no difference and this contributed to their statement that we had not shown an incremental benefit. The chewing study (109) showed the same thing no real difference which the FDA used to claim no incremental benefit.

15. Endo executives knew that both Original and Reformulated Opana ER were abused, in particular via intravenous injection. In July 2012, on the same day that USA Today reported widespread abuse of Opana ER, including in New York, Endo executives developed talking points for sales representatives to use when asked about the article. In particular, sales representatives were instructed to tell HCPs that

- Endo takes very seriously the problem of prescription drug abuse and is also strongly committed to providing solutions to the medical needs of patients suffering with chronic pain.
- Part of our corporate mission is a commitment to educating physicians and patients about the appropriate and responsible use of pain management therapies.
- Endo discontinued the manufacturing of the original formulation of Opana ER in early 2012 and now only manufactures the new formulation of Opana ER with INTAC technology which is designed to be crush-resistant.

16. In an internal document that that the OAG obtained via subpoena, Endo's consultant reported to the Company in February 2013, after reviewing national data from substance abuse treatment facilities, that "[t]he initial data presented do not necessarily establish that the reformulated Opana ER is tamper resistant," and that there were reports of higher levels of abuse of Reformulated Opana ER via injection.

17. Despite the above-stated facts, from May 2012 to May 2013, in pamphlets that its sales representatives distributed to HCPs in New York State, Endo marketed the Reformulated Opana ER as "designed to be" crush resistant.[7]

18. Moreover, an Endo sales representative testified to OAG that she described Reformulated Opana ER as "crush resistant," without any qualifying language. In training its sales representatives, Endo identified Reformulated Opana ER as "CR," short for "crush resistant."

19. In May 2013, the FDA rejected Endo's request to be able to state on the Reformulated Opana ER label that the product is crush-resistant. Shortly thereafter, Endo ceased marketing Reformulated Opana ER as "designed to be crush resistant."

ii. <u>The Addictiveness of Opana</u>

20. Until at least April 2012, Endo disseminated to New York HCPs, and stated on its website <u>www.opana.com</u> that "[m]ost healthcare providers who treat patients with pain agree that patients treated with prolonged opioid medicines usually do not become addicted." Endo has not conducted nor does it possess a survey that shows that most healthcare providers who treat patients with pain agree that patients treated with prolonged opioid medicines usually do not become addicted.

[7] In December 2011, the FDA had approved Reformulated Opana ER, based on its bioequivalence to Original Opana ER.

21. In a training script issued in May 2011, Endo instructed its New York sales representatives to give the following response to HCPs who expressed specific concerns about Opana ER. The sales representatives were instructed to ask, "Doctor, are you concerned with abuse potential associated with a long-acting opioid?" If the physician answered "Yes," the representative was instructed to say that Opana ER carries the same abuse liability as other long-acting opioids.

22. In training materials it provided to its New York sales representatives, Endo stated that "[s]ymptoms of withdrawal do not indicate addiction," when in fact withdrawal is a symptom of opioid-use disorder, a diagnosis under the Diagnostic and Statistical Manual of the American Psychiatric Association (Fifth Edition). Endo's training materials also included assertions that addiction to opioids is not common.

23. Endo also trained its sales representatives to distinguish addiction from "pseudoaddiction," a purported condition in which patients exhibit drug-seeking behavior that resembles but is not the same as addiction. The "pseudoaddiction" concept has never been empirically validated and in fact has been abandoned by some of its proponents. Endo's Vice President for Pharmacovigilance and Risk Management testified to OAG that he was not aware of any research validating the "pseudoaddiction" concept, and that it would take "a really good clinician" or a behavioral scientist to distinguish between addiction and "pseudoaddiction."

iii. <u>Endo's Other Claims</u>

24. Endo sales representatives testified to OAG that in sales calls to New York HCPs, they distinguished Opana ER from its main competitor, OxyContin, by stating that patients who take Opana ER need less rescue medication (additional, as-needed opioids) than those who take OxyContin. This statement was not supported by any clinical evidence or study.

25. An Endo sales representative also testified to OAG that she was trained to distinguish Opana ER from OxyContin by informing New York HCPs that patients who take Opana ER only need to take it twice a day, whereas those who take OxyContin need to take it three times per day. This statement was not supported by any clinical evidence or study.

26. Endo distributed a pamphlet in New York and posted on its public website, www.opana.com, photographs of purported Opana ER patients that implied that patients can achieve higher functioning with Opana ER. The photos depict individuals with physically demanding jobs (construction worker, chef, and teacher), and portray seemingly healthy, unimpaired people.

B. Endo's Statements And Omissions Regarding Opana ER Studies

27. Endo did not mention Study 108 or Study 109 in its Reformulated Opana ER "managed care dossier" (the "Dossier"), which it distributed to formulary committees of health plans and pharmacy benefit managers to encourage them to include Reformulated Opana ER in their formularies and, as Endo's Vice President for Pharmacovigilance and Risk Management testified to OAG, is supposed to be a complete compendium of all research on the drug. Endo did describe certain aspects of the 901 and 902 studies in the Dossier.

28. Endo briefly summarizes on its public website only some of the studies it has conducted regarding Opana ER.[8] The Hale Study, which Endo has used extensively in marketing, is described on the website. However, Study 108 and Study 109, which showed that Reformulated Opana ER can be ground and chewed, are not mentioned on the website. Further, the website does not mention studies that the FDA concluded failed to show the efficaciousness of Original Opana ER.

[8] *See* http://www.endo.com/endopharma/r-d/clinical-research/clinical-trial-study-results.

29. Endo published only certain studies regarding Opana ER, including the Hale Study and Study 901 and Study 902, but it did not publish Study 108 or Study 109.

30. Endo omitted information about the Hale Study in marketing pamphlets distributed to HCPs. Specifically, although the Hale Study showed that 5.7% of patients who took the drug in the "treatment" phase of the study experienced pain exacerbation,[9] and 6.9% of patients given placebo in that phase experienced opioid withdrawal, Endo omitted these adverse events from marketing pamphlets it distributed to HCPs in New York.

C. Endo's Detailing Of Problem Health Care Providers

31. As described above, Endo knew that Opana was being abused in New York, as early as 2011. Although Endo had issued a written policy requiring detailers to report signs of abuse, diversion and inappropriate prescribing,[10] certain Endo sales representatives who detailed New York HCPs testified that they did not know about any policy or duty to report problematic conduct observed in HCPs' offices, and did not report anyone, even when they saw suspicious behavior. At the same time, Endo's New York sales representatives received incentive compensation for Opana ER sales, and Endo expanded its HCP target list in January 2012 to include HCPs without experience prescribing long-acting opioids.

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[9] *See* Martin E. Hale, et al., *Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: a 12-week, randomized, double-blind, placebo-controlled study*, 8 J. of Pain 175 (2007).

[10] Endo's Code of Conduct provides that if any Endo employee has "any knowledge or suspicion about the improper handling, transfer, loss or diversion of a controlled substance, [that employee must] immediately report it to [their] manager or the [Endo] Ethics Hotline." All Endo employees are required to certify that they have 'reviewed, read, understand and shall abide by' the Code of Conduct and are subject to discipline, up to and including termination, for violating the Code of Conduct. Endo's Health Care Compliance Guide states that "[i]f an Endo employee receives a report from an external party regarding suspected diversion of Endo's products or if an Endo employee suspects that diversion is occurring at a customer's site, the employee must report that information" to Endo. The Health Care Compliance Guide describes signs of potential diversion of which Endo employees should be aware, including (i) prescriptions being paid for in cash; (ii) a large demographic distance between the doctor, patient and pharmacy; (iii) high frequency of prescriptions to replace lost prescriptions or medication; (iv) drugs or doses not being individualized; (v) lack of qualified staff; and (vi) special entrance requirements for patients of the practice. However, there is no indication that Endo's New York sales representatives ever received training in this policy, and certain New York sales representatives testified to OAG that they did not know about such a policy.

32. Endo detailed certain HCPs who were subsequently arrested and/or convicted for illegal prescribing of opioids in New York State. Endo detailed the following HCPs a total of 326 times, and they collectively wrote 1,370 scripts for Opana ER:

i. Matthew Bennett: Endo detailed this Buffalo-area physician 61 times between July 16, 2010 and August 8, 2012. He wrote a total of 642 Opana ER prescriptions between July 2009 and July 2012. He was arrested by the U.S. Drug Enforcement Agency on August 10, 2012, for illegal prescribing of opioids, pleaded guilty on April 20, 2015, and was sentenced to three years in prison.

ii. David Brizer: Endo detailed this Rockland psychiatrist 26 times between March 25, 2011 and August 24, 2012. He wrote a total of 324 Opana ER prescriptions between March 2011 and August 2012. He was arrested by OAG on February 11, 2013, for illegally selling opioid prescriptions, and in February 2014, pleaded guilty.

iii. Richard Cedeno: Endo detailed this Bronx physician's assistant 19 times between August 17, 2012 and May 22, 2013. He wrote a total of 51 Opana ER prescriptions between August 2008 and May 2013. He was arrested by OAG on June 19, 2013, in connection with illegal prescribing of opioids, and pleaded guilty in 2015.

iv. Rools Deslouches: Endo detailed this Long Island physician's assistant 7 times between January 13, 2012 and May 17, 2012. He wrote a total of 13 Opana ER prescriptions between February and May 2012. He was arrested by federal agents on June 6, 2012, for illegal distribution of opioids, pleaded guilty, and was sentenced to more than 6 years in prison.

v. Eric Jacobson: Endo detailed this Queens/Nassau physician 3 times between March 3, 2011 and March 21, 2012. He wrote a total of 22 Opana ER prescriptions in March 2011.

He was charged in June 2011, with conspiracy to distribute opioids illegally, and pleaded guilty.

vi. Leonard Marchetta: Endo detailed this Staten Island physician's assistant 82 times between January 8, 2009 and July 18, 2013. He wrote a total of 38 Opana ER prescriptions between April 2009 and April 2013. On October 27, 2010, a news report identified Marchetta as a supplier for an arrested Staten Island drug dealer.[11] He was indicted by the United States Attorney for the Southern District of New York in September 2014, for conspiracy to distribute narcotics, pleaded guilty in January 2015, and was sentenced to 11 years in prison.

vii. Anand Persaud: Endo detailed this Long Island physician 47 times between February 27, 2009 and July 29, 2013. He wrote a total of 195 Opana ER prescriptions between June 2009 and July 2013. He was arrested by OAG in July 2013, for illegally selling opioid prescriptions.[12]

viii. Rohan Wijetilaka: Endo detailed this Westchester cardiologist 79 times from January 16, 2009 and July 18, 2012. He wrote a total of 85 Opana ER prescriptions between September 2009 and July 2012. His license was revoked by the New York State Department of Health on June 27, 2012, and he was arrested by the United States Drug Enforcement Administration on July 25, 2012, and charged with illegal distribution of opioids. He pleaded guilty to health care fraud (giving opioid scripts to patients who allowed him to bill insurers for unnecessary tests) and was sentenced to 3 years in prison. In testimony to the OAG, an Endo sales representative described Wijetilaka's Yonkers,

[11] *See* http://www.silive.com/eastshore/index.ssf/2010/10/richmond_man_faces_host_of_dru.html.
[12] Endo stopped detailing certain New York HCPs based on concerns of suspected diversion, but, of the HCPs listed in this section, only stopped detailing Marchetta and Persaud after they were arrested.

New York office as follows: "Just very crowded, very crowded offices, very -- people looking to fill their prescriptions, younger demographic…. People looking just for pills as opposed to different offices that would have -- people you could tell who had chronic pain, who had back braces who were older or had different disease states. A lot of these were patients, if I recall, looked like they were looking for meds to get high on." The sales rep never told anyone at Endo about what he observed in Wijetilaka's office.

33. While the above charges did not involve Opana ER, and the OAG did not charge that promotion by Endo played a role in cases it prosecuted, in certain limited circumstances it may have been possible for Endo sales representatives to recognize a potential sign of diversion that should have been reported per Endo's policy and could have resulted in the sales representative stopping detailing that HCP sooner.

D. Limitations in HCPs' Knowledge of Appropriate Prescribing Practices

34. A recently published survey showed that many primary care physicians do not understand basic facts about how people may abuse opioids or how addictive opioids can be. Nearly half of the internists, family physicians and general practitioners surveyed incorrectly thought that "abuse-deterrent" pills were less addictive than their standard counterparts.[13] One-third of the HCPs erroneously said they believed that most prescription drug abuse is by means other than swallowing the pills as intended. As noted above, oral ingestion is the most common route by which opioids are abused.

E. Opioid Patients' Need For Information Regarding Addiction Treatment

35. Patients undergoing opioid therapy need information about the risks of addiction and the availability of addiction treatment resources. Recent studies have indicated that opioid

[13] *See* Catherine S. Hwang et al., *Primary Care Physicians' Knowledge And Attitudes Regarding Prescription Opioid Abuse and Diversion*, Clinical J. of Pain (Jun. 22, 2015).

use disorders appear to be highly prevalent in chronic pain patients treated with opioids, with up to 40% of chronic pain patients treated in specialty and primary care outpatient centers meeting the clinical criteria for an opioid use disorder.[14] A study published in 2015, based on computer-assisted review of electronic health records, concluded that 13.5% of patients receiving chronic opioid therapy had either problem opioid use or a diagnosis for opioid abuse or dependence.[15] Although there is presently no consensus regarding the incidence or prevalence of abuse or addiction to opioids among patients treated with chronic opioid therapy, the above-mentioned studies suggest that efforts to reduce opioid abuse and overdose deaths should address not only those who abuse opioids such as Opana ER without a prescription, but also those who take the medication as prescribed, yet begin to abuse opioids or become addicted to them.

III. RELEVANT LAW

36. The New York General Business Law prohibits "deceptive acts or practices in the conduct of any business, trade or commerce or in the furnishing of any service" in New York State. N.Y. Gen. Bus. Law § 349.

37. The New York General Business Law also prohibits "false advertising in the conduct of any business," N.Y. Gen. Bus. Law § 350, such that the advertising is misleading in a material respect. Whether an advertisement is materially misleading depends on "the extent to which the advertising fails to reveal facts material in the light of such representations with respect to the commodity to which the advertising relates under the conditions prescribed in said advertisement." N.Y. Gen. Bus. Law § 350-a.

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[14] *See* Joseph A. Boscarino et al., *Risk Factors For Drug Dependence Among Out-Patients On Opioid Therapy In A Large US Health-Care System*, 105 Addiction 1776 (2010); Joseph A. Boscarino et al., *Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 versus DSM-4 diagnostic criteria*, 30 J. Addictive Diseases 185 (2011).

[15] *See* Roy E. Palmer et al., *The Prevalence Of Problem Opioid Use In Patients Receiving Chronic Opioid Therapy: Computer Assisted Review Of Electronic Health Record Clinical Notes*, 156 Pain 1208 (2015).

38. The New York Executive Law prohibits "illegal or fraudulent acts" in the conduct of any business, trade or commerce, and allows the OAG to institute a special proceeding for restitution, damages, and/or injunctive relief against any party which has committed such acts. N.Y. Exec. Law § 63(12).

39. The OAG concludes that certain Endo marketing practices, statements and omissions violated the above-referenced provisions.

40. The OAG concludes that Endo's unlawful acts in violation of General Business Law §§ 349 and 350 constitute violations of New York Executive Law § 63(12).

NOW, WHEREAS, Endo neither admits nor denies the Attorney General's findings in Paragraphs 11 through 35 above; and

WHEREAS, New York laws prohibiting deceptive business practices, and false and misleading advertising, and off-label marketing of prescription drugs confer important consumer and public health protections; and

WHEREAS, Endo has cooperated with the OAG's investigation; and

WHEREAS, the Attorney General is willing to accept the terms of this Assurance under Executive Law Section 63(15) and to discontinue his investigation; and

WHEREAS, the parties each believe that the obligations imposed by this Assurance are prudent and appropriate; and

WHEREAS, the Attorney General has determined that this Assurance is in the public interest.

IT IS HEREBY UNDERSTOOD AND AGREED, by and between the parties that:

IV. PROSPECTIVE RELIEF

A. Truthful Statements Regarding Addiction Risk And Crush Resistance

41. In the promotion and marketing of Opana ER, Endo shall maintain its policies prohibiting any written or oral claim that is false, misleading or deceptive. In particular, Endo shall not:

a. make statements that Opana ER or opioids generally are non-addictive.

b. make statements that most patients who take opioids do not become addicted, unless such statements are supported by competent and reliable evidence. If Endo believes that such evidence exists, it shall provide such evidence to the OAG at the time of initial dissemination of the statement, along with a copy of such statement.

c. make statements describing what most HCPs believe, unless such statements are supported by competent and reliable evidence. If Endo believes that such evidence exists, it shall provide such evidence to the OAG at the time of initial dissemination of the statement, along with a copy of such statement.

d. make statements that Reformulated Opana ER is, is designed to be, or is crush resistant, unless such statements are supported by the FDA-approved product labeling.

e. use the term “pseudoaddiction” in any training or marketing.

B. Truthful Disclosures Regarding Studies

42. Endo shall make available on its website truthful and balanced summaries of the results of all Endo-Sponsored Studies,[16] including studies regarding the purported tamper-resistant features of Reformulated Opana ER. These summaries shall take the form of a publication reference or link to a journal article, for published studies; a link to the relevant clinicaltrials.gov study record; or a copy of the clinical study report synopsis. Studies that are considered to be "Phase 1,"[17] if they do not concern the purported tamper-resistant features of Reformulated Opana ER, shall not be subject to the requirements of this Paragraph. Endo may redact from the summaries required by this paragraph (i) personal identification information; (ii) trade secret and confidential commercial information; and (iii) information that may provide a road map for defeating a product's abuse deterrent properties. Endo shall have a reasonable basis for any such redactions. Upon request, Endo shall provide the OAG and HCPs with un-redacted study summaries.

43. Endo shall (a) comply with the current version of the Academy of Managed Care Pharmacy Format for Formulary Submissions; and also (b) provide truthful and balanced summaries of the results of all Endo-Sponsored Studies regarding the purported tamper-resistant features of Reformulated Opana ER, in documents it provides to managed care companies summarizing its clinical research, such as Managed Care Dossiers. Studies that are considered to be Phase 1, if they do not concern the purported tamper-resistant features of Reformulated Opana

[16] The term "Endo Sponsored Studies" means pre-marketing clinical research and post-marketing clinical research that Endo "takes responsibility for and initiates" as "sponsor," as "sponsor" is defined in 21 C.F.R. § 312.3(b), and that involves an intervention with human subjects with an Opioid Medication. "Opioid Medications" as used in this Assurance means Opana ER and any other FDA-approved prescription drug that contains an opioid as an active pharmaceutical ingredient and is distributed by Endo within the United States.

[17] "Phase 1" shall mean, as defined in FDA regulations, studies concerning "the initial introduction of an investigational new drug into humans. . . . and . . . designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness." 21 C.F.R. § 312.21(a)(1).

ER, shall not be subject to the requirements of this Paragraph. Endo may redact from the summaries required by this paragraph (i) personal identification information; (ii) trade secret and confidential commercial information; and (iii) information that may provide a road map for defeating a product's abuse deterrent properties. Endo shall have a reasonable basis for any such redactions. Upon request, Endo shall provide the OAG and HCPs with un-redacted study summaries.

44. Endo shall comply with federal regulations regarding the registration of Endo-Sponsored Studies on the National Institutes of Health (NIH)-sponsored website (www.clinicaltrials.gov).

45. Endo shall continue its good faith efforts to publish information about the results of Endo-Sponsored Studies, not including Phase 1 studies, in peer-reviewed journals.

46. Endo shall maintain its policy of requiring all authors of articles about Endo-Sponsored Studies to disclose any Endo financial support for the study and any financial relationship with Endo (including any financial interest the author may have in Endo or an Endo product). Endo shall continue to require that an individual may be considered an "author" on a publication about Endo-Sponsored Studies only if the individual has made substantial contributions to the study and has given final approval to the version of the publication ultimately published. Endo shall maintain its policies and procedures that prohibit guest/honorary/gift authorship, ghostwriting, and plagiarism.

C. Establishment Of Abuse And Diversion Detection Program

47. Endo shall maintain and enhance its program consisting of internal procedures designed to identify potential abuse, diversion, or inappropriate prescribing of opioids (such enhanced program shall be referred to herein as the "ADD Program"), as set forth below. The

ADD Program shall remain in place for as long as Endo promotes Opioid Medications to HCPs through its sales representatives. Endo may seek modification of the ADD Program by sending a written request for modification to the OAG. The OAG shall give such petition reasonable consideration and shall respond to Endo within 30 days of receiving such request, but need not grant any such request.

48. The ADD Program shall apply to Endo sales representatives and medical liaisons who contact HCPs for the purpose of promoting Opioid Medications ("Endo Covered Persons"). The Program shall require those persons to file a written report (an "ADD Report") with Endo's Legal Department when they observe or learn of situations that may suggest that an HCP whom they contact for the purpose of promoting Opioid Medications may be involved in the abuse or diversion of opioids. Nothing in this paragraph shall be read as requiring Endo Covered Persons to perform tasks outside their regular duties. The ADD program shall specify that such facts may include but are not limited to the following examples:

a. An apparent pattern of an excessive number of patients for the practice type. For example: on a consistent basis, a long line of patients waiting to get prescriptions; a waiting room filled to capacity or standing room only; or patient contact with an HCP that is exceedingly brief or non-existent.

b. A pattern of prescribing outside the HCP office or after HCP office hours.

c. Information from a credible source or several sources (*e.g.*, pharmacists, law enforcement, or others) that an HCP or his/her patients are diverting medication.

d. An HCP who has a disproportionate number of patients who pay cash for office visits and dispensed medication.

e. An HCP with a sudden unexplained change in prescribing or dispensing patterns that are not accounted for by changes in patient numbers or the practice type.

f. A credible allegation that a HCP, staff or patient has abused or is actively abusing opioids.

g. An HCP's practice where unauthorized individuals are signing prescriptions or dispensing controlled substances.

h. An HCP's practice with large numbers of patients who travel significant distances, for example across state lines, to obtain and/or fill their prescriptions without a rational explanation.

i. An HCP's practice where there are reports that patients make frequent early requests for new prescriptions significantly in advance of the time the initial prescription would normally have been completed.

j. A credible allegation that an HCP is under active investigation related to diversion or substance abuse by any law enforcement or regulatory authority.

k. An HCP who moves his or her practice from one state to another on more than one occasion within a couple of years without rational explanation.

l. Facts that suggest that patients are seeking opioids for misuse and abuse, including but not limited to facts that suggest that an HCP has failed to comply with New York's Internet System for Tracking Over-Prescribing (I-STOP), which is New York's Prescription Drug Monitoring Program.

m. Drugs and doses being prescribed are not individualized.

n. Lack of qualified office staff, such as registered nurses or nurse practitioners.

o. Special entrance requirements to the practice and/or lack of signage.

p. Large distances between the doctor, patients and pharmacy.

q. A high frequency of prescriptions to replace lost prescriptions or medications.

r. A managed care organization excluded the HCP from writing prescriptions.

s. Law enforcement presence in or around the office.

t. HCP personally informs an Endo Covered Person that the HCP is no longer able to prescribe scheduled products.

49. The ADD Program shall contain the following elements:

a. When an ADD Report of potential abuse, diversion, or inappropriate prescribing of opioids involving an HCP with whom Endo Covered Persons interact is filed, Endo's Legal Department shall conduct an internal inquiry which shall include but not be limited to a review of the HCP's prescribing history and relevant facts about the HCP's practice. Endo shall then take such further steps as may be appropriate based on the facts and circumstances. Such further steps, if warranted by the facts and circumstances, shall include ceasing to promote Opioid Medications to the particular HCP or providing further education to the HCP about appropriate use of opioids.

b. When an ADD Report is filed about an individual HCP, the sales representative who filed that ADD Report shall immediately cease promoting Opioid Medications to that HCP, and Endo shall, as soon as practicable and in all events no later than ten (10) business days after the filing of such Report, place such HCP on an exclusion list (the "No-Call List"). Endo shall resume promoting Opioid Medications to an HCP placed on the No-Call List only after Endo's Legal Department ***in writing*** reasonably concludes, based on available information, that

it is appropriate to resume sales calls on that HCP. The HCP may then be removed from the No-Call List. If, after conducting its investigation, Endo's Legal Department determines that the HCP about whom an ADD Report has been filed should not thereafter be contacted for purposes of promoting Opioid Medications, that HCP shall remain on the No-Call List.

c. Endo shall implement and maintain a training and education program with respect to the ADD Program, which training shall cover the details of the ADD Program, and shall require all Endo Covered Persons to complete the training and education program no later than four (4) months after the Effective Date of this Assurance, and to complete the training each calendar year thereafter.

d. Prior to each call on an HCP, Endo Covered Persons shall check whether that HCP is on the No-Call List. If an Endo Covered Person promotes Opioid Medications to an HCP on the No-Call List, that individual shall be subject to review for potential disciplinary action, including but not limited to censure, probation and termination.

e. Endo may resume promoting Opioid Medications to an HCP about whom an ADD Report has been filed only after its Legal Department ***in writing*** reasonably concludes, based on available information, that it is appropriate to resume sales calls on that HCP.

f. Endo shall implement additional measures to identify HCPs who should be reviewed for potential placement on the No-Call List, including but not limited to reviewing, on a quarterly basis: (i) news media stories addressing the potential abuse, diversion, or inappropriate prescribing of opioids and/or the governmental

investigation and/or arrest of HCPs to whom Endo has promoted Opioid Medications; and (ii) data sources, such as HCPs' prescription history.

g. Endo's performance evaluations of Endo Covered Persons shall meaningfully take into account that sales representatives inform HCPs to whom the sales representatives promote Opioid Medications about their potential for abuse and diversion, and how to minimize those risks. No sales incentive (bonus) program for sales of Opioid Medications shall allow incentive credit to be earned for prescriptions by an HCP written after that HCP has been placed on the No-Call List.

h. If an Endo Covered Person fails to file an ADD Report regarding an HCP and Endo determines that that person knew or should have known that an HCP was engaged in conduct that should have been reported, that person shall be subject to disciplinary action by Endo, including but not limited to censure, probation and termination.

50. Endo Covered Persons in New York shall maintain records of sales calls to HCPs, and the Endo compliance department, in connection with Endo's Legal Department, shall, on at least a quarterly basis, audit and review a sample of such records to, *inter alia*, evaluate compliance with the ADD Program and determine whether ADD Reports need to be filed regarding particular HCPs. In creating such records of sales calls, Endo Covered Persons shall note topics related to their discussions with HCPs, which topics shall be drawn from a list provided by Endo, which topics shall include but not be limited to: (i) "facts suggesting potential abuse or diversion of opioids;" and (ii) "training regarding the appropriate prescribing of opioids."

51. Endo shall not employ a compensation structure for Endo Covered Persons in which more than 30% of the individual's total compensation (including bonus) is based on the volume of Opana ER prescriptions.

D. HCP Training

52. Endo Covered Persons shall, within four (4) months of the Effective Date and at the first visit each year thereafter, orally inform each New York HCP to whom Endo promotes Opioid Medications of the availability of training regarding the appropriate prescribing of opioids, the content of which is compliant with the FDA's Risk Evaluation and Mitigation Strategy ("REMS") for Extended Release/Long-Acting Opioids, and shall provide to HCPs written information about such training, in the form of the document set forth as Exhibit A.

E. Information About Treatment Resources

53. Endo shall make available and provide upon request, written information regarding the New York State HOPEline maintained by the Office of Alcoholism and Substance Abuse Services, to New York HCPs to whom it markets or promotes Opioid Medications. The HOPEline is a free, confidential number that provides general information regarding addiction treatment resources. The information described in this Paragraph shall be provided to Endo by the OAG, and is set forth as Exhibit B.

V. PENALTIES, FEES AND/OR COSTS

54. Within 30 days of the Effective Date, Endo shall pay $200,000.00 (two hundred thousand dollars) to the OAG for penalties, fees and/or costs of the OAG's investigation. Such sum shall be payable by check to "State of New York Department of Law."

VI. LIQUIDATED DAMAGES

55. If Endo violates any material provision of this Assurance, the OAG may elect to demand that Endo pay liquidated damages of $1,000 per episode of non-compliance. Before liquidated damages may be imposed, the OAG shall give Endo written notice that Endo may be subject to liquidated damages under this Paragraph. In the event that Endo does not cure the violation or provide the requested information within thirty (30) days of receipt of the OAG's written notice, the OAG may impose liquidated damages pursuant to this Paragraph. The damages period shall commence on the next business day after the period to cure has lapsed.

VII. COMPLIANCE

56. Within four (4) months of the Effective Date, Endo shall submit a detailed letter, along with supporting documentation, certifying its compliance with Paragraphs 41 through 54 of this Assurance. Endo shall then, on an annual basis for three years, certify in writing its continuing compliance with the provisions of this Assurance.

57. Internal Compliance Monitor: to evaluate the ADD Program, Endo shall appoint an Internal Compliance Monitor (the "Monitor"), who shall have the following duties:

a. Each year after the Effective Date, the Monitor shall provide the OAG with a written report (the "Monitor's Report") evaluating Endo's implementation of the ADD Program. The first Monitor's Report shall be due one (1) year after the Effective Date.

b. In compiling each Monitor's Report, the Monitor shall review information about Endo's implementation of the ADD Program, including but not limited to the following:

i. Training materials and sessions provided to Endo Covered Persons.

ii. ADD Reports filed by Endo Covered Persons.

iii. The final determination regarding each ADD Report and the reasonableness of Endo's determination regarding each Report.

iv. Endo's implementation of additional measures to identify HCPs who should be reviewed for potential placement on the No-Call List.

v. The evaluation by Endo's compliance department of Endo Covered Persons' records of sales calls.

vi. Endo's compensation structure for Endo Covered Persons.

c. In the Monitor's Reports, the Monitor shall evaluate Endo's compliance with Section IV.C. above and the reasonableness of Endo's decisions regarding whether to continue marketing or promoting Opioid Medications to the HCP identified in each ADD Report.

d. If, after the third Monitor's Report, the Monitor has concluded that Endo has complied with Section IV.C. above and has made reasonable determinations regarding whether to continue marketing or promoting Opioid Medications to HCPs about whom ADD Reports have been filed, the Monitor shall cease to function. If the Monitor has, in any of the Monitor's Reports, concluded that Endo has not complied with Section IV.C. above or has not made reasonable determinations regarding whether to continue marketing or promoting Opioid Medications to HCPs about whom ADD Report has been filed, it shall continue to function until such time as it concludes in a subsequent Monitor's Report that Endo is in compliance and has made reasonable determinations.

VIII. GENERAL PROVISIONS

58. Endo's Representations: The OAG has agreed to the terms of this Assurance based on, among other things, the representations made to the OAG by Endo and its counsel and the OAG's own factual investigation as set forth in the above Findings. To the extent that any material representations are later found to be inaccurate or misleading, this Assurance is voidable by the OAG in its sole discretion.

59. Communications: All communications, reports, correspondence, and payments that Endo submits to the OAG concerning this Assurance or any related issues is to be sent to the attention of the person identified below:

Michael Reisman, Esq.
Assistant Attorney General
Health Care Bureau
Office of the New York State Attorney General
120 Broadway
New York, New York 10271

60. Receipt by the OAG of materials referenced in this Assurance, with or without comment, shall not be deemed or construed as approval by the OAG of any of the materials, and Endo shall not make any representations to the contrary.

61. All notices, correspondence, and requests to Endo shall be directed as follows:

Jonathan L. Stern
Arnold & Porter LLP
601 Massachusetts Ave., NW
Washington, DC 20001-3743

Joshua M. Davis
Arnold & Porter LLP
601 Massachusetts Ave., NW
Washington, DC 20001-3743

62. Valid Grounds and Waiver: Endo hereby accepts the terms and conditions of this Assurance and waives any rights to challenge it in a proceeding under Article 78 of the Civil Practice Law and Rules or in any other action or proceeding.

63. No Deprivation of the Public's Rights: Nothing herein shall be construed to deprive any member or other person or entity of any private right under law or equity.

64. No Blanket Approval by the Attorney General of Endo's Practices: Acceptance of this Assurance by the OAG shall not be deemed or construed as approval by the OAG of any of Endo's acts or practices, or those of its agents or assigns, and none of them shall make any representation to the contrary.

65. Monitoring by the OAG: To the extent not already provided under this Assurance, Endo shall, upon request by the OAG, provide all documentation and information necessary for the OAG to verify compliance with this Assurance.[18] Endo may request an extension of particular deadlines under this Assurance, but OAG need not grant any such request. This Assurance does not in any way limit the OAG's right to obtain, by subpoena or by any other means permitted by law, documents, testimony, or other information.

66. No Limitation on the Attorney General's Authority: Nothing in this Assurance in any way limits the OAG's ability to investigate or take other action with respect to any non-compliance at any time by Endo with respect to this Assurance, or Endo's noncompliance with any applicable law with respect to any matters that are not part of the Covered Conduct.

[18] If Endo believes that documentation or information requested by the OAG pursuant to this Paragraph is protected by a privilege or other legal doctrine, and seeks to withhold such documentation or information, it shall provide a statement in writing under oath, stating: (a) the type of documentation or information withheld; (b) the date of documentation or information withheld; (c) the author and recipient of the documentation or information withheld; (d) the general subject matter of the documentation or information withheld; and (e) the legal ground for withholding the documentation or information. The OAG shall have the right to challenge any such withholding of documentation or information.

67. No Undercutting of Assurance: Endo shall not take any action or make any statement denying, directly or indirectly, the propriety of this Assurance or expressing the view that this Assurance is without factual basis. Nothing in this paragraph affects Endo's testimonial obligations, or right to take legal or factual positions in defense of litigation or other legal proceedings to which the OAG is not a party. This Assurance is not intended for use by any third party in any other proceeding and is not intended, and should not be construed, as an admission by Endo of any liability or finding set forth herein.

68. This Assurance shall be governed by the laws of the State of New York without regard to any conflict of laws principles.

69. If a court of competent jurisdiction determines that Endo has breached this Assurance, Endo shall pay to the OAG the cost, if any, of such determination and of enforcing this Assurance, including, without limitation, legal fees, expenses, and court costs.

70. None of the parties shall be considered to be the drafter of this Assurance or any provision for the purpose of any statute, case law, or rule of interpretation or construction that would or might cause any provision to be construed against the drafter hereof. This Assurance was drafted with substantial input by all parties and their counsel, and no reliance was placed on any representation other than those contained in this Assurance.

71. In the event that any one or more of the provisions contained in this Assurance shall for any reason be held to be invalid, illegal, or unenforceable in any respect, such invalidity, illegality, or unenforceability shall not affect any other provision of this Assurance.

72. No representation, inducement, promise, understanding, condition, or warranty not set forth in this Assurance has been made to or relied upon by Endo in agreeing to this Assurance.

73. This Assurance contains an entire, complete, and integrated statement of each and every term and provision agreed to by and among the parties, and the Assurance is not subject to any condition not provided for herein. This Assurance supersedes any prior agreements or understandings, whether written or oral, between and among the OAG and Endo regarding the subject matter of this Assurance.

74. This Assurance may not be amended or modified except in an instrument in writing signed on behalf of all the parties to this Assurance.

75. The division of this Assurance into sections and subsections and the use of captions and headings in connection herewith are solely for convenience and shall have no legal effect in construing the provisions of this Assurance.

76. Binding Effect: This Assurance is binding on and inures to the benefit of the parties to this Assurance and their respective successors and assigns, provided that no party, other than the OAG, may assign, delegate, or otherwise transfer any of its rights or obligations under this Assurance without prior written consent of the OAG.

77. Effective Date: This Assurance is effective on the date that it is signed by the Attorney General or his authorized representative (the "Effective Date"), and the document may be executed in counterparts, which shall all be deemed an original for all purposes.

AGREED TO BY THE PARTIES:

Dated: _____, 2016

ENDO HEALTH SOLUTIONS INC.
ENDO PHARMACEUTICALS INC.

By: _____
RAJIV DE SILVA, CEO

Dated: March 1, 2016

ERIC T. SCHNEIDERMAN
Attorney General of the State of New York

LISA LANDAU
Chief, Health Care Bureau

By: _____
Michael Reisman,
Assistant Attorney General

By: _____
Carol Hunt,
Assistant Attorney General

EXHIBIT A

ER/LA Opioid Analgesics REMS

The Extended-Release and Long-Acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS)

REMS-Compliant Prescriber Training

In 2007, Congress granted the FDA the authority to require manufacturers of medicinal products to implement a Risk Evaluation and Mitigation Strategy (REMS) if the FDA determines a REMS is necessary to ensure that a drug's benefits outweigh its risks. A REMS is a safety strategy required by the FDA from manufacturers to manage a known or potential serious risk associated with a medication and to enable patients to have continued access to such medications by managing their safe use.

FDA has required a shared REMS for all extended-release (ER) and long-acting (LA) opioid medications called the "ER/LA Opioid Analgesics REMS".

If you prescribe ER/LA opioid analgesics, FDA strongly encourages you to complete a REMS-compliant continuing education (CE) program that provides updated training on the risks and safe use of ER/LA opioids. Numerous CE activities that meet REMS standards (also known as "REMS-compliant CE") are currently available in both live and online formats. These activities are offered by accredited providers of CE at nominal or no cost to you. A listing of the ER/LA Opioid Analgesics REMS-compliant CE activities supported by the REMS Program Companies (RPC), a consortium of ER/LA opioid companies, can be found at: https://search.er-la-opioidrems.com/.

Providers of REMS-compliant CE adhere strictly to the accreditation standards of the Accreditation Council for Continuing Medical Education® (ACCME) or other CE accrediting bodies.

The REMS also includes a one-page document that prescribers can use to counsel patients on the risks and safe use of ER/LA opioid analgesics. This patient counseling document can be accessed at:
http://www.er-la-opioidrems.com/IwgUI/rems/pcd.action

EXHIBIT B

If you or someone you care about needs help for

HOPE / HELP

Drugs, Alcohol, Gambling

Call or Text

1-877-8-HOPENY

1-877-846-7369

Text: HOPENY (467369)

There is hope and help.

- All calls and texts are free and confidential
- 24 hours a day, 7 days a week
- Information and referrals from masters-level clinicians

NEW YORK STATE | **Office of Alcoholism and Substance Abuse Services**

Addiction Services for Prevention, Treatment, Recovery

www.oasas.ny.gov

EXHIBIT 70

PAINMEDICINE NEWS
ANESTHESIOLOGY NEWS

Supported by
ENDO PHARMACEUTICALS

FROM THE bench TO THE bedside

Case Challenges in Pain Management:
Opioid Therapy for Chronic Pain

CLINICAL EDITOR

CHARLES E. ARGOFF, MD
Assistant Professor Neurology
New York University School of Medicine
New York, New York

An estimated 50 to 60 million people in the United States suffer from chronic pain resulting from injury, bone and joint diseases, diabetes, infection, malignancy, and other conditions. Patients with uncontrolled chronic pain often are unable to meet the demands of their personal and professional lives; not surprisingly, chronic pain has been estimated to cost U.S. employers at least $61.2 billion per year in lost productivity, while expenditures on pain treatments may be as much as $1.5 billion globally.[1,2]

Opioids represent a highly effective but controversial and often misunderstood class of analgesic medications for controlling both chronic and acute pain. The phenomenon of tolerance to opioids—the gradual waning of relief at a given dose—and fears of abuse, diversion, and misuse of these medications by patients have led many clinicians to be wary of prescribing these drugs, and/or to restrict dosages to levels that may be insufficient to provide meaningful relief.[3]

Case 1

Success on Morphine Is Wearing Off

A right-handed 35-year-old woman with complex regional pain syndrome (CRPS) Type II, following a traumatic left brachial plexus avulsion injury 3 years ago, presents to your office for pain management. Upon interviewing her, you discover that the injury occurred following a boating accident, but there is no active litigation regarding this incident. She has seen a neurologist, physiatrist, orthopedist, and another interventional pain specialist. She reports having good relationships with these other physicians but was told by each of them that "nothing more" could be done for her. An electromyelography/nerve conduction velocity test conducted in the past supports the diagnosis of a left brachial plexopathy. Past treatments have included multiple sympathetic blocks (stellate as well as Bier blocks), spinal stimulator placement, cognitive behavioral therapy, physical therapy, and the use of multiple pharmacologic therapies (gabapentin, pregabalin [Lyrica, Pfizer], hydrocodone/ APAP, diclofenac, duloxetine, nortriptyline, tizanidine, baclofen, and mexiletine). These treatments either provided her with insufficient pain relief or were poorly tolerated. She is single, lives alone, and works as a customer service representative for an auto insurance company. Close family members live nearby; she describes them as supportive. She has an active social life.

The patient states that she is currently experiencing left shoulder and left upper extremity pain and that the left upper extremity is intermittently swollen, often ice cold—especially distally—and occasionally discolored. During the physical examination there is tenderness upon palpation of her left shoulder, but it cannot be fully evaluated because of the severe increase in left upper extremity pain that this causes. You cannot fully assess her left upper extremity function because of the pain associated with the examination. She has normally active reflexes, and the sensory examination demonstrates severe tactile allodynia and hyperalgesia in the left upper extremity in a non-dermatomal distribution. The remainder of her neurological examination is unremarkable. You concur with the diagnosis and order x-rays of the left shoulder, which are non-diagnostic.

In the past, the combined use of gabapentin and extended-release morphine had helped to decrease her pain from 9 on a scale of 10 (10 being the most excruciating pain imaginable) to 6 out of 10. She found this impact quite meaningful to her but recently, without any clear etiologies for such an exacerbation, her pain increased to an 8. She feels morphine is no longer working, and she cannot tolerate higher doses. She smokes half a pack of cigarettes a day, rarely uses alcohol, and has no history of aberrant behaviors while using morphine, nor is there a personal or family history of substance abuse. What other pharmacological therapies might be offered to her at this time?

The patient's pain syndrome has been responsive to opioids in the past, yet she has reached a point where her dose of morphine would need to be increased beyond tolerability. Since she is likely to require a combination of pharmacological therapies for her chronic neuropathic pain, and because she is likely to require such treatment for an extended period of time—given her history of CRPS Type II—the optimal therapy would be an extended-release opioid with a minimal potential for drug–drug interactions and a history of a durable response at an effective dose. The patient may therefore be a good candidate for oxymorphone.

Oxymorphone is a semi-synthetic opioid first approved by the FDA in 1959. An extended-release form of oxymorphone (Opana® ER, Endo Pharmaceuticals) was approved in June 2006 for use in patients with moderate to severe pain that requires continuous and long-term treatment. In a 12-week study of patients with chronic low back pain who were switched from their current opioid to Opana ER, treatment with extended-release oxymorphone led to clinically and statistically significant lower average pain intensity compared with placebo. Efficacy was maintained throughout the trial.[7]

Extended-release oxymorphone at clinically relevant doses has no significant cytochrome p450 (CYP450) activity, and recently published studies demonstrate that patients can successfully remain on a stable dose for up to 3 months or longer. Because the patient has had experience with hydrocodone and extended-release morphine, switching her to extended-release oxymorphone should be relatively straightforward. The conversion formula used in clinical trials and seen in the prescribing information of this agent would suggest starting this patient at one-third of the total daily morphine dose, split into 2 equal q12h doses of extended-release oxymorphone. Her dose may need to be titrated to a maximally effective level, and short-acting opioids should be used during the titration period for a smooth transition to extended-release oxymorphone.

Although opioids can be extremely efficacious for pain relief, they do not provide sufficient analgesia for many patients even at maximally tolerated doses. In addition, the use of opioids is associated with many potential adverse reactions, including nausea, vomiting constipation, thought and memory impairment, sedation, hypotension, and respiratory depression.[3] Hypogonadism has been observed in cancer patients with chronic exposure to opioids.[4] Pruritus also has been associated with opioid use, but in most patients is not a true allergic reaction.[5]

A given opioid may be initially ineffective, yet use of a different opioid may provide sufficient analgesia upon subsequent therapy. Although the risk of opioid side effects as listed above may be shared among all medications in this class, many patients find that they tolerate certain opioids better than others. These observations, along with substantial anecdotal evidence, support the practice of rotating opioid medications, both to improve the prospects of effective long-term treatment and to minimize the risk of adverse reactions.[6]

The following case studies illustrate patients for whom opioids, and in particular synthetic compounds, represent promising treatment options.

Case 2

The Opioid-Naïve Patient With a Long History of Inadequate Pain Control

A 58-year-old man presents to your office with 3 months of severe low back and right lower extremity pain. He has a known 8-year history of osteoarthritis affecting both shoulders, both hips, and both knees, and has taken over-the-counter and prescription non-steroidal anti-inflammatory drugs (NSAIDs), including celecoxib (Celebrex, Pfizer), for many years under the guidance of his internist and rheumatologist.

He has seen an orthopedist more than once, has undergone numerous x-ray examinations, and has been advised to undergo physical therapy and exercise for his multiple joint pains. He was advised that he was not a joint replacement candidate.

The patient has no other significant past medical or surgical history and continues to work despite his chronic pain complaints. He lives with his wife, has 2 grown children, does not smoke, and uses alcohol socially. He denies any personal or family history of substance abuse or known misuse.

When he was able to use NSAIDs, his osteoarthritis-related pain was bearable, and he continued to work as a computer consultant. However, he was hospitalized 1 year ago with a massive upper gastrointestinal bleed believed to be related to his protracted use of NSAIDs. Upon discharge, he was advised to discontinue and avoid use of these medications, including celecoxib.

He then began taking the dietary supplements glucosamine and chondroitin sulfate, but 6 months of daily therapy proved unhelpful.

He describes the pain in his lower back as "aching," "sharp," "dull," and "occasionally stabbing." The pain often radiates to his distal right lower extremity both at rest and with ambulation, and is often associated with burning and tingling in this extremity. He rates his pain as 8/10 most of the time. He denies loss of strength, loss of sensation, and bowel or bladder complaints. His internist does not find any loss of strength, loss of sensation, or reflex abnormalities on examining him. His lumbar spine is diffusely tender to palpation, with active myofascial dysfunction and painful muscle spasm demonstrated in both paralumbar regions. There is slight tenderness upon palpation of both sacroiliac joints, and straight-leg raising is positive at 75 degrees, with tightness reported in his hips at that point. His internist orders a magnetic resonance imaging scan of the lumbosacral spine, which shows diffuse degenerative disk disease and multiple osteophytes but no neural compression. Sacroiliac joint x-rays are negative. His neurological examination is normal with absent straight-leg raising. He does not want injection therapy. Physical therapy and past treatment with gabapentin, nortriptyline, metaxalone, and tizanidine at appropriate doses has not provided adequate relief. What other medical therapies might now be considered?

Although this patient has never taken an opioid, such a therapy should be considered. His pain is severe, and his risk for opioid abuse is low.

In a 12-week, randomized, placebo-controlled trial involving opioid-naïve patients with chronic low back pain, extended-release oxymorphone provided stable, durable analgesia for the duration of the study.[8] The substantial decreases in pain intensity (mean change approximately 47 mm) in stabilized patients reflected the success with Opana ER titration: starting with the lowest dose then titrating gradually.[8]

Discussion

Not all opioids interact uniformly with metabolic pathways regulated by the CYP450 system of isoenzymes.[9] As a result, in some patients, certain opioids may be more likely to cause drug–drug reactions that can weaken or magnify the effects of the medications they are taking for their underlying condition. Adams et al demonstrated that extended-release oxymorphone at therapeutic doses does not significantly alter the ability of two isoforms of CYP, CYP2C9 and CYP3A4, to metabolize tolbutamide or midazolam plus erythromycin—suggesting that oxymorphone ER is not likely to cause drug–drug interactions mediated by these two enzymes, and no evidence suggests such reactions involving other isoenzymes would occur.[9]

In addition, patients with underlying illness may be more likely to experience adverse events related to use of opioids. Stimulants and antipsychotic medications may be warranted to alleviate effects on the central nervous system.[5]

Finally, multimodal therapy—opioids as well as nonopioid analgesics and other pain treatments, as well as antidepressants for mood—should always be considered for patients with chronic pain.

While recognizing that use of opioids may be effective in the management of chronic pain, one must also recognize that not all opioids are equivalent with respect to metabolic issues as well as in durability of response and effectiveness when dosed as indicated. This should be kept in mind when one is prescribing opioids in order to maximize analgesia and minimize adverse effects for patients with chronic pain.

References:

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Indications

· OPANA® ER is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time

· OPANA® ER is not intended for use as a prn analgesic

· OPANA® ER is not indicated for pain in the immediate post-operative period (12–24 hours following surgery) for patients not previously taking opioids because of the risk of oversedation and respiratory depression requiring reversal with opioid antagonists

· OPANA® ER is not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time

Important Safety Information

OPANA® ER has a boxed warning as follows:

WARNING: OPANA® ER contains oxymorphone, which is a morphine-like opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics.

Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OPANA® ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OPANA® ER is an extended-release oral formulation of oxymorphone indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

OPANA® ER is NOT intended for use as a prn analgesic.

OPANA® ER TABLETS are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed OPANA® ER TABLETS leads to rapid release and absorption of a potentially fatal dose of oxymorphone.

Patients must not consume alcoholic beverages, or prescription or nonprescription medications containing alcohol, while on OPANA® ER therapy. The co-ingestion of alcohol with OPANA® ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

· OPANA® ER is **contraindicated** in patients with a known hypersensitivity to oxymorphone hydrochloride, morphine analogs such as codeine, or any of the other ingredients of OPANA® ER; in patients with moderate or severe hepatic impairment or in any situation where opioids are contraindicated such as: patients with or in unmonitored settings), acute or severe bronchial asthma, hypercarbia, and in any patient who has or is suspected of having paralytic ileus

· OPANA® ER is not indicated for pain in the immediate post-operative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OPANA® ER is only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate or severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (see American Pain Society guidelines)

· Respiratory depression is the chief hazard of OPANA® ER, particularly in elderly or debilitated patients. OPANA® ER should be administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, central nervous system (CNS) depression, or coma

· Patients receiving other opioid analgesics, general anesthetics, phenothiazines or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) may experience additive effects resulting in respiratory depression, hypotension, profound sedation, or coma

· OPANA® ER should be used with caution in elderly and debilitated patients and in patients who are known to be sensitive to CNS depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease. OPANA® ER should be used with caution in patients with mild hepatic impairment and in patients with moderate to severe renal impairment. These patients should be started cautiously with lower doses of OPANA® ER while carefully monitoring for side effects

· OPANA® ER is not indicated for preemptive analgesia (administration pre-operatively for the management of post-operative pain)

· The most common adverse drug reactions (≥10%) in all clinical trials for OPANA® ER were nausea, constipation, dizziness (excluding vertigo), vomiting, pruritus, somnolence, headache, increased sweating, and sedation

· Patients and their families should be instructed to flush any OPANA® ER tablets that are no longer needed

Please see the the Important Safety Information for OPANA® ER, including boxed WARNING, on this page and the accompanying full Prescribing Information.

OP-0144/April 2007

EXHIBIT 71

Understanding Your Pain

Taking Oral Opioid Analgesics

This brochure was developed by Margo McCaffery, RN, MS, FAAN, and Chris Pasero, RN, MS, FAAN authors of *Pain: Clinical Manual* (2nd ed. Mosby; 1999). Edited by Russell K. Portenoy, MD.

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 PM-0120

The information contained in this brochure does not take the place of talking with your healthcare provider about your pain and your pain medications.

Taking Oral Opioid Analgesics

What are opioid analgesics?

Opioid (oh'-pea-oyd) analgesics used to be called narcotics, but today the correct term for these pain medicines is opioids. Opioids are one type of pain medicine; another type is nonopioids which includes medicines like acetaminophen (such as Tylenol® tablets, caplets, or gelcaps) and ibuprofen (such as Motrin® IB tablets, caplets, or gelcaps). Nonopioids are generally used to treat mild pain, whereas opioid analgesics are used to treat moderate to severe pain.

Like all medicines, only the person who is prescribed opioids should take them. They should be kept in a safe place where children and others cannot reach them.

Opioids may be given by mouth, by injection into the muscle, vein, or spine, or by other methods. The most common and convenient way to take opioids is by mouth (known as oral opioids). Most oral opioids are available as pills; some are available as liquids. In this brochure, we will discuss the pills.

How long does pain relief from an oral opioid last?

Opioids may be short-acting or long-acting.

Short-acting opioids are sometimes called immediate release. These opioids usually have an effect within an hour and relieve pain for about 4 hours.

- Short-acting opioids are usually taken when pain lasts only a few days.
- Examples of oral short-acting opioids:
  - codeine (as in Tylenol #3® tablets)
  - hydrocodone (as in Zydone® tablets or Vicodin® tablets)
  - hydromorphone (such as Dilaudid® tablets)
  - morphine (such as MSIR® tablets or capsules)
  - oxycodone (as in Percocet® tablets, Tylox® capsules, or Roxicodone® tablets or oral solution)
  - propoxyphene (as in Darvon® capsules or Darvocet-N® tablets)
- Some short-acting opioid medicines contain the opioid alone while others contain a combination of an opioid and a nonopioid, often acetaminophen (such as Tylenol® tablets, caplets or gelcaps). For example, oxycodone may be given alone (such as Roxicodone® tablets or oral solution) or in combination with acetaminophen as in Percocet® tablets.

- When an opioid is combined with acetaminophen, the total dose of acetaminophen taken in one day should not be more than 4000 mg. Higher doses could damage your liver. People who have liver disease or drink alcohol heavily should take even less acetaminophen. Be aware of how much acetaminophen is in your medicine, both prescribed medicine and medicine you get without a prescription, such as cold remedies.

Long-acting forms of opioids are sometimes called controlled-release or extended-release. This means the medicine is gradually released into the body over an 8 to 12 hour period or longer.

- Long-acting opioids are usually used for chronic pain that lasts most of the day. They are taken at regularly scheduled times, such as every 12 hours. In addition, a short-acting pain medicine is usually prescribed at the same time, with instruction to take a dose as needed should the pain temporarily increase.
- Examples of oral long-acting opioids:
  morphine
  (such as Oramorph® tablets, MS Contin® tablets, or Avinza® capsules)
  oxycodone
  (such as OxyContin® tablets)

What should I know about opioids and addiction?

You or your family may have questions about addiction. It is important to understand what addiction is. Addiction **IS** a chronic brain disease that can occur in some people exposed to certain substances such as alcohol, cocaine, and opioids. Taking opioids for pain relief is not addiction. People addicted to opioids crave the opioid and use it regularly for reasons other than pain relief.

Addiction **IS NOT** when a person develops "withdrawal" (such as abdominal cramping or sweating) after the medicine is stopped quickly or the dose is reduced by a large amount. Your doctor will avoid stopping your medication suddenly by slowly reducing the amount of opioid you take before the medicine is completely stopped. Addiction also **IS NOT** what happens when some people taking opioids need to take a higher dose after a period of time in order for it to continue to relieve their pain. This normal "tolerance" to opioid medications doesn't affect everyone who takes them and does not, by itself, imply addiction. If tolerance does occur, it does not mean you will "run out" of pain relief. Your dose can be adjusted or another medicine can be prescribed.

Some questions you may have are:

Is it wrong to take opioids for pain?

- No. Pain relief is an important medical reason to take opioids as prescribed by your doctor. Addicts take opioids for other reasons, such as unbearable emotional problems. Taking opioids as prescribed for pain relief is not addiction.

How can I be sure I'm not addicted?

- Addiction to an opioid would mean that your pain has gone away but you still take the medicine regularly when you don't need it for pain, maybe just to escape from your problems.
- Ask yourself: Would I want to take this medicine if my pain went away? If you answer no, you are taking opioids for the right reasons—to relieve your pain and improve your function. You are not addicted.

If I take the opioid now, will it work later when I really need it?

Some patients with chronic pain worry about this, but it is not a problem.

- The dose can be increased or other medicines can be added.
- You won't "run out" of pain relief.

What can I do about side effects?

Talk to your doctor, nurse, or pharmacist about the side effects of opioids. If they occur, remember that most opioid side effects can be treated or prevented.

Constipation

- Constipation from opioids is very common, but it can be prevented. If it does occur, it can be treated.
- Prevention is the best approach. If you take opioids daily, you need to eat more fiber and drink more liquids than you usually do. Many people also need to take a laxative. The most common type is a combination of stool softener and mild stimulant laxative. Those that can be purchased without a prescription include Peri-Colace® capsules or syrup and Senokot-S® tablets. Ask your pharmacist about less expensive generic forms.

Nausea or vomiting (upset stomach)

- This does not always occur, but if it does, it can be treated. Ask your doctor, nurse, or pharmacist for medicine to relieve this. After a few days, the nausea usually stops.
- Try sitting still and breathing slowly through your mouth.
- Nausea medicines that you can buy without a prescription include Dramamine® tablets and Emetrol® oral solution.
- If your pain is under good control, you may be able to reduce the nausea by taking a lower dose of opioid.

Drowsiness (sleepiness)

- Some degree of sleepiness would be normal when you start taking an opioid, but after a few days the drowsiness usually goes away.

- To offset the drowsiness, try beverages that contain caffeine, such as coffee or sodas.
- If your pain is under good control, you may be able to reduce the drowsiness by taking a lower dose of opioid.
- Be careful. If you feel drowsy, do not drive a car or operate any dangerous machinery. Steady yourself when you walk.

"Slowed breathing"

- The medical term for "slowed breathing" is "respiratory depression."
- This is very rare when oral opioids are used appropriately for pain relief.
- If you become so sleepy that you cannot make yourself stay awake, you may be in danger of slowed breathing. Stop taking your opioid and call your doctor immediately.

How much and how often should I take my pain medicine?

Keep on top of your pain—don't wait until pain becomes severe to take your medicine. Pain is easier to control before it reaches full force. Set a goal with your doctor or nurse for pain relief that makes it easy for you to sleep at night and to do your daily activities.

Plan a schedule with your doctor or nurse that provides enough pain medicine to keep you comfortable and that is timed to prevent you from becoming uncomfortable from pain. *Only you and your doctor or nurse can determine the proper dosing schedule for your pain.*

Your doctor or nurse may instruct you to do some of the following:

- Take the next dose before the last dose wears off. If pain is present most of the day and night, the pain medicine may be taken at regularly scheduled times. If you are taking a short-acting opioid, this usually means taking it every 4 hours. You may need to set your alarm, especially at night, to be sure you take your dose before the pain returns and wakes you up.
- If your pain comes and goes, take your pain medicine when pain first begins, before it becomes severe.
- If you are taking a long-acting opioid, you may only need to take it every 8 to 12 hours, but you may also need to take a short-acting opioid in between for any increase in pain.
- If you take an opioid regularly for longer than a week, don't suddenly stop taking it. When your therapy is complete, your doctor will slowly decrease your dose safely.

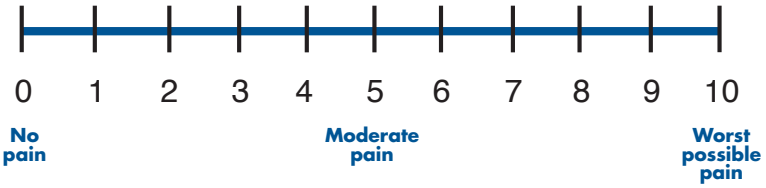
If you need to take more or less pain medicine than planned, contact your doctor to get the plan changed.

Keeping track of your pain

- Try using the "Pain Control Record" on the last page if you have any difficulty getting relief from your pain. This will help you keep track of how well your pain medicines are working and may make it easier to explain problems to your doctor or nurse.
- Use a pain rating scale. Most people use the 0 to 10 scale or the faces scale to rate the intensity of their pain (see below).
- Set a goal for pain relief. Ask yourself what activities you need to do, such as getting out of bed, sleeping, or walking. Then decide what pain rating will make it easy for you to carry out those activities. Everyone is different, but many people need a pain rating of 3 or less to be able to function well.

  See completed "Pain Control Record" on the next page for an example.

0-10 Numeric Pain Rating Scale



Faces Pain Rating Scale†

†Adapted from McCaffery M, Pasero C. *Pain: Clinical Manual*, 1999: p. 67, Mosby, Inc. Faces pain rating scale modified from Wong DL. *Whaley & Wong's Essentials of Pediatric Nursing*, 5th ed., 1997: pp. 1215-1216, Mosby, Inc.

Example: Pain Control Record

This is a record of how your pain medicines are working. Please keep this record until you and your nurse/doctor find the dose and frequency of medicine that provides satisfactory pain relief for you most of the time. After that, you only need to keep this record when you have problems related to your pain medicines.

Name: John Date: Tuesday

GOALS Satisfactory pain rating: 3 Activities: care for self—perform prescribed exercises

Prescription: oxycodone 5mg every 4 hours as needed

My pain rating scale:

0 1 2 3 4 5 6 7 8 9 10

NO PAIN — MODERATE PAIN — WORST POSSIBLE PAIN

Directions: Rate your pain before you take pain medication and 1 to 2 hours later.

Time	Pain Rating	Medicine I took:	Side Effects (drowsy? upset stomach?)	Activities
6 am	6	oxycodone 5mg		
8 am	3		no	shower, exercises
10 am	4	oxycodone 5mg		

EXAMPLE

If pain is greater than 6, or if you have other problems with your pain medicine, call:

Nurse: Name/phone Steve Jones 555-1111

Doctor: Name/phone Anne Smith 555-2222

Adapted with permission from McCaffery M, Pasero C: Pain: Clinical Manual, Mosby, p.87.

The example on this page shows that the pain medicine worked to relieve the pain to the patient's goal of 3 and allowed the patient to perform the necessary activities. This patient does not need to continue to use the pain control record because the pain medicine was successful. If it had not relieved the pain down to the goal of 3 or if the patient could not perform the activities because of pain, continued use of the record would help decide what additional pain relief is necessary.

Pain Control Record

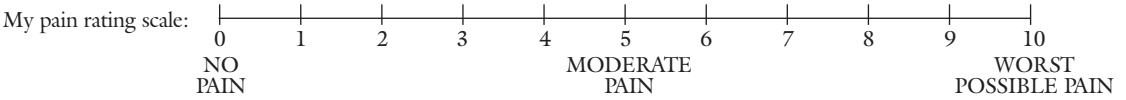
(May be copied for future use.)

This is a record of how your pain medicines are working. Please keep this record until you and your nurse/doctor find the dose and frequency of medicine that provides satisfactory pain relief for you most of the time. After that, you only need to keep this record when you have problems related to your pain medicines.

Name: _____ Date: _____

GOALS Satisfactory pain rating: _____ Activities: _____

Prescription: _____ _____



Directions: Rate your pain before you take pain medication and 1 to 2 hours later.

Time	Pain Rating	Medicine I took:	Side Effects (drowsy? upset stomach?)	Activities

If pain is greater than _____, or if you have other problems with your pain medicine, call:

Nurse: Name/phone _____

Doctor: Name/phone _____

Adapted with permission from McCaffery M, Pasero C: Pain: Clinical Manual, Mosby, p.87.

EXHIBIT 72

Resources for Education on Pain and Its Management: A Practitioner's Compendium

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Knowing enough information about pain and its management to adequately care for people in pain may seem challenging, especially for primary care providers who provide the bulk of pain management services in the United States. Few, if any, primary care providers received training beyond the names of a few analgesics and the rudiments of pain assessments. Fortunately, many national and international societies provide health care practitioners with pain-related education, resources, and tools. Education may be tied to pain certification or specialization, or provided solely for the benefit of practitioners. Due in large part to the World Wide Web, much information about pain is readily available online.

Introduction

The need to know about managing pain has grown beyond traditional pain specialists (mostly anesthesiologists, along with some neurologists, physiatrists, and psychiatrists) to primary care providers (eg, family physicians, internists, nurse practitioners, physician assistants) [1••]. Very few health care providers, including practicing pain specialists, have received formal pain education as part of a defined pain fellowship, and most do what they can for their patients by extrapolating beyond the minimal training they received during their years of professional training [2••]. For most practitioners, what they know about pain and its management comes from continuing education (CE) programs, articles in pain-related publications, promotional presentations, pharmaceutical detailing, advertisements, and word-of-mouth from peers and patients [3••].

With no single source of information about pain that is universally recognized, most practitioners do what they can to keep abreast of the latest information relative to their primary discipline and/or specialty. An article such as this one is intended to provide a brief historical overview of pain education, linkages between education and certification/credentialing, useful sources of pain information, information about the many pain organizations, and trends in continuing professional education. Examples are provided in the following sections and their associated tables, with these intended to be illustrative but not "all inclusive" (Table 1 and Table 2). What follows is one pain educator's take on the world of pain education and information in late 2008.

Overview of Pain Education in the United States

Pain education occurs at two fundamentally different levels: professional and lay. Professional pain education is intended for health care practitioners, directed to allied therapists (occupational and physical), nurses (practical/vocational, registered, and advanced practice), pharmacists (hospital and retail), physicians, physician assistants, psychologists, social workers, and others [4,5]. Lay pain education is directed to patients and their family members and caregivers, or to the general public. Although there is considerable overlap in the subject matter at the conceptual level, there are distinct educational differences between professional and lay learners about pain and its management. No single pain education program is adequate for all audiences, especially when looking at the learning needs of each of the two major groups. Practitioners need to know what to do for the people they care for, and those in pain need to find answers, practical advice and solutions, and "how to" tips for negotiating the medical system.

For health care professionals, pain-related membership organizations offer the bulk of pain education in the United States. The American Academy of Pain Management (AAP-

Table 1. Pain organizations and useful websites

Pain organizations having an emphasis on pain education
American Academy of Orofacial Pain (www.aaop.org)*
American Academy of Pain Management (www.aapainmanage.org) †
American Academy of Pain Medicine (www.painmed.org) ‡
American Pain Society (www.ampainsoc.org)*
American Society of Interventional Pain Physicians (www.asipp.org) ‡
American Society of Pain Educators (www.paineducators.org) †
American Society of Pain Management Nurses (www.aspmn.org) ‡
American Society of Regional Anesthesia and Pain Medicine (www.asra.com)*
Canadian Pain Society (www.canadianpainsociety.ca)*
International Association for the Study of Pain (www.iasp-pain.org)*
International MYOPAIN Society (www.myopain.org)*
Society for Pain Practice Management (www.sppm.org)*
Disease/syndrome-specific organizations with information about their condition
American Arthritis Society (www.americanarthritis.org)
American Cancer Society (www.acs.org)
American Headache Society (www.americanheadachesociety.org)
National Fibromyalgia Research Association (www.nfra.nt)
National Vulvodynia Association (www.nva.org)
Reflex Sympathetic Dystrophy Syndrome Association (www.rsds.org)
Trigeminal Neuralgia Association (www.endthepain.org)
Pain advocacy groups providing information for the public and professionals
American Chronic Pain Association (www.theacpa.org)
American Pain Foundation (www.painfoundation.org)
Arthritis Foundation (www.arthritis.org)
National Fibromyalgia Association (www.fmaware.org)
National Headache Foundation (www.headaches.org)
National Pain Foundation (www.nationalpainfoundation.org)
Neuropathic Pain Network (www.neuropathicpainnetwork.org)
Race Against Pain (www.raceagainstpain.com)
The Neuropathy Association (www.neuropathy.org)
Pharmaceutically supported websites providing pain education/information
Chronic Pain Network ([King Pharmaceuticals, Inc., Bristol, TN]; www.chronicpainnetwork.com)
Emerging Solutions in Pain ([Cephalon, Inc., Frazer, PA]; www.emergingsolutionsinpain.com)
Pain Balance ([Alpharma Inc., Bridgewater, NJ]; www.painbalance.org)
PainEDU ([Endo Pharmaceuticals, Chadds Ford, PA, and King Pharmaceuticals, Inc.]; www.painedu.org)
Pain Knowledge ([Endo Pharmaceuticals]; www.painknowledge.org)
Partners Against Pain ([Purdue Pharma LP, Stamford, CT]; www.partnersagainstpain.com)

*Provides an annual/biennial/triennial meeting or more specifically addresses pain and its management.
†Provides credentialing/certification in pain management/medicine or pain education.
‡Provides preparation for another entity granting credentialing/certification in pain.

Man) partners with CECity to offer online pain education through its Learning Center in addition to the content of its Annual Clinical Meeting and various CE offerings in its publication, The Pain Practitioner [6]. The American Academy of Pain Medicine (AAPMed) says that as the "voice of pain care professionals everywhere," it provides

Table 2. Useful publications

Publications for opioid prescribers (sponsoring/granting entity, year of publication)
Responsible Opioid Prescribing: A Physician's Guide (Federation of State Medical Boards, 2007)
Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain , 5th Edn (American Pain Society, 2003)
Practitioner's Manual (Drug Enforcement Administration, Office of Diversion Control, 2006)
Pharmacist's Manual (Drug Enforcement Administration, Office of Diversion Control, 2004)
PainEdu.org Manual (PainEdu.org with a grant from Endo Pharmaceuticals [Chadds Ford, PA], 2007)
A Practical Guide for Prescribing Controlled Substances (Alpharma Inc. [Bridgewater, NJ], 2007)
A Clinical Guide to Opioid Analgesia (Vendome Group LLC [New York, NY] with a grant from Endo Pharmaceuticals, 2007)
Major comprehensive pain textbooks (first editor/author, year of publication)
Bonica's Pain Management , 3rd Edn (Loeser JD, 2001)
Principles and Practice of Pain Medicine , 2nd Edn (Warfield CA, 2004)
Raj's Practical Management of Pain , 4th Edn (Benzon HT, 2008)
Wall and Melzack's Textbook of Pain , 5th Edn (McMahon SB, 2006)
Weiner's Pain Management: A Practical Guide for Clinicians , 7th Edn (Boswell MV, 2006)
Useful pain books, not textbooks (first editor/author, year of publication)
Atlas of Common Pain Syndromes , 2nd Edn (Waldman SD, 2008)
Atlas of Uncommon Pain Syndromes , 2nd Edn (Waldman SD, 2008)
Clinical Manual of Pain Management in Psychiatry (Leo RJ, 2007)
Clinical Pain Management: Acute Pain (Rowbotham DJ, 2003)*
Clinical Pain Management: Cancer Pain (Sykes N, 2003)*
Clinical Pain Management: Chronic Pain (Jensen TS, 2003)*
Clinical Pain Management: Practical Applications and Procedures (Breivik H, 2003)*
Decision Making in Pain Management , 2nd Edn (Ramamurthy S, 2006)
Ethical Issues in Chronic Pain Management (Schatman ME, 2007)
Pain Medicine: A Comprehensive Review , 2nd Edn (Raj PP, 2003)
Pelvic Pain: Diagnosis and Management (Howard FM, 2000) †
Physical Diagnosis of Pain: An Atlas of Signs and Symptoms (Waldman SD, 2006)
The Massachusetts General Hospital Handbook of Pain Management , 2nd Edn (Ballantyne J, 2002)
The Pain Clinic Manual , 2nd Edn (Abram SE, 2000)
Travell and Simons' Myofascial Pain and Dysfunction: The Trigger Point Manual Volume 1, Upper Half of Body , 2nd Edn (Simons DG, 1999)
Travell and Simons' Myofascial Pain and Dysfunction: The Trigger Point Manual Volume 2, The Lower Extremities (Simons DG, 1992) ‡

*A new edition is expected in late 2008.
†A new edition is expected in early 2009.
‡A new edition is expected (date remains unknown).
§Atlases by Walden listed in this section accompany this book.
¶No new edition since 1998, so dated.

"premier . . . educational opportunities for pain specialists and nonspecialists alike" through its publications, newsletters, and Annual Meeting [7]. The American Pain Society (APS) provides practitioner education through its Annual Scientific Meeting, numerous publications, and consensus clinical practice guidelines [8]. The American Society of Pain Educators (ASPE) holds an annual Pain Educators Forum specifically addressing education from the perspective of pain educators and posts many of its presentations online, along with disseminating information through its publications [9]. Dental, medical, nursing, and pharmacy societies include pain-related articles in their organizations' publications, offer pain lectures and pain-themed tracks at their annual meetings, and have pain materials available on their websites. Many easily accessible learning opportunities are available for health care professionals interested in knowing more about pain regardless of their discipline.

Table 2. Useful publications (Continued)

Clinically useful volumes from the Progress in Pain Research and Management series and more recent publications from IASP Press (first editor/author, year of publication)
Molecular Neurobiology of Pain , Vol. 9 (Borsook D, 1997)
Sickle Cell Pain , Vol. 11 (Ballas SK, 1998)
Assessment and Treatment of Cancer Pain , Vol. 12 (Payne R, 1998)
Opioid Sensitivity of Chronic Noncancer Pain , Vol. 14 (Kalso E, 1999)
Sex, Gender, and Pain , Vol. 17 (Fillingim RB, 2000)
Neuropathic Pain , Vol. 21 (Hansson PT, 2001)
Spinal Cord Injury Pain , Vol. 23 (Yezierski RP, 2002)
Opioids and Pain Relief , Vol. 25 (Meldrum ML, 2003)
Psychosocial Aspects of Pain , Vol. 27 (Dworkin RH, 2004)
The Genetics of Pain , Vol. 28 (Mogil JS, 2004)
Psychosocial Methods of Pain Control , Vol. 29 (Price DD, 2004)
Hyperalgesia , Vol. 30 (Brune K, 2004)
CRPS , Vol. 32 (Wilson PR, 2005)
Pain in Older Persons , Vol. 35 (Gibson SJ, 2005)
Emerging Strategies for the Treatment of Neuropathic Pain (Campbell JN, 2006)
Central Neuropathic Pain: Focus on Poststroke Pain (Henry JL, 2007)
Sleep and Pain (Lavigne G, 2007)
Interventional pain textbooks and atlases (first editor/author, year of publication)
Atlas of Interventional Pain Management , 2nd Edn (Waldman SD, 2004)
Atlas of Pain Management Injection Techniques , 2nd Edn (Waldman SD, 2007)
Interventional Pain Management , 2nd Edn (Waldman SD, 2001) §
Interventional Pain Management: Low Back Pain—Diagnosis and Treatment (Manchikanti L, 2002)
Interventional Radiology in Pain Treatment (Kastler B, 2006)
Neural Blockage in Clinical Anesthesia and Management of Pain , 3rd Edn (Cousins MJ, 1998) ¶
Textbook of Regional Anesthesia and Acute Pain Management (Hadzic A, 2006)

*A new edition is expected in late 2008.
†A new edition is expected in early 2009.
‡A new edition is expected (date remains unknown).
§Atlases by Walden listed in this section accompany this book.
¶No new edition since 1998, so dated.

For lay people, pain education is commonly tied to the provision of treatment and improving treatment outcome [10–12]. Through pain-related education about specific treatment options, informed consent is obtained (not just for interventional methods, but increasingly for the use of opioids and other services), treatment adherence is improved through better understanding about the purpose for the therapy, and treatment compliance is enhanced (leading to better outcome). Several pain advocacy organizations for pain sufferers (eg, American Pain Foundation, National Pain Foundation, National Fibromyalgia Association) offer lay education, serve as information clearinghouses and referral centers for the public, and help those in pain connect with willing providers. Some professional groups maintain portals for the public to use when visiting their websites, allowing lay people to learn more about pain and its control.

Linkages Between Pain Education and Certification/Credentialing

For health care professionals, lifelong learning is expected. Information changes rapidly, and most health care providers have licensure requirements for continuing education. In very few states is pain knowledge specifically mandated, but over the past decade some states have required pain education as a condition for license renewal. California requires medical students to receive formal education about pain during medical school (in 1999, AB 791 amended Business and Professions Code section 20890 [13]) and all medical license holders (except for pathologists and radiologists) to obtain 12 hours of pain education once (in 2001, AB 487 amended Business and Professions Code section 2190.5) [14]. Oregon

Table 2. Useful publications (Continued)

Peer-reviewed pain journals and magazines (sponsoring organization)
Acute Pain (affiliated with the Special Interest Group on Acute Pain of the International Association for the Study of Pain)
Clinical Journal of Pain (Eastern Pain Association)
European Journal of Pain (European Federation of Chapters of the International Association for the Study of Pain)
Journal of Musculoskeletal Pain (International MYOPAIN Society)
Journal of Pain (American Pain Society)
Journal of Pain and Palliative Care Pharmacotherapy
Journal of Pain and Symptom Management (American Academy of Hospice and Palliative Medicine)
Journal of Opioid Management
Journal of Orofacial Pain (American Academy of Orofacial Pain)
Molecular Pain
Pain (International Association for the Study of Pain)
Pain Management Nursing (American Society of Pain Management Nurses)
Pain Medicine (American Academy of Pain Medicine)
Pain Physician (American Society of Interventional Pain Physicians)
Pain Research & Management (Canadian Pain Society)
Regional Anesthesia and Pain Medicine (American Society of Pain Management Nurses)
Techniques in Regional Anesthesia and Pain Management
Non–peer-reviewed pain publications (sponsoring organization)
Current Pain & Headache Reports
The Pain Practitioner (American Academy of Pain Management)
Practical Pain Management
PainView (American Society of Pain Educators)
Pain Medicine News
MDNG: Pain Management

*A new edition is expected in late 2008.
†A new edition is expected in early 2009.
‡A new edition is expected (date remains unknown).
§Atlases by Walden listed in this section accompany this book.
¶No new edition since 1998, so dated.

mandates that all health care providers obtain 7 hours of pain education once (in 2001, SB 885 created the Oregon Pain Management Commission and the "one-time only" pain management CE requirement tied to health care providers' license renewals) [15]. These mandated pain education requirements have not yet become requirements in most other jurisdictions, but suggest the need for more organized pain education during professional training and practice.

For health care professionals interested in highly specializing in pain management/medicine, there are formal pain fellowships commonly lasting for 12 to 24 months. However, most pain practitioners acquire pain education less formally. Beyond fulfilling the CE requirements for their license renewal, many pain professionals obtain CE in pain as part of their process of self-specialization, thereby enhancing their professional credibility. Many national pain organizations (eg, AAPMan, AAPMed, American Society of Interventional Pain Physicians [ASIPP] [16], ASPE, American Society of Pain Management Nurses [ASPMN] [17]) provide curriculum intended to improve one's likelihood of passing a certification/credentialing examination offered directly by the organization itself or some other entity doing so (eg, American Board of Medical Specialties' [ABMS] constituent boards in anesthesia, neurology, physical medicine and rehabilitation, and psychiatry; American Board of Pain Medicine [ABPM]; American Board of Interventional Pain Physicians [ABIPP]; and American Nurses Credentialing Center [ANCC]). Although voluntary certification/credentialing does not prove that someone is the best pain practitioner, it does demonstrate a commitment to professionalism and sets the holder of such a credential apart from those unwilling or unable to become certified.

Although certification/credentialing may be necessary for pain professionals, there is no equivalent for the

lay community required or recommended. With "peer counselors" as the best example, the degree of training for them is ill defined for the most part and defined by the organizations they represent. This does not mean that peers providing pain information through national advocacy groups lack formal training, but that information about their training is not well defined or consistent.

Useful Sources of Pain Information

Many pain organizations offer annual meetings, websites with useful resources, and publications with research articles and current news. Pharmaceutical companies with pain medications maintain "objective" websites, support CE programs, underwrite national and regional conferences, and distribute nonbranded disease state publications. Although the national pain organizations universally accept financial support from the pharmaceutical companies, as nonprofit groups (some with provider status with the Accreditation Council for Continuing Medical Education [ACCME] or parallel bodies for nurses, pharmacists, and others), they provide curriculum that is less biased. Manufacturers historically support education that has some connection to their therapeutic area. In recent years, there has been much concern about the potentially self-serving nature of education provided by manufacturers and resistance on the part of health care professionals to shoulder the real costs associated with unsupported educational offerings. Finding the balance between industry support and scientific knowledge has proved vexing and may lead to significant changes in the way education is provided.

Pain organizations

American Academy of Orofacial Pain (AAOP) is the professional organization for orofacial pain specialists, most of whom are dentists. Organizationally, the AAOP is dedicated to the alleviating of pain and suffering through the promotion of excellence in education, research, and patient care in the field of orofacial pain and associated disorders. It holds an annual Scientific Meeting each spring and publishes the Journal of Orofacial Pain [18].

AAPMan is the inclusive, interdisciplinary organization serving clinicians who treat people with pain through education, setting standards of care, and advocacy. It provides continuing education for acupuncturists, allopathic physicians (including family physicians), athletic trainers, chiropractors, counselors, dentists, nurses, nurse anesthetists, pharmacists, physical therapists, psychologists, social workers, and others as an approved provider or a cosponsor with other bodies. It holds an annual Clinical Meeting each fall and publishes The Pain Practitioner [6]. Through its Learning Center, members may obtain CE offerings "on demand." In the past, AAPMan published the American Journal of Pain Management .

AAPMed is the medical specialty society representing physicians practicing in the field of pain medicine; it is involved in education, training, advocacy, and research in the specialty of pain medicine. The group describes itself as multidisciplinary in approach, incorporating modalities from various medical specialties to ensure the comprehensive evaluation and treatment of the pain patient. It holds an Annual Meeting each winter and publishes a monthly journal, Pain Medicine [7]. Through its efforts, the ABPM was created and offers certification for allopathic and osteopathic physicians who have done allopathic residency programs and are now Board Certified by the ABMS.

American Pain Society (APS, a national chapter of the International Association for the Study of Pain [IASP] and the parent organization for several regional chapters within the United States) is a multidisciplinary community that brings together a diverse group of scientists, clinicians, and other professionals to increase the knowledge of pain and transform public policy and clinical practice to reduce pain-related suffering. APS is the most research oriented of the US pain organizations. It holds an annual Scientific Meeting each spring and publishes its Journal of Pain monthly. In the past 4 years, APS has continued the work started by the former Agency for Health Care Policy and Research and has issued several pain guidelines, including Management of Cancer Pain in Adults and Children ; Management of Fibromyalgia Syndrome Pain in Adults and Children ; Management of Pain in Osteoarthritis ; Rheumatoid Arthritis and Juvenile Chronic Arthritis ; and Management of Acute and Chronic Pain in Sickle-Cell Disease [8].

ASIPP is an organization representing interventional pain physicians. It publishes the Pain Physician monthly and issues practice guidelines frequently. The organization offers a variety of live meetings focusing on specific interventional methods of pain control (eg, spinal cord stimulation, intrathecal pumps, vertebroplasty, kyphoplasty, sacroplasty, and cadaver courses), political action, and an Annual Meeting. Its certification arm, the ABIPP, provides Board Certification in Interventional Pain Management and Competency Certification in Controlled Substance Management; Competency Certification in Coding, Compliance, and Practice Management; and Competency Certification in Fluoroscopic Interpretation and Radiological Safety [16].

ASPE is dedicated to improving pain management through the education and training of health care professionals to become Certified Pain Educators (CPEs), with the organization teaching health care professionals to serve as resources to educate their clinical peers, as well as patients, families, and caregivers, on ways to relieve pain by the safest means possible. ASPE holds its annual Pain Educators Forum each September in conjunction with the PAINWeek Annual Conference in Las Vegas. ASPE offers certification for pain educators and publishes a quarterly PainView newsletter with teaching tips and instructional methods [9].

ASPMN advances and promotes optimal nursing care for people affected by pain by promoting best nursing practices. The nursing Pain Management certification examination is a partnership venture between ANCC and ASPMN. Their annual meeting is held each September and the official publication is Pain Management Nursing [17].

American Society of Regional Anesthesia and Pain Medicine (ASRA) is the largest subspecialty society in anesthesiology. The three interconnected functions of the society include education in regional anesthesia and pain management, research in regional anesthesia and pain management, and pain medicine grounded in continuing education and quality scientific research. Educationally, ASRA is an organization addressing the clinical and professional educational needs of physicians and scientists; assuring excellence in patient care utilizing regional anesthesia and pain medicine; and investigating the scientific basis of the specialty. ASRA presents spring and fall meetings, the former devoted to regional anesthesia and acute pain medicine and the latter devoted to chronic pain medicine. It publishes a bimonthly journal, Regional Anesthesia and Pain Medicine [19].

Canadian Pain Society (CPS, a national chapter of IASP) includes as its members physicians, dentists, nurses, physiotherapists, psychologists, and other clinicians involved with pain management; scientists involved in the design of improved methods of pain management and the identification of basic mechanisms of pain and analgesia; professionals involved in education, training, and publication of new information in the field of pain; and lay persons with an interest in the field of pain. CPS publishes Pain Research and Management and holds an Annual Meeting each spring.

International MYOPAIN Society (IMS) is a nonprofit health professionals' organization dedicated to promoting information about soft-tissue pain disorders like myofascial pain syndrome and fibromyalgia syndrome. IMS publishes the Journal of Musculoskeletal Pain and holds a MYOPAIN conference every 3 years that alternates between the United States and other countries.

Society for Pain Practice Management (SPPM) is dedicated to educating specialists in the area of pain treatment and practice management. The objectives of SPPM are to promote health and wellness by advancing the art and science of the specialty of pain management. SPPM offers an annual spring Pain Management Symposium and an annual fall Comprehensive Interventional Pain Management Anatomical Course [20].

Organizations for painful disorders

Many disease-specific groups offer extensive education for professionals and the public alike. American Arthritis Society, American Cancer Society, American Headache Society, National Fibromyalgia Research Association, National Vulvodynia Association, Reflex Sympathetic Dystrophy Syndrome Association, and Trigeminal Neuralgia Association are the better known of these groups. Most hold annual clinical meetings, have specialty journals, and promote research into their specific condition. The largest one that is broken up into state chapters is American Cancer Society, with educational activities distinctly directed to professionals and the general public through different arms of the organization.

Pain advocacy organizations

Pain advocacy groups provide direct support for patients and their family members. Many serve as clearinghouses for information about pain in general (eg, American Chronic Pain Association, American Pain Foundation, National Pain Foundation, Race Against Pain) and others focus on particular painful disorders (eg, Arthritis Foundation, National Fibromyalgia Association, National Headache Foundation, Neuropathic Pain Network, The Neuropathy Association). Unlike the groups listed in the previous section, these do not provide professional education.

Commercially supported websites

Many opioid manufacturers have become sponsors of pain information websites managed by medical education companies. Although none of the following websites overtly promotes the medications of the sponsoring companies, these websites clearly address issues related to the prescribing of opioids, especially for long-term management of chronic pain. Some of these sites include the Chronic Pain Network, Emerging Solutions in Pain, Pain Balance, PainEDU, Pain Knowledge, and Partners Against Pain. Most of these sites offer a number of useful tools and screening forms to identify the presence of prescribing risk, stratification of risk, and modification of therapy to mitigate risk. Some websites offer CE programs, webinars, and links to live dinner meetings.

Publications intended for prescribers of opioids

Prescribers of opioids for pain management may wish to obtain some of these publications: Responsible Opioid Prescribing: A Physician's Guide ; Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain , 5th Edn; Practitioner's Manual ; Pharmacist's Manual ; The PainEdu.org Manual ; A Practical Guide for Prescribing Controlled Substances ; and A Clinical Guide to Opioid Analgesia . The Practitioner's Manual and the Pharmacist's Manual are official publications of the Drug Enforcement Administration's Office of Diversion Control and functionally are the "rule" books from the US Department of Justice on the prescribing and dispensing of controlled substances.

Comprehensive textbooks about pain

Numerous comprehensive textbooks exist for those wishing to prepare for certification examinations and to read for a deep understanding about pain, its management,

and the modern field of pain management. Some of the better known comprehensive textbooks include: Bonica's Pain Management , 3rd Edn; Principles and Practice of Pain Medicine , 2nd Edn; Raj's Practical Management of Pain , 4th Edn; Wall and Melzack's Textbook of Pain , 5th Edn; and Weiner's Pain Management: A Practical Guide for Clinicians , 7th Edn. These books have different perspectives, with Wall and Melzack's Textbook of Pain considered to be the most academic of the grouping, and the others intended to benefit clinicians. Raj's Practical Management of Pain has just been updated and is considered by some to be the ideal textbook for certification examination preparation. Weiner's Pain Management offers information about integrative (ie, complementary and alternative) medicine not found in the others.

Useful books

There are many useful books ranging from atlases to series to single tomes intended for clinicians at different levels of practice and with different levels of interest in specific aspects of pain management. The best known of the atlases include Atlas of Common Pain Syndromes , 2nd Edn and its companion, Atlas of Uncommon Pain Syndromes , 2nd Edn; and Physical Diagnosis of Pain: An Atlas of Signs and Symptoms. For those interested in a clinically focused series, the four volumes of the Clinical Pain Management series are quite good: Acute Pain , Cancer Pain , Chronic Pain , and Practical Applications and Procedures . The two Travell and Simons' books (Travell and Simons' Myofascial Pain and Dysfunction: The Trigger Point Manual Volume 1, Upper Half of Body , 2nd Edn and Travell and Simons' Myofascial Pain and Dysfunction: The Trigger Point Manual Volume 2, The Lower Extremities) unravel the mystery of soft-tissue pain better than most others. Many other books focus on specific situations and are intended for practitioners from specific disciplines (Clinical Manual of Pain Management in Psychiatry and Pelvic Pain: Diagnosis and Management). Other helpful books address decision making, ethics, board preparation, and pain management in general: Decision Making in Pain Management, 2nd Edn; Ethical Issues in Chronic Pain Management; Pain Medicine: A Comprehensive Review , 2nd Edn; The Massachusetts General Hospital Handbook of Pain Management , 2nd Edn; and The Pain Clinic Manual , 2nd Edn.

Progress in Pain Research and Management series from IASP Press

For more than a decade, IASP had been offering outstanding books within the series Progress in Pain Research and Management, and more recently as specialty offerings. The most useful of the series for practitioners include The Molecular Neurobiology of Pain , Vol. 9; Sickle Cell Pain , Vol. 11; Assessment and Treatment of Cancer Pain , Vol. 12; Opioid Sensitivity of Chronic Noncancer Pain , Vol. 14; Sex, Gender, and Pain , Vol. 17; Neuropathic Pain , Vol. 21; Spinal Cord Injury Pain , Vol. 23; Opioids and Pain Relief , Vol. 25; Psychosocial Aspects of Pain , Vol. 27; The Genetics of Pain , Vol. 28; Psychosocial Methods of Pain Control , Vol. 29; Hyperalgesia , Vol. 30; CRPS: Current Diagnosis and Treatment , Vol. 32; and Pain in Older Persons , Vol. 35. IASP offers recent single topic titles not included in the series, including Emerging Strategies for the Treatment of Neuropathic Pain , Sleep and Pain , and Central Neuropathic Pain: Focus on Poststroke Pain . IASP also publishes *Classification of Chronic Pain*, 2nd Edn; Epidemiology of Pain ; Back Pain in the Workplace ; Pain in the Elderly ; and Core Curriculum for Professional Education in Pain , 3rd Edn. Information in the Core Curriculum aided the work group developing the job analysis for the CPE's examination given by the ASPE.

Interventional pain textbooks and atlases

For those interested in interventional pain medicine, a number of atlases and books provide extensive information about patient selection, benefits and risks, methods available, and more about this aspect of pain management. Whereas many of the comprehensive textbooks previously mentioned give adequate coverage of interventional pain management, these books just address this specific topic. Useful atlases include Atlas of Interventional Pain Management, 2nd Edn and Atlas of Pain Management Injection Techniques , 2nd Edn. Specific textbooks on the subject include Interventional Pain Management , 2nd Ed; Interventional Pain Management: Low Back Pain—Diagnosis and Treatment ; Interventional Radiology in Pain Treatment ; Interventional Techniques in Chronic Spinal Pain ; Neural Blockage in Clinical Anesthesia and Management of Pain , 3rd Edn; and Textbook of Regional Anesthesia and Acute Pain Management .

Peer-reviewed pain journals and magazines

Over the past 20 years, there has been continuous growth in the number of pain publications. The most significant of the publications are peer reviewed and indexed for online searches. Most professional pain publications serve as the official publication of a pain organization, and therefore provide society news as well as scholarly research. These publications include Clinical Journal of Pain ; European Journal of Pain ; Journal of Musculoskeletal Pain ; Journal of Orofacial Pain ; Journal of Pain ; Journal of Pain and Symptom Management; Pain; Pain Medicine ; Pain Physician; Pain Research and Management ; and Regional Anesthesia and Pain Medicine . These publications serve as sources of information about emerging medications, procedures, and technologies. Pain is in a class by itself and is the standard bearer for the field of pain. Other publications are unique in that they are not linked to any professional societies but provide focused reviews on specific aspects of pain: Journal of Opioid Management ;

Journal of Pain & Palliative Care Pharmacotherapy ; and Techniques in Regional Anesthesia and Pain Management. The latter presents interventional techniques in a highly visual format. Molecular Pain is unique in being an open-access, online "publication."

Non–peer-reviewed pain publications

These publications are not peer reviewed but address practical issues related to providers working with patients in pain. The Pain Practitioner is the monthly publication of AAPMan and is intended for its members; some issues are focused on specific topics and many have CE inserts. Practical Pain Management is intended for the top 10% of analgesic prescribers in the United States and is sent to pain specialists and primary care providers (PCPs). Its articles cover selected pain treatments, and most issues have relevant opioid-prescribing information. PainView is the quarterly publication of ASPE and intended for its members. Issues include articles with a focus on pain education and contain "teaching tips" to aid pain educators. Pain Medicine News and MDNG: Pain Management are also both intended for the top 10% of analgesic prescribers in the United States and sent to pain specialists and PCPs. The former provides information presented at recent meetings, newsworthy information, and similar topics, and the latter provides information about professional societies, sources of pain information, and "deconstruct" websites to allow readers to preview them in advance. Current Pain & Headache Reports provides reviews on specific aspects of pain and rotates topics on an annual basis.

Comments About Pain Education

The purpose of pain education is multifaceted. Overtly, practitioners want to be able to match therapies to conditions. Educators need resources understandable by health care professionals at many levels of knowledge about pain, its mechanisms of generation, means by which therapeutic methods relieve pain, and methods of determining outcomes developed to identify deficits about pain management (eg, KnowPain-50) [21••]. Lay people want to get the "big" picture about their pain, and want to know what can be done. Education for patients leads to better understanding about the reasons for pain, the approaches used for its control, and the importance of adhering with treatment recommendations. Currently, there is no single group or body charged with pain education for these different needs. As the Executive Director for ASPE, I know that pain educators are needed to take education to the next level just as diabetes educators have professionalized the delivery of diabetes education. There will likely never be a single best way to teach anything, but the need to teach more people about pain management must not be left to well-intentioned, yet unprepared, "teachers." At this point of maturation in our professional development, it is necessary to move beyond the "see one, do one, teach one" approach to pain management.

Conclusions

My apologies are offered to websites, societies, publications, or entities that were not cited in this article. The number of offerings now available to educate pain specialists, PCPs, and others is staggering. The bottom line is that there are plenty of resources to serve as primers for those just interested in dipping their toes into the world of pain, there are many more that take those so inclined for a "deeper dive," and there are many specialized resources to prepare candidates for the successful passage of pain certification examinations and to aid clinicians in their day-to-day understanding of complicated aspects of pain. The atlases are helpful for patient education and prove the old saying: "A picture is better than a thousand words." This article gives readers a "quick take" on pain resources, and challenges the field to develop a single repository for available resources to make the practice of pain management/medicine easier.

Disclosure

Dr. Cole is a speaker and an advisor for Eli Lilly. He is also an advisor for Abbott Laboratories and Meda Pharmaceuticals, Inc.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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Using pretest-posttest design knowledge, attitudes and beliefs about chronic pain were modified by an educational intervention. Scores improved immediately and then persisted for 3 months.

2.•• Roth CS, Burgess DJ: Changing residents' beliefs and concerns about treating chronic noncancer pain with opioids: evaluation of pilot workshop. Pain Med 2008, 9:890–902.

Residents' beliefs and concerns about using opioids for chronic pain changed after participating in a 4-hour interactive workshop.

3.•• Chen I, Goodman B, Galicia-Castillo M, et al.: The EVMS pain education initiative: a multifaceted approach to resident education. J Pain 2007, 8:152–160.

A 1-day workshop for residents using a combination of standardized patients, small groups, and large group lectures addressing residents' needs regarding chronic pain management resulted in significant gains in knowledge, clinical skills, and increased comfort regarding chronic pain management.

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21.•• Harris JM, Fulginiti JV, Gordon PR, et al.: KnowPain-50: a tool for assessing physician pain management education. Pain Med 2008, 9: 542–554.

The KnowPain-50 showed good psychometric validity and appears to distinguish among physicians with different levels of pain management experience.

EXHIBIT 73

PAINKNOWLEDGE

Search PainKnowledge.org

GO

Dynamic Slide Library
On-Demand Activities
Current Literature
Calendar of Events
Physician Tools
Pain Resources
Patient Education
Clinical Trials

The Steering Committee

Dennis C. Turk, PhD

Chairman

View Steering Committee

About PainKnowledge.org

The Burden of Pain
Pain is a distinctive characteristic of many chronic conditions, including diabetes, cancer, and cardiovascular disease. It is estimated that more than half of Americans live with some form of chronic pain, the causes of which can range widely—from injuries to the natural course of aging. While many patients cope with the discomfort associated with painful conditions, diminished quality of life becomes an important consideration as duration of pain increases, particularly if the pain is not adequately managed.

Where We Come In
PainKnowledge.org is a one-stop repository for print materials, educational resources, and physician tools across the broad spectrum of pain assessment, treatment, and management approaches. Unique site offerings include:

- **Dynamic Slide Library** featuring fully referenced downloadable slides on such topics as epidemiology, assessment, treatment options, and more
- **Physician Tools,** including the Opioid Analgesia Tool Kit and the Pain Activity and Tracking Log, for quick reference
- **Patient Education Materials** that augment patient management and improve patients' and caregivers' understanding of pain-causing conditions
- **Current Literature** featuring synopses of cutting-edge clinical trials and data

PainKnowledge.org also hosts content developed for the National Initiative on Pain Control® (NIPC®), an integrated education initiative that provides clinical tools and information to assist healthcare professionals in improving management techniques and, ultimately, outcomes among their patients with pain.

Steering Committee
All resources and programs hosted on PainKnowledge.org are continuously evaluated by our Steering Committee, an expert multidisciplinary team of specialists, researchers, and practicing physicians in pain management. The Editorial Board includes experts in the pain management field.

Click here to learn more about The PainKnowledge.org Steering Committee.

The information found on PainKnowledge.org is designed to support, not to replace, the relationship between the patient and the physician.

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EXHIBIT 74

to the Coalition for Iraq + Afghanistan Veterans website.
The Coalition for Iraq and Afghanistan Veterans (CIAV) is a national non-partisan partnership of organizations committed to working with and on behalf of all military, veterans, families, survivors and providers to strengthen the existing system of care and support for all those affected by the wars in Iraq and Afghanistan.

Iraq War Veteran Amputee, Pain Advocate and New Author Releases Exit Wounds: A Survival Guide to Pain Management for Returning Veterans and Their Families

"Its now four years since I lay in the dirt, near death, on the side of the road in Fallujah. I'm grateful for all the things I have, and proud of all I've accomplished. In the end though, I don't measure how far I've come by goals achieved, or academic degrees earned, or running trophies won. For me, what counts is that pain no longer rules my life." – Derek McGinnis

The American Pain Foundation (APF) announces the release of Iraq War Veteran and Pain Advocate Derek McGinnis' first book, *Exit Wounds: A Survival Guide to Pain Management for Returning Veterans and Their Families.* Written in collaboration with nationally renowned pain experts, the release date of September 21 for Exit Wounds coincided with September's designation as Pain Awareness Month.

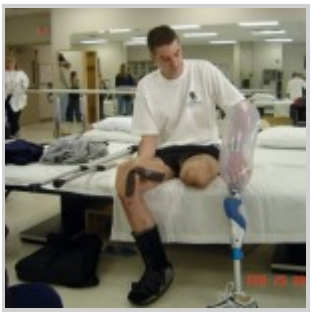
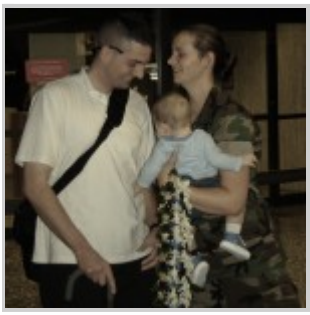
> McGinnis, who sustained a traumatic brain injury, extensive shrapnel wounds, damage to his eye and amputation of his left leg above the knee from an Improvised Explosive Device (IED) while serving in the U.S. Navy in Iraq, said, "I wrote Exit Wounds because when I was struggling with horrific pain caused by my injuries, there was no guide, no map, no mentor to steer me through the minefield I was navigating. Exit Wounds contains the information my family and I desperately needed back in 2004."

Exit Wounds is both a guide to pain management for veterans and their family members, and also the inspiring story of how one man, with the support of his family and fellow veterans, fought to survive and even thrive despite his traumatic injuries and painful path to recovery. Exit Wounds and its companion website offer veterans and family members information about acute and chronic pain syndromes afflicting veterans, treatment options, including medications, procedures, complementary therapies and other interventions; strategies for self-advocating for optimal pain care; medical resources inside and outside the Veterans Administration (VA) system; and caregiver needs, perspectives and resources.

> "With hundreds of thousands of military personnel expected to return from the wars in Iraq and Afghanistan over the next few years, many of them will struggle with acute pain and face the possibility of a lifetime of chronic pain," said McGinnis. "They and their families deserve a resource to help them navigate through the barriers and obstacles that can prevent effective pain care."

McGinnis now serves as the Military/Veterans Initiative Amputee Outreach Advocate with APF and travels the country advocating for the pain management needs of veterans, military personnel and their caregivers. He has spoken to many influential groups and individuals within the Department of Defense, Veterans Affairs, Veterans Service Organizations and Congress to bring military and veterans' pain issues to the forefront. McGinnis provides information, education, outreach, support and resources to those who are affected by pain.

To read an excerpt of Exit Wounds or to learn more on where you can obtain a copy of Exit Wounds, visit www.exitwoundsforveterans.org. The book is currently being distributed to veterans and service members for free through the Wounded Warrior Project and the Injured Marine Semper Fi Fund. McGinnis is searching for partners to support the printing of the book so that it can be given for free to every service member, veteran, or family member who needs one. It is available to civilians through Amazon.


About Derek: Derek McGinnis, age 31, grew up in Fremont, California, and currently lives in Waterford, California, with his wife, Andrea, and their two young sons. In addition to his advocacy position with APF, McGinnis is currently pursuing a Masters Degree in Social Work. He enjoys competing in endurance races including, biathlons and triathlons and aspires to represent his country again one day as a member of the U.S. Paralympic team.

Available for Interview: To schedule an interview with Derek McGinnis to discuss Exit Wounds, his struggle with pain and his advocacy work with APF, please contact Tina Regester at 443-690-4707 or tregester@painfoundation.org.

EXHIBIT 75

FDA News Release

FDA requests removal of Opana ER for risks related to abuse

For Immediate Release

June 8, 2017

Release

Español (/NewsEvents/Newsroom/ComunicadosdePrensa/ucm562499.htm)

Today, the U.S. Food and Drug Administration requested that Endo Pharmaceuticals remove its opioid pain medication, reformulated Opana ER (oxymorphone hydrochloride), from the market. After careful consideration, the agency is seeking removal based on its concern that the benefits of the drug may no longer outweigh its risks. This is the first time the agency has taken steps to remove a currently marketed opioid pain medication from sale due to the public health consequences of abuse.

“We are facing an opioid epidemic – a public health crisis, and we must take all necessary steps to reduce the scope of opioid misuse and abuse,” said FDA Commissioner Scott Gottlieb, M.D. “We will continue to take regulatory steps when we see situations where an opioid product’s risks outweigh its benefits, not only for its intended patient population but also in regard to its potential for misuse and abuse.”

The FDA’s decision is based on a review of all available postmarketing data, which demonstrated a significant shift in the route of abuse of Opana ER from nasal to injection following the product’s reformulation. Injection abuse of reformulated Opana ER has been associated with a serious outbreak of HIV and hepatitis C, as well as cases of a serious blood disorder (thrombotic microangiopathy). This decision follows a March 2017 FDA advisory committee meeting where a group of independent experts voted 18-8 that the benefits of reformulated Opana ER no longer outweigh its risks.

Opana ER was first approved in 2006 for the management of moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. In 2012, Endo replaced the original formulation of Opana ER with a new formulation intended to make the drug resistant to physical and chemical manipulation for abuse by snorting or injecting. While the product met the regulatory standards for approval, the FDA determined that the data did not show that the reformulation could be expected to meaningfully reduce abuse and declined the company’s request to include labeling describing potentially abuse-deterrent properties for Opana ER. Now, with more information about the risks of the reformulated product, the agency is taking steps to remove the reformulated Opana ER from the market.

“The abuse and manipulation of reformulated Opana ER by injection has resulted in a serious disease outbreak. When we determined that the product had dangerous unintended consequences, we made a decision to request its withdrawal from the market,” said Janet Woodcock, M.D., director of the FDA’s Center for Drug Evaluation and Research. “This action will protect the public from further potential for misuse and abuse of this product.”

The FDA has requested that the company voluntarily remove reformulated Opana ER from the market. Should the company choose not to remove the product, the agency intends to take steps to formally require its removal by withdrawing approval. In the interim, the FDA is making health care professionals and others aware of the particularly serious risks associated with the abuse of this product.

The FDA will continue to examine the risk-benefit profile of all approved opioid analgesic products and take further actions as appropriate as a part of our response to this public health crisis.

The FDA, an agency within the U.S. Department of Health and Human Services, promotes and protects the public health by, among other things, assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation’s food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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888-INFO-FDA

Related Information

- **FDA: March 13-14, 2017 Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/u**
- **FDA: Opioid Medications (/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm)**
- **FDA: How does FDA decide when a drug is not safe enough to stay on the market? (/AboutFDA/Transparency/Basics/ucm194984.htm)**
- **FDA: Drug-Specific Information, Opana ER (/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm562339.htm)**

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EXHIBIT 76

NARCOTIC 'LOLLIPOP' BECOMES BIG SELLER DESPITE FDA CURBS

THE WALL STREET JOURNAL.

Published on:
November 3rd, 2006

While pregnant with her second child three years ago, Tiare Frontera suffered from bad migraines. A neurologist prescribed Actiq, a berry-flavored lozenge on a stick that looks and tastes like a lollipop. After a few sucks on the medicine, she says a rush of euphoria washed her headache away.

Soon, Mrs. Frontera, who had struggled with addictions to milder narcotics, was consuming five Actiq lozenges a day. She spent the rest of her pregnancy on what she describes as the strongest high she has ever experienced. When she gave birth, her baby son was cranky and wouldn't sleep. Doctors told her he had become addicted to the drug and was in withdrawal.

Mrs. Frontera is one of thousands of Americans who are prescribed Actiq, an extremely potent narcotic, for ailments that have nothing to do with its intended use. The Food and

Drug Administration approved the drug eight years ago for use only in cancer patients who suffer intense bouts of pain that other narcotics don't relieve.

In the first half of this year, oncologists, or cancer doctors, accounted for only 1% of the 187,076 Actiq prescriptions filled at retail pharmacies in the U.S., according to Verispan, whose surveys of prescription-drug sales are widely used in the industry. Data gathered from a network of doctors by research firm ImpactRx between June 2005 and October 2006 suggest that more than 80% of patients who use the drug don't have cancer. Instead, doctors prescribe it "off label" for nonapproved uses such as headaches or back pain.

Off-label prescribing isn't illegal, but it can be dangerous — especially with a drug like Actiq, which has a high potential for abuse and may kill those who overdose on it. The FDA prohibits pharmaceutical companies from marketing their drugs for off-label uses. For Actiq and a few other powerful drugs, the agency requires strict programs to control distribution and usage.

Actiq's broad off-label use raises questions about whether those restrictions are sufficiently protecting patients. "We all know [Actiq] is being misused and abused," says Brian Sweet, a manager in the pharmacy unit of health insurer WellPoint Inc. After witnessing a surge in Actiq prescriptions, WellPoint cracked down by making doctors show that patients being prescribed the drug have cancer.

Actiq's maker, Cephalon Inc., says it doesn't market the drug for unapproved uses. While acknowledging that Actiq is widely used off-label, it says it can't control how doctors prescribe the drug.

Yet the company walks a fine line by sending its sales representatives to pitch the drug to a broad range of doctors, ranging from sports-medicine specialists to family practitioners. It gives these doctors coupons for free samples. Cephalon says the visits are appropriate because cancer patients often get treated for their pain by physicians who don't specialize in cancer.

Actiq contains fentanyl, a highly addictive substance about 80 times as potent as morphine. Fentanyl is classified as a Schedule II substance by the Drug Enforcement

Administration, which puts it in the same category as opium, cocaine, methamphetamine and methadone. Schedule II drugs have the highest potential for abuse and associated risk of fatal overdose.

Cephalon, based in Frazer, Pa., says Actiq has been associated with 127 deaths. Two of them involved children who confused the drug for candy. Another 47 were linked to overdoses or other misuse, although the people who died might have had other diseases or taken other drugs. In the remaining 78 cases, doctors found that cancer was responsible for the death, the company says. Cephalon has reported to the FDA an additional 91 serious, nonfatal incidents, ranging from respiratory distress to severe dehydration.

The U.S. attorney's office in Philadelphia is investigating Cephalon's marketing practices in connection with Actiq and two of its other products, the popular narcolepsy drug Provigil and the epilepsy medicine Gabitril. No charges have been filed.

BROADER CRACKDOWN

Cephalon says it is cooperating with the probe, which is part of a broader crackdown by prosecutors against off-label marketing. In August, the Justice Department fined Schering-Plough Corp. $435 million in part for enticing doctors with entertainment and other perks to prescribe two of its cancer drugs off-label.

Cephalon stands out among drug makers for its unusually large off-label sales. Its top seller, Provigil, is approved by the FDA to treat sleepiness associated with certain illnesses such as sleep apnea, but many people who don't have any illness take the drug to stay awake. Analysts estimate about 80% of Provigil prescriptions are off-label. Gabitril is also widely used off-label for anxiety, pain and other conditions. Under FDA pressure, Cephalon last year curtailed its marketing of the epilepsy drug because it was causing seizures in patients without the disease, and sales dropped 23%.

Founded in 1987 by a former DuPont Co. scientist named Frank Baldino Jr., Cephalon expects revenue to exceed $1.6 billion this year, more than double the figure of three years

NEWS & MEDIA

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ago although still a small fraction of the industry's top companies. Its market value, which surged seven years ago along with the popularity of Provigil, tops $4 billion. Dr. Baldino earned $2.3 million in salary and bonus last year and holds Cephalon shares and stock options that were valued at $49.6 million as of the end of last year.

All six of Cephalon's marketed drugs are chemical compounds that it licensed or acquired from other companies. Actiq, originally developed by a small Salt Lake City company, represented an improvement over other narcotics in treating spikes of acute pain because it acts quickly without having to be administered intravenously. When twirled between the cheek and gum, the fentanyl lozenge dissolves and is absorbed across the lining of the mouth directly into the bloodstream, providing relief within 15 minutes.

Actiq had sales of $15 million in 2000, when Cephalon acquired it. By last year, sales had grown to $412 million, making it Cephalon's No. 2 drug. In the first nine months of this year, sales jumped to $471 million. Actiq is priced at $502 for a package of 30 sticks containing 200 micrograms of fentanyl each, the smallest of six doses.

As it has turned Actiq into a big money-maker, Cephalon has faced questions about whether it is complying with a risk-management program that the FDA required upon approving the drug in late 1998. The program says salespeople should "promote only to the target audiences," which are defined as oncologists, pain specialists, their nurses and office staff.

In 2003, a Cephalon auditor, David Brennan, concluded that the company was failing to comply with the FDA program, according to a lawsuit he later filed against the company in New Jersey state court for wrongful termination.

An important provision of the program says Actiq's maker should report to the FDA every quarter whether "groups of physicians (such as a particular specialty)" who represent "potential off-label usage greater than 15%" are prescribing the drug. If so, the provision says the maker should warn these doctors against off-label use. Mr. Brennan's lawsuit says that means Cephalon must act if all noncancer medical specialties together account for more than 15% of prescriptions.

CAUGHT IN OPIOID EPIDEMIC

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Cephalon interprets the provision differently. It says it only needs to act if any individual specialty exceeds 15% of the total — and then only if it can be shown that doctors in that specialty are prescribing Actiq inappropriately. Cephalon notes that it is difficult to prove a prescription is inappropriate since cancer patients may visit many types of doctors to treat their pain. It believes the 15% clause has yet to be triggered. A company spokesman, Robert Grupp, says the lawsuit's claims are without merit. The FDA declined to comment.

According to Verispan data for the first half of 2006, two specialties exceed 15% of Actiq prescriptions: anesthesiologists at 29.5% and physical medicine and rehabilitation specialists at 16%. The data show oncologists and pain specialists account for less than 3% of prescriptions. Cephalon doesn't dispute the data.

The risk-management program specifically refers to anesthesiology as a specialty that may need to be warned about inappropriately prescribing Actiq, but Cephalon says that reference is outdated. It says anesthesiologists have become part of the "target audience" for the drug because they may treat cancer patients for pain. Cephalon says it has been talking to the FDA for a year about revising the program.

After Mr. Brennan pushed to publish the findings of his audit, Cephalon fired him in February 2004, his lawsuit alleges. Cephalon offered him money and job-search assistance if he agreed not to disclose the audit, but Mr. Brennan refused, the suit says. Mr. Grupp declined to discuss Mr. Brennan's dismissal but noted that he is "a former disgruntled employee."

Mr. Brennan has been interviewed twice by investigators working for the U.S. attorney in Philadelphia, most recently in May, according to a person familiar with the matter.

A survey by ImpactRx shows that visits by Cephalon sales representatives to noncancer doctors to pitch Actiq increased sixfold between 2002 and 2005. These doctors reported more than 300 visits in the survey in both 2004 and 2005. Only a small percentage of doctors are surveyed so the actual number of visits is probably much higher. Cephalon says it can't confirm the numbers but it doesn't

dispute that it has stepped up its marketing of Actiq to various types of doctors over that period.

Stephen Leighton, a general practitioner in Winston-Salem, N.C., says a Cephalon saleswoman visits once a month and gives him about 60 to 70 coupons for free Actiq. Patients can trade each coupon for six Actiq sticks. Dr. Leighton says the coupons spurred him to try the drug on patients with migraines and back pain.

POSITIVE EXPERIENCE

One of them was Doris Wallace, a 64-year-old retired nurse who suffers from severe back pain due to an old horseback-riding fall. Ms. Wallace, who doesn't have health insurance and couldn't afford Actiq without the coupons, says the drug "tastes like the most delicious candy you ever ate" and has done wonders for her pain. At the height of her use, she was consuming 24 Actiq sticks a month.

The positive experience of patients like Ms. Wallace has led Dr. Leighton to prescribe Actiq more widely for different types of pain. Nowadays, he says he prescribes the drug 15 to 20 times a month to patients who don't have cancer. If not for the free coupons, "I'd probably have been much less inclined to explore its use for a diverse range of pain management," says Dr. Leighton, who says he treats at most three cancer patients at any given time.

Dr. Leighton says he thinks the FDA-approved usage of Actiq is too narrow. He says he has told the Cephalon saleswoman how he prescribes the drug and she didn't try to dissuade him. Mr. Grupp of Cephalon says Dr. Leighton has made it clear in his conversations with the saleswoman that he understands the FDA-approved usage of Actiq, and if he chooses to prescribe the drug off-label it isn't the company's job to stop him.

Mr. Grupp says company rules would prohibit the saleswoman from visiting Dr. Leighton only if he never prescribed the drug for cancer pain. "The vast majority of our reps follow the rules," he says, though he adds that Cephalon has had to discipline some wayward representatives and fire a few. When Cephalon receives a report of a doctor prescribing the drug off-label — for example, via a call or letter from a patient — it sends a letter

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If you are looking for help, this is the place to come. It is everything and then some on what they say about the method. - J.G. Read more…

Thank you all. Thanks to you, I'm drug free & feeling great! - F.G. Read more…

to that doctor reminding him or her that Actiq is only for cancer pain, Mr. Grupp says. The company has sent more than 3,300 such letters, he says.

Earlier this year, Dr. Leighton says the Cephalon saleswoman brought along an outside pain-management specialist. Over lunch, Dr. Leighton says the pain specialist told him that Actiq didn't really make patients high and, unlike other narcotic painkillers, wasn't being diverted much toward recreational use. Cephalon declined to comment on the conversation.

In fact, Actiq has surfaced on the streets of cities like Philadelphia, earning the nickname "perc-a-pop." Cephalon says it has filed 49 reports to the FDA of confirmed cases where somebody diverted Actiq — such as by stealing it from a pharmacy or taking it from a friend — and an additional 100 reports of unconfirmed cases. Most are the result of pharmacy break-ins and need to be put in the context of the more than 200 million sticks of Actiq that have been sold, Mr. Grupp says.

Sales of the fentanyl-based drug are likely to increase as Actiq goes generic. In late September, Barr Pharmaceuticals Inc. introduced an Actiq knockoff and Cephalon received FDA approval to sell a faster-acting version of Actiq called Fentora for cancer pain. Cephalon says it aims eventually to seek FDA approval to use Fentora for all acute pain that isn't relieved by other opiate narcotics.

Mrs. Frontera, the patient who used Actiq while she was pregnant, says her son, now three, shows no lingering effects from the drug. Mrs. Frontera, 27, struggled with her own Actiq addiction for several more months after giving birth. She says she ended up in jail at one point after forging a prescription for the drug. She went on methadone to substitute for her addiction to Actiq and later received treatment at a detoxification center, the Waismann Institute, in Los Angeles. Now she lives in San Luis Obispo, Calif.

"It makes me angry that it was prescribed to me," she says of Actiq. "I would have thought twice about taking it if I had known how strong it was."

Philip Delio, the neurologist who prescribed Actiq to Mrs. Frontera, says he did so because she wasn't getting relief from other narcotic painkillers and described herself as

desperate. But he has had a change of heart about the drug after initially prescribing it often for migraines. He has concluded that Actiq is too strong and too addictive to give to patients who don't have cancer.

Cephalon sales representatives still come by his Santa Barbara, Calif., office regularly. But Dr. Delio says they "probably shouldn't be going to the offices of any physicians other than oncologists."

Source: The Wall Street Journal

actiq lollipop lozenges off-label

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EXHIBIT 77

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Cephalon, Inc.

Address:
145 Brandywine Parkway
West Chester, Pennsylvania 19380
U.S.A.

Telephone: (610) 344-0200
Fax: (610) 738-6590
http://www.cephalon.com

Statistics:
Public Company
Incorporated: 1987
Employees: 650
Sales: $111.79 million (2000)
Stock Exchanges: NASDAQ
Ticker Symbol: CEPH
NAIC: 54171 Research and Development in the Physical, Engineering and Life Sciences

Company Perspectives:
Cephalon seeks to discover, develop and market innovative products to treat neurological and sleep disorders, cancer, and pain. The company is committed to providing patients and the medical community with novel therapies to treat unmet medical conditions through its proprietary research programs and by acquiring promising products for clinical development and commercial sale.
Our success is supported by a proven strategy of marketing high-growth, innovative products, building our worldwide marketing and distribution channels, and investing in research and development of unique

compounds that may change the course of a disease.

Key Dates:
1987: Biologist Frank Baldino, Jr., founds Cephalon as a small research house.
1991: Cephalon goes public with a $59.4 million IPO.
1994: News of positive test results for Myotrophin send stock soaring.
1995: Cephalon establishes a sales force.
1999: Myotrophin is abandoned following difficulties gaining full FDA approval; Provigil and Actiq are launched.
2001: Rights to Gabitril are acquired.

Company History:

Cephalon, Inc. is an international biopharmaceutical company that specializes in drugs to treat neurological and sleep disorders. The company's activities encompass the discovery, research, and development of new treatments as well as the sales and marketing of finished products.

Cephalon has three proprietary products that account for almost all of its sales revenue in the United States. The drug Provigil promotes daytime wakefulness and is used to treat narcolepsy, a disease characterized by a propensity to fall asleep during the day. Provigil is also used to combat fatigue associated with other disorders, such as depression and multiple sclerosis. A second product, Gabitril, treats partial seizures associated with epilepsy. Finally, the drug Actiq is prescribed to manage pain in cancer patients. Cephalon's European headquarters in Guildford, England, manages the sale of eight products in the United Kingdom, France, Germany, Switzerland, and Austria. Branch offices are located in France and Germany. The company has also expanded its international reach through marketing collaboration agreements with pharmaceutical companies in Asia, Mexico, and Europe. Under the agreements, Cephalon is able to sell its products through a third party without having to maintain its own sales force abroad.

True to its roots as a small research house, Cephalon continues working to develop new treatments. Products currently under development include therapies for prostate and pancreatic cancer as well as Parkinson's disease. The company is also working on finding new applications for its three centerpiece products. Meanwhile, sales and marketing has become an ever more prominent sector of the company's operations. Of Cephalon's 650 worldwide employees, about 250 work in the sales and marketing organizations.

A Small Research House: 1987-91

Cephalon was founded in 1987 by two venture capital firms, Burr, Egan, Deleage & Co. and Hambrecht & Quist Life Science Partners. The firms recruited Frank Baldino, Jr., a senior biologist who was conducting neuroscience research for DuPont, to head the company. In the early years, Baldino kept Cephalon focused on research. About 30 scientists worked in a 10,000-square-foot laboratory, specializing in the discovery of neurological growth factors that could be used to treat diseases such as multiple sclerosis, strokes, and amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease). The chemicals under development were intended to prevent the brain cell death associated with the diseases.

As a small research house, Cephalon initially avoided involving itself in activities that would require maintaining a sales staff, managing clinical trials, and shepherding new drugs through the Food and Drug Administration (FDA) approval process. With no product to sell, Cephalon's only asset was its scientific expertise. That expertise proved sufficient to attract investors, and the company managed to fund its operations through research grants and contracts with larger pharmaceutical firms. The 1990 discovery of an enzyme, Clipsin, that plays a major role in Alzheimer's disease, for example, led to an agreement with Schering-Plough. Under the agreement, Schering-Plough provided Cephalon with $20 million to continue its Alzheimer's research in exchange for exclusive worldwide rights to any technologies developed.

By the end of 1990, Cephalon had accumulated a deficit of $7.26 million since it began operating in November 1987. However, the company continued on a path of confident expansion. In March 1991 the staff had grown to 49 employees, who worked in an enlarged 31,000-square-foot lab. That April Cephalon completed its initial public offering, raising $59.4 million at a price of $18 a share. However, the share price dipped to $14.75 several weeks later amid general concern that biotechnology stocks were overvalued. The company would have to produce tangible results to retain investor confidence.

Banking on Myotrophin in the Mid-1990s

In late 1991 Cephalon received orphan drug approval for its product Myotrophin. Orphan drug status gives a company the right to market a product exclusively for seven years, and is granted for drugs not considered profitable enough to justify development without such a guarantee. Thus Cephalon began an eight-year, ultimately unsuccessful, occupation with Myotrophin. The drug, known as a neurotrophic factor, promoted the survival of neurons and was being developed as a treatment for ALS. Cephalon subsequently bought a plant in Maryland to manufacture Myotrophin for research purposes, and entered into an agreement with Chiron Corporation to manufacture the drug on a larger scale if it should be approved by the FDA.

Meanwhile, a successful $23 million equity offering in April 1993 showed that investors retained confidence in Cephalon. The company received $17 million in revenues that year from contracts with large pharmaceutical firms, and grew to 222 employees by year's end. Besides Schering-Plough and Chiron, Cephalon worked with two other firms. In a collaboration with SmithKline Beecham, Cephalon was researching the use of protease inhibitors, chemicals that impede the process of cell death, to aid in the treatment of Alzheimer's. It was also working with SmithKline Beecham on a line of drugs that had potential for stopping abnormal cell growth in cancer patients. With the Japanese firm Kyowa Hakko Kogyo Co. Ltd., Cephalon was developing chemicals to inhibit the action of kinases, a type of protein that causes cell death in Alzheimer's and Parkinson's patients. In addition, the first step toward the development of the narcolepsy treatment Provigil was taken in February 1993, when Cephalon bought from the French company Laboratoire L. Lafon all rights to develop, market, and sell Provigil's main ingredient, modafinil. Such wide-ranging research efforts caused the accumulation of a $35.6 million deficit between 1987 and the end of 1993.

In 1994 failures at other clinics made Wall Street wary of biotechnology stocks, and Cephalon's share price fell from a high of $19.50 in the first quarter of 1994 to $5.75 in mid-1995. But the company trusted in the potential of its own technologies. On June 12, Cephalon announced positive results of clinical tests of Myotrophin. The tests showed that Myotrophin appeared to slow the progression of ALS. Cephalon's shares rose 400 percent on the news. Although European tests, announced in the fall, showed less conclusive results, the company's stock continued to climb.

In 1995 Cephalon took a decisive step away from its research-only roots by establishing a sales force. Because Cephalon did not yet have a product to sell, the sales force sold other companies' drugs. In an arrangement with Bristol-Myers Squibb, Cephalon sold the company's drugs to neurologists, thus giving its own sales force the opportunity to establish the connections and experience that would pay off once Cephalon was marketing its own products.

The first major stumbling block for Myotrophin came at the beginning of 1996, when the FDA refused to allow Cephalon to expand tests of the drug. On January 19, shares fell 34 percent to $23.37 in reaction to the news. The FDA pointed to conflicting results between European and American tests as the basis for its decision. Critics of the tests also charged that the clinical trials of Myotrophin were poorly designed. The test groups were too small, they said, and records were kept in such a way that many patient deaths were not counted. Because the trials were testing disease progression, not mortality rates, patients who were taking Myotrophin were sometimes removed from the study before they died and hence were not included in the final statistics. The confusion over clinical trial results led a group of investors to file a suit against Cephalon charging that the company was misleading in its reporting of Myotrophin test results. The suit was eventually settled in August 1999 for $17 million, although Cephalon denied any wrongdoing.

In 1996 Cephalon sold the plant that it had been using to manufacture Myotrophin. However, Cephalon and its partner Chiron still hoped that the drug would gain final approval. In June 1996 the FDA made Myotrophin available to some ALS patients, but strongly urged the company to conduct a third study of the drug. Cephalon was reluctant to do so, however, since it had already invested $180 million in a drug with a fairly small potential market. More bad news came in May 1997, when an FDA advisory panel rejected Myotrophin as an ALS treatment. Once again Cephalon stock plummeted 35 percent to $13. Nevertheless, both Chiron and Cephalon planned to continue to pursue approval for Myotrophin, pointing out that the panel's recommendation did not amount to a final decision by the FDA.

In May 1998 the FDA ruled that Myotrophin was potentially approvable, contingent on additional clinical studies. However, Cephalon had already poured too many resources into Myotrophin to embark on another multi-year study. The company finally gave up on the drug in 1999, disappointing both the National ALS Association, which had hoped the drug could become an effective treatment, and ALS patients who had been given special access to Myotrophin. CEO Frank Baldino expressed regret that a potentially useful drug failed to gain FDA approval. He said additional tests would be justified for a drug designed to treat a disease that affected five or six million people, but only 25,000 to 30,000 people nationwide had ALS.

Developing a Solid Product Line: 1998-2001

Fortunately, Cephalon's other drug development projects had been proceeding more successfully. The narcolepsy drug Provigil received preliminary approval from the FDA in December 1997 and final approval in December 1998. Company stock rose 12 percent as investors hoped the new product would make up for the Myotrophin fiasco. In February 1999 Provigil was launched in the United States. Sales of the drug exceeded expectations, reaching $25 million by the end of the year. Sales in 2000 were $72.1 million and 2001 sales were expected to reach $130 million.

Cephalon hoped to expand the applications for Provigil beyond narcolepsy. In January 2000 test results were announced showing that the drug was effective in warding off fatigue in multiple sclerosis patients and shift workers. According to test results released in October 2001, Provigil also increased daytime wakefulness in patients suffering from obstructive sleep apnea, a disorder causing a person to wake frequently throughout the night because of obstructed breathing passages. Tests in 2000, however, failed to demonstrate that the drug was effective in treating attention deficit hyperactivity disorder (ADHD). Use of Provigil also expanded geographically through marketing collaborations with foreign companies, including an October 1998 agreement with Mercke GmbH to market Provigil in Austria and Switzerland and a November 2000 agreement with Choongwae Pharma Corporation in Korea.

Actiq, Cephalon's second major proprietary drug, received FDA approval in November 1998 and was launched in the United States in March 1999. At the time, the drug was manufactured and marketed by Abbott Laboratories. Cephalon acquired worldwide product rights to the drug in October 2000 through its merger with Anesta Corporation of Salt Lake City.

Actiq is prescribed to treat pain in cancer patients. Specifically, the drug targets sporadic flare-ups, known as breakthrough cancer pain, that overcome the medication already being used to treat chronic pain. Actiq provides fast-acting, short-term relief from breakthrough pain, which can last from 30 minutes to several hours.

Besides the acquisition of a new product, Cephalon's merger with Anesta gave the company access to a new drug-delivery technology, the Oral Transmucosal System. Using the OTS system, Actiq is absorbed through the mucous membranes of the cheek and passes directly into circulation without having to go through the liver. As a result, a flare-up of pain can be eased within 15 minutes. Sales of Actiq in 2000 were $15 million, and 2001 sales were expected to reach $45 or $50 million as Cephalon worked to establish the product as the medication of choice for breakthrough cancer pain.

Like Provigil, Actiq developed a worldwide reach. In October 2000 the drug was approved for sale in the United Kingdom, and in June 2001 the drug was granted marketing authorization in 16 other European counties. Through marketing collaborations with companies such as Swedish Orphan AB, Elan Pharmaceuticals Ltd. in

the United Kingdom, and Grupo Ferrer Internacional SA in Spain, Cephalon planned to launch Actiq commercially throughout Europe. Cephalon also granted rights to Orphan Australia to market and distribute Actiq in Australia and New Zealand.

Cephalon acquired a third major product in January 2001. All rights to Gabitril, a treatment for partial seizures related to epilepsy, were bought from Abbott Laboratories for $100 million. The drug had been approved by the FDA in September 1997 and was launched in the United States in 1998. Numerous epilepsy drugs already on the market competed with Gabitril, but the drug nevertheless garnered $23 million in sales in 2000. In order to widen the market for the drug, Cephalon began investigating the use of Gabitril as a mood stabilizer for various psychiatric disorders.

Besides its three main products in the United States, Cephalon marketed seven products through its European subsidiary. In the United Kingdom, those products included Anafranil, a treatment for depression and obsessive compulsive disorder; Lioresal and ITB Therapy, treatments for spasticity; Ritalin, an ADHD drug; and Tegretol, for epilepsy. The company also marketed two Parkinson's medications in Europe: Xilopar in Germany and Apokinon in France. A 30-person sales team in Europe supported Cephalon's activities there.

Research and development remained central to ensuring Cephalon's long-term profitability. In collaborations with such international partners as TAP Holdings, Kyowa Hakko Kogyo, H Lundbeck, and, as of December 2000, the R.W. Johnson Pharmaceutical Research Institute, the company was researching kinase inhibitors, compounds that either enhance cell survival or cause cell death. The compounds had potential for treating neurological and oncological diseases.

Cephalon's extensive library of proprietary compounds provided ample fodder for research. Products under development in 2001 included CEP-701, a compound that had been shown to cause the death of cancer cells by inhibiting the activity of a certain kinase, or protein. The compound was being developed to treat prostate and pancreatic cancer. Phase one testing was also just beginning on a second compound, CEP-7055, which was found in preclinical studies to prevent the development of the blood supply required for tumors to grow. Cephalon hoped that the experience with Actiq would pave the way for success with these further cancer drugs. The company was also working on a compound, CEP-1347, that could inhibit the progression of Parkinson's and Alzheimer's.

The deals leading to the acquisition of Actiq and Gabitril, as well as the resources invested in continued research, contributed to Cephalon's growing net loss. The company reported losses of $55.4 million for 1998, $70 million for 1999, and $101.1 million for 2000. But the establishment of three successful proprietary drugs finally gave Cephalon the prospect of stable sales revenue, while the products under development gave the company growth potential. CEO and founder Frank Baldino believed that the company was laying a solid foundation for profitability in the near future.

Principal Subsidiaries: Anesta Corporation; Cephalon (UK) Limited.

Principal Competitors: American Biogenetic; Amgen, Inc.; Athena Neurosciences; Cell Pathways; Cortex Pharmaceuticals; Draxis Health Inc.; Genset; GlaxoSmithKline; Builford Pharmaceuticals; NeoTherapeutics; Neurocrine; Orphan Medical; Sanofi-Sunthélabo.

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Source: *International Directory of Company Histories*, Vol. 45. St. James Press, 2002.

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- # Company Histories

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- Prada Holdings B.V.
- Gulfstream Aerospace Corporation
- Cannondale Corporation
- New Balance Athletic Shoe, Inc.
- Ocean Spray Cranberries, Inc
- Nordstrom, Inc
- Banta Corporation

EXHIBIT 78

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug
Administration
Rockville MD 20857

NDA 20-747/S-010

Anesta Corporation
C/O Cephalon, Inc.
145 Brandywine Parkway
West Chester, PA 19380-4245

Attention: Kenneth L. White, Pharm.D.
Vice President, Regulatory Affairs

Dear Dr. White:

Please refer to your supplemental new drug application dated January 28, 2002, received January 29, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actiq (oral trasmucosal fentanyl citrate).

This "Changes Being Effected" supplemental new drug application provides for revisions to the **PRECAUTIONS** section of the Package Insert and to the Patient leaflet.

We have completed the review of this supplemental application, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

1. In the package insert, remove the "°" (degrees) symbol after the 2.51 number from the second sentence of the 5th paragraph of the "**Pharmacokinetic, absorption** subsection of the **CLINICAL PHARMACOLOGY** section.

2. The following revisions pertain to the Patient Leaflet.

   a. Underline the word "not" to read "If the person is not awake and alert…" in the first sentence of the "If Someone Accidentally Takes Actiq" subheading in the black box.

   b. Underline and bold the word "not" to read "You should **not** use Actiq if you are having short term…" and "You should **not** use Actiq unless you have breakthrough cancer…" in the first and second sentence of "When Not To Use Actiq" subsection.

   c. Underline the word "not" to read "**If the person is not awake and alert**…" in the third bullet of the "What To Do If A Child Or Adult Accidentally Takes Actiq*" subsection.*

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert and patient leaflet submitted January 28, 2002). These revisions are terms of the approval of this application.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-747/S-010." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Parinda Jani, Acting Chief, Project Management Staff, at (301) 827-7410.

Sincerely,

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Cynthia McCormick
3/12/02 02:14:33 PM

EXHIBIT 79

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2002

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission file number 0-19119

Cephalon, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**23-2484489**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
145 Brandywine Parkway, West Chester, Pennsylvania	**19380-4245**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: **(610) 344-0200**

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Name of each exchange on which registered**

None None

Securities registered pursuant to Section 12(g) of the Act:

Common Stock, par value $.01 per share

(Title of Class)

Indicate by check mark whether the registrant (1) has filed all reports to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports) and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. / /

Indicate by check mark whether the registrant is an accelerated filer (as defined in Rule 12b-2 of the Securities Act of 1933). Yes ☒ No ☐

The aggregate market value of the voting stock held by non-affiliates of the registrant, as of June 30, 2002, was approximately $2.5 billion. Such aggregate market value was computed by reference to the closing price of the Common Stock as reported on the Nasdaq National Market on June 30, 2002. For purposes of making this calculation only, the registrant has defined affiliates as including all directors and executive officers.

The number of shares of the registrant's Common Stock outstanding as of March 14, 2003 was 55,472,671.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2003 annual meeting of stockholders are incorporated by reference into Items 10, 11, 12, and 13 of Part III of this Form 10-K.

TABLE OF CONTENTS

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

In addition to historical facts or statements of current condition, this report and the documents into which this report is and will be incorporated contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements contained in this report constitute our expectations or forecasts of future events as of the date this report was filed with the SEC and are not statements of historical fact. You can identify these statements by the fact that they do not relate strictly to historical or current facts. Such statements may include words such as "anticipate," "will," "estimate," "expect," "project," "intend," "should," "plan," "believe," "hope," and other words and terms of similar meaning in connection with any discussion of, among other things, future operating or financial performance, strategic initiatives and business strategies, regulatory or competitive environments, our intellectual property and product development. In particular, these forward-looking statements include, among others, statements about:

- our dependence on sales of PROVIGIL, ACTIQ and GABITRIL and the market prospects and future marketing efforts for these products;

- any potential expansion of the authorized uses of our existing products;
- our anticipated scientific progress in our research programs and our development of potential pharmaceutical products including our ongoing or planned clinical trials, and the timing of revenues from these products, if any;
- the timing and unpredictability of regulatory approvals, including with respect to our planned sNDA submission, and product rollout;
- our ability to adequately protect our technology and enforce our intellectual property rights and the future expiration of patent and/or regulatory exclusivity on certain of our products;
- our sales, costs, EBITDA and earnings per share projections and permitted, similar non-GAAP performance measures for 2003 and beyond, including our ability to maintain profitability in the future;
- our future cash flow and our ability to raise additional funds, if needed; and
- other statements regarding matters that are not historical facts or statement of current condition.

Any or all of our forward-looking statements in this report and in the documents we have referred you to may turn out to be wrong. They can be affected by inaccurate assumptions we might make or by known or unknown risks and uncertainties. Therefore, you should not place undue reliance on any such forward-looking statements. The factors that could cause actual results to differ from those expressed or implied by our forward-looking statements include, among others:

- the acceptance of our products by physicians and patients in our current markets and new markets;
- our ability to obtain regulatory approvals of expanded indications for certain of our products;
- scientific or regulatory setbacks with respect to research programs, clinical trials and/or our existing products;
- unanticipated cash requirements to support current operations, expansion of our business or capital expenditures;
- the inability to adequately protect our key intellectual property rights;
- the loss of key management or scientific personnel;
- the activities of our competitors in the industry, including the filing of an ANDA with a Paragraph IV certification for any product containing modafinil;
- market conditions in the biotechnology industry that make raising capital difficult, expensive or both; and
- enactment of new government regulations, court decisions, regulatory interpretations or other initiatives that are adverse to us or our interests.

We do not intend to update publicly any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law. We discuss in more detail the risks that we anticipate in the section above included in Item 7 hereof and entitled "Certain Risks Related to our Business." This discussion is permitted by the Private Securities Litigation Reform Act of 1995.

PART I

ITEM 1. BUSINESS

Overview

Cephalon is an international biopharmaceutical company dedicated to the discovery, development and marketing of products to treat sleep disorders, neurological and psychiatric disorders, cancer and pain. In addition to conducting an active research and development program, we market three products in the United States and a number of products in various countries throughout Europe.

Our corporate and research and development headquarters are in West Chester, Pennsylvania, and we have offices in Salt Lake City, Utah, France, the United Kingdom, Germany and Switzerland. We operate manufacturing facilities in France for the production of modafinil, which is the active drug substance in PROVIGIL® (modafinil) tablets [C-IV]. We also operate manufacturing facilities in Salt Lake City, Utah for the production of ACTIQ® (oral transmucosal fentanyl citrate) [C-II] for distribution and sale in the European Union and, beginning in the second quarter of 2003, the United States.

Our three biggest products in terms of product sales, PROVIGIL, ACTIQ and GABITRIL® (tiagabine hydrochloride), comprised approximately 80% of our total worldwide net product sales for the year ended December 31, 2002. The majority of PROVIGIL, ACTIQ and GABITRIL sales are in the U.S. market. Outside the United States, our commercial activities are concentrated primarily in France, the United Kingdom and Germany. The following table summarizes the major markets for our three most significant products:

PRODUCT	BRAND NAME	COUNTRY	INDICATION
Modafinil	PROVIGIL®	United States; Republic of Ireland; Italy	Excessive daytime sleepiness associated with narcolepsy
		United Kingdom	Excessive daytime sleepiness associated with narcolepsy and with obstructive sleep apnea/hypopnea syndrome
	MODIODAL®	France	Narcolepsy with or without cataplexy; idiopathic hypersomnia
	VIGIL®	Germany	Narcolepsy with or without cataplexy
	MODASOMIL®	Austria; Switzerland	Narcolepsy with or without cataplexy
Oral transmucosal fentanyl citrate	ACTIQ®	United States; Germany; Ireland; France; United Kingdom	Management of breakthrough cancer pain in patients with malignancies who are opioid tolerant
Tiagabine hydrochloride	GABITRIL®	United States; France; United Kingdom; Republic of Ireland; Germany; Austria; Switzerland	Partial seizures associated with epilepsy

In the United States, we market PROVIGIL, ACTIQ and GABITRIL through our specialty sales organization of approximately 330 persons, which includes:

- an approximately 240-person field sales and sales management and support team that details PROVIGIL and GABITRIL to neurologists, psychiatrists and sleep specialists; and
- an approximately 90-person field sales and sales management team that details ACTIQ to pain specialists and oncologists.

Outside of the United States, we have a sales organization in France numbering approximately 150 persons detailing products to office-based and hospital-based physicians, and a sales and marketing organization numbering approximately 50 persons that supports our presence in other European countries, principally the United Kingdom and Germany. In territories where we have not established our own sales and marketing groups, we have chosen to market our products through a select group of distribution companies with expertise in the development, marketing and sale of pharmaceuticals in those territories. In most cases, we have granted rights to our distribution partner to market, sell and distribute our products in their respective territories,

and we supply finished product for resale in that territory. The revenues and net income generated from these arrangements were not significant to our results of operations for 2002.

During 2002, we continued to pursue our strategy for PROVIGIL and GABITRIL to broaden the range of clinical uses that are approved by the FDA and European regulatory authorities. For PROVIGIL, we submitted a supplemental new drug application (sNDA) with the FDA in December 2002 requesting marketing approval for the treatment of excessive sleepiness associated with disorders of sleep and wakefulness in adults. The FDA's targeted review period for standard sNDAs is 10 months. Also in December 2002, we announced that we had received marketing approval from the Medicines Control Agency of the United Kingdom to expand the label of PROVIGIL to include the treatment of excessive daytime sleepiness in patients with obstructive sleep apnea/hypopnea syndrome. We plan to apply for a similar label expansion in France and Germany. In 2003, we plan to discuss with the FDA the steps necessary to pursue a label for PROVIGIL for attention deficit/hyperactivity disorder (ADHD) in children, which likely will require us to conduct additional clinical trials. For GABITRIL, we initiated pilot studies during 2002 in three areas: generalized anxiety disorder, neuropathic pain and insomnia. The results of the studies in generalized anxiety disorder and neuropathic pain were analyzed in early 2003 and generally provide support for the potential role of GABITRIL in treating these disorders. As a result, we intend to pursue larger studies in 2003 with GABITRIL in generalized anxiety disorder and post-traumatic stress syndrome. Results from the pilot studies in insomnia are expected later in 2003.

During the past year, we also continued our strategy of acquiring and consolidating worldwide product rights to PROVIGIL, ACTIQ and GABITRIL. In January 2002, we announced that we had acquired additional product rights to GABITRIL from Sanofi-Synthelabo and Novo Nordisk A/S and now control rights worldwide, excluding Canada, Latin America and Japan. In October 2002, we reacquired rights to ACTIQ in 12 countries, principally in Europe, from Elan Pharma International Limited. In December 2002, we announced that we had reacquired all rights to modafinil (the active drug substance in PROVIGIL) in Germany, Austria, Switzerland and certain countries in Central and Eastern Europe from Merckle GmbH, and in Spain from Cepa Schwarz Pharma. In March 2003, we announced that we had signed a license agreement for Tanabe Seiyaku to commercialize ACTIQ in Japan.

In addition to clinical programs focused on our marketed products, we have significant research programs that seek to discover and develop treatments for neurological and oncological disorders. Our technology principally focuses on an understanding of kinases and the role they play in cellular survival and proliferation. We have coupled this knowledge with a library of active, selective, small molecule inhibitors of kinases that allows us to intervene in these processes. This technology base has resulted in three molecules that are currently in clinical development. With respect to neurology, we have a program with a molecule, CEP-1347, that has entered into a Phase 2/3 clinical trial for the treatment of patients with early stage Parkinson's disease. In the cancer area, we have a program with a lead molecule, CEP-701, and have completed Phase 2 studies with this molecule to study its effect in patients refractory to other therapies and suffering from prostate cancer, pancreatic cancer and acute myeloid leukemia (AML). In early studies in prostate cancer and AML we observed positive signals from the use of CEP-701, although the treatment effect seen was not sufficient to justify continued studies as monotherapy in refractory patients. We are initiating additional studies with earlier stage patients and in combination with other therapies. Our efforts in pancreatic cancer have been halted due to lack of efficacy. Additionally, we are conducting a Phase 1 clinical study with another molecule, CEP-7055, for the treatment of solid tumors. As part of our corporate strategy, we often seek to share the risk of our research and development activities with corporate partners and, to that end, we have entered into agreements to share the costs of developing and/or commercializing certain of these molecules.

For the year ended December 31, 2002, our total revenues and income before income taxes were $506.9 million and $62.4 million, respectively. The third quarter of 2001 was our first profitable quarter from commercial operations since

inception. Our accumulated deficit at December 31, 2002 was $405.2 million. These accumulated losses have resulted principally from costs incurred in research and development, including clinical trials, and from selling, general and administrative costs associated with our commercial operations. Prior to 2001, we funded our operations principally from the proceeds of private and public sales of our equity and debt securities. While we seek to increase profitability and cash flow from operations, we will need to continue to achieve product sales and other revenue sufficient for us to attain these objectives. The rate of our future growth will depend, in part, upon our ability to obtain additional regulatory approvals for our currently marketed products, or successfully acquire, develop and commercialize new product candidates.

We are a Delaware corporation with our principal executive offices located at 145 Brandywine Parkway, West Chester, Pennsylvania, 19380. Our telephone number is (610) 344-0200 and our web site address is www.cephalon.com. We make available free of charge through the Investor Relations section of our web site our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, current reports on Form 8-K and all amendments to those reports as soon as reasonably practicable after such material is electronically filed with or furnished to the Securities and Exchange Commission. We include our web site

address in this Annual Report on Form 10-K only as an inactive textual reference and do not intend it to be an active link to our web site.

Subsequent Events

In January 2003, we announced that we had entered into a five-year agreement with MDS Proteomics Inc. (MDSP), a subsidiary of MDS Inc., to utilize MDSP's technologies with the objective of accelerating the clinical development of and broadening the market opportunities for our pipeline of small chemical compounds. MDSP will receive payments upon the successful achievement of specified milestones and will receive royalties on sales of products resulting from the collaboration. As part of the agreement, we purchased from MDSP a $30.0 million 5% convertible note due 2010. The note is convertible into MDSP's common stock at an initial conversion price of $22.00 per share, subject to adjustment if MDSP sells shares of its common stock at a lower price.

On February 5, 2003, we announced that the FDA had accepted an abbreviated new drug application (ANDA) for a generic form of modafinil, the active ingredient in PROVIGIL. On March 28, 2003, we filed a patent infringement lawsuit in U.S. District Court in New Jersey against Teva Pharmaceuticals USA, Inc., Mylan Pharmaceuticals Inc., Ranbaxy Pharmaceuticals Inc., and Barr Laboratories, Inc. based upon the ANDAs filed by each of these companies with the FDA. See "—PROVIGIL—Intellectual Property Position" for more information.

On March 7, 2003, our wholly-owned subsidiary, Cephalon Australia Pty. Limited, formally commenced a takeover bid for SIRTeX Medical Limited (ASX: SRX). SIRTeX markets SIR-Spheres®, a product approved in the United States, Europe, Australia and portions of Asia for the treatment of certain types of liver cancer. Under its bid, Cephalon Australia intends to offer A$4.85 cash for each SIRTeX ordinary share including any SIRTeX shares that are issued on the exercise of SIRTeX options. Cephalon Australia also has obtained an option to acquire shares from SIRTeX's largest shareholder representing up to 19.9 percent of the total issued share capital of SIRTeX at a price of A$4.85 per SIRTeX share. The total bid value is approximately US$161 million. If successful, we intend to fund the bid price using a portion of our existing cash and investment balance. We believe there are a number of risks inherent in SIRTeX's business, post-acquisition. Specifically, we believe that we will need to significantly increase manufacturing capacity to meet projected demand in the U.S. and European markets over the next few years. Increasing capacity in the pharmaceutical industry is expensive, time consuming and requires approval of appropriate regulatory authorities. Until such expansions are complete, there can be no assurance that product will be available to satisfy anticipated demand for SIR-Spheres. We also believe that substantial investment will be necessary in many other aspects of SIRTeX's business, including sales, marketing and distribution, for us to realize the full potential of its technologies.

PROVIGIL

Overview

Modafinil is the first in a new class of wakefulness-promoting agents. While its exact mechanism of action remains to be fully elucidated, modafinil appears to act selectively in regions of the brain believed to regulate normal sleep and wakefulness. The FDA approved PROVIGIL for the treatment of excessive daytime sleepiness associated with narcolepsy in December 1998 and we launched the product in the United States in February 1999. Modafinil currently is approved in more than 20 countries, including France, the United Kingdom, Ireland, Italy and Germany, for the treatment of excessive daytime sleepiness associated with narcolepsy. In December 2002, we also received approval to market modafinil in the United Kingdom to treat excessive daytime sleepiness in patients with obstructive sleep apnea/hypopnea syndrome.

In 2002, we marketed PROVIGIL in the United States through an approximately 185-person field sales and sales management team that details the product primarily to neurologists, psychiatrists and sleep specialists. In early 2003, we increased this sales team by approximately 55 persons. Outside the United States, we market modafinil using both our existing European sales force (e.g., in France, the United Kingdom and Germany) and through marketing collaborations with third parties.

Excessive sleepiness is a common and disabling symptom across many different disease states. Excessive sleepiness may negatively impact daytime functioning, including awareness, judgment, productivity and quality of life. Over the past few years, we have focused significant clinical development efforts on exploring the potential use of PROVIGIL in treating conditions beyond narcolepsy where excessive sleepiness is a significant clinical problem. On December 20, 2002, we filed an sNDA with the FDA requesting marketing approval of PROVIGIL in the United States for the treatment of excessive sleepiness associated with disorders of sleep and wakefulness in adults. This filing represented the achievement of an important milestone for us in our development efforts for PROVIGIL.

While applicable laws and regulations prevent us from promoting our products for uses beyond those contained in the approved label, our analysis of prescription data for PROVIGIL in the United States indicates that some physicians have elected to prescribe the product to treat indications outside its currently labeled indication of excessive daytime sleepiness associated with narcolepsy, including for excessive sleepiness associated with depression or obstructive sleep apnea, fatigue associated with multiple sclerosis and ADHD.

Narcolepsy

Narcolepsy is a debilitating, lifelong disorder whose symptoms often first arise in late childhood. Its most notable symptom is an uncontrollable propensity to fall asleep during the day. There is no cure for narcolepsy, which is estimated to affect approximately 200,000 people in the United States. Estimates indicate that approximately 35% of this population currently is diagnosed and receiving treatment for narcolepsy. PROVIGIL has been recognized by the American Academy of Sleep Medicine as a standard therapy for the treatment of excessive daytime sleepiness associated with narcolepsy.

Before we received FDA approval to market PROVIGIL, we conducted many clinical studies, including two Phase 3, double-blind, placebo-controlled, nine-week multi-center studies of PROVIGIL with more than 550 patients who met the American Sleep Disorders Association criteria for narcolepsy. Both studies demonstrated improvement in objective and subjective measures of excessive daytime sleepiness compared to placebo. PROVIGIL was found to be generally well tolerated, with a low incidence of adverse events relative to placebo. The most commonly observed adverse events were headache, infection, nausea, nervousness, anxiety and insomnia.

Market expansion strategies

Given the efficacy of PROVIGIL in reducing excessive daytime sleepiness associated with narcolepsy and the results of completed clinical trials, it became clear to us that PROVIGIL could be useful in treating excessive sleepiness associated with disorders of sleep and wakefulness beyond narcolepsy. Excessive sleepiness may be caused by a number of clinical conditions in addition to narcolepsy. For example, patients who suffer from obstructive sleep apnea often are tired during the day as a result of disrupted nighttime sleep. In addition, many people receive inadequate sleep due to nighttime work schedules that require them to function at the lowest point of their daily alertness cycle, followed by shortened and fragmented daytime sleep (shift work sleep disorder). Multiple well-controlled, multi-center clinical studies conducted in patients suffering from obstructive sleep apnea and shift work sleep disorder have shown that PROVIGIL may be useful in alleviating the excessive sleepiness experienced by these patients.

The sNDA that we filed with the FDA in December 2002 was based on positive data from six double-blind, placebo-controlled clinical studies evaluating the safety and efficacy of PROVIGIL versus placebo in more than 1,500 patients with excessive sleepiness associated with a disorder of sleep and wakefulness. Specifically, we submitted clinical data from three patient populations in the sNDA: (1) resubmission of the data submitted in the initial NDA, together with extended follow-up information, from studies of patients suffering from narcolepsy as a model for sleep-wake cycle dysregulation associated with central nervous system disease; (2) data from previously reported studies of patients suffering from obstructive sleep apnea as a model for disrupted sleep; and (3) data from the shift work sleep disorder study reported in late 2002 as a model for circadian rhythm disorders. While each of these clinical studies met their primary endpoints, and we believe that these studies are appropriate models to support a broader label for PROVIGIL, we cannot be sure that we will succeed in obtaining FDA approval for an expanded label. If the FDA does not approve the sNDA, it is not clear what impact this will have on sales and earnings. The FDA's targeted review period for standard sNDAs is 10 months.

A main focus of our ongoing clinical program continues to be the exploration of the potential use of PROVIGIL in treating excessive sleepiness that may be caused by a variety of clinical conditions. To that end, we have conducted clinical studies in patients suffering from a number of representative disorders of sleep and wakefulness. We also are interested in exploring the utility of PROVIGIL in other areas, including ADHD in children. In September 2002, we announced positive results from an investigational clinical study in children suffering from ADHD. In the four-week, randomized, double-blind, placebo-controlled, parallel design study, 248 children and adolescents between the ages of six and 13 were assigned to one of four daily dose regimens of PROVIGIL or placebo. The primary efficacy endpoint measure was the teacher-completed school version of the ADHD Rating Scale IV. All of the PROVIGIL treated groups showed a reduction in symptoms of ADHD, with certain dosage groups reaching statistical significance compared to placebo ($p<0.05$) and with the dosage group receiving 300mg of PROVIGIL, once a day, reaching statistical significance at all primary endpoints. PROVIGIL generally was well tolerated with the most commonly reported adverse events in this study consistent with those described in the current product label. We expect that the complete study data will be presented at the American Psychiatric Association meeting in May 2003. We plan to initiate a Phase 3 program in ADHD in 2003.

Finally, an important focus of our PROVIGIL strategy is the development of follow-on compounds. In 2003, we expect to begin human clinical trials with the R-isomer of modafinil. We are hopeful that these trials will, among other things, confirm in humans a longer duration of action of this isomer relative to the current PROVIGIL formulation. If successful, we would seek to launch this new compound in late 2005. In addition, we continue to engage in pre-clinical efforts and have identified second generation new chemical entities designed to provide additional clinical benefits.

Intellectual Property Position

We own U.S. and foreign patent rights that expire between 2014 and 2015 covering pharmaceutical compositions and uses of modafinil having certain particle sizes. Ultimately, these particle-size patents might be found invalid if challenged by a third party or a potential competitor could develop a competing product or product formulation that avoids infringement of these patents. On February 5, 2003, we announced that the FDA had accepted an abbreviated new drug application, or ANDA, for a pharmaceutical product containing modafinil. Any ANDA for modafinil filed with the FDA prior to December 2003 must contain a Paragraph IV certification in which the ANDA applicant certifies that the U.S. particle-size modafinil patent covering PROVIGIL is either invalid or will not be infringed by the ANDA product.

While we intend to vigorously defend the validity, and prevent infringement, of our patents, these efforts will be both expensive and time consuming and there can be no assurance that they will be successful. On March 28, 2003, we filed a patent infringement lawsuit in U.S. District Court in New Jersey against Teva Pharmaceuticals USA, Inc., Mylan Pharmaceuticals Inc., Ranbaxy Pharmaceuticals Inc., and Barr Laboratories, Inc. based upon the ANDAs filed by each of these companies with the FDA. If an ANDA or an NDA is approved, a competitor could begin selling a modafinil-based product upon the expiration of our FDA orphan drug exclusivity, currently in December 2005, which, in the absence of a marketed isomer version of modafinil, would significantly and negatively impact revenues from our current modafinil-based products. We expect to perform an additional clinical study of PROVIGIL in pediatric patients, pursuant to which the FDA could grant us a six-month extension of our orphan drug exclusivity and particle-size patent so that we would retain exclusivity until June 2006. However, we cannot be sure that the FDA will grant such extensions.

The U.S. composition of matter patent for modafinil expired in 2001. Corresponding patents outside the United States either have expired or will expire in March 2003, except in Italy where a patent extension beyond the original 1998 expiration remains possible.

We own composition of matter patents directed to the R-isomer of modafinil that is set to expire in May 2007 in the United States and January 2007 outside the United States. Assuming we are successful in attaining FDA approval for this compound in late 2005, we would expect to receive a three year period of marketing exclusivity (until late 2008). Furthermore, assuming this same timetable for approval, we would anticipate that the patent life would be extended until approximately early 2009. If we perform an additional clinical study of this product in pediatric patients, the FDA could grant us a six-month extension of the patent (until mid-2009) and of our marketing exclusivity. We also hold rights to other patents and patent applications directed to further pharmaceutical compositions, manufacturing processes and uses of next generation modafinil. We own rights to various trademarks covering pharmaceutical products containing the active drug substance modafinil.

Manufacturing and Product Supply

At our manufacturing facilities in France, we produce the active drug substance modafinil. We have two qualified manufacturers, Watson Pharmaceuticals and DSM Pharmaceuticals, for finished commercial supplies of PROVIGIL. Any future change in manufacturers or manufacturing processes requires regulatory approval. We seek to maintain inventories of active drug substance and finished products to protect against supply disruptions.

Competition

There are several other products used for the treatment of narcolepsy or excessive daytime sleepiness in the United States and in our other licensed territories, including methylphenidate products such as RITALIN® by Novartis, many of which have been available for a number of years and are available in inexpensive generic forms. Under current FDA and European medical authority regulations, we are restricted from promoting the use of PROVIGIL outside its labeled indication of excessive daytime sleepiness associated with narcolepsy.

ACTIQ

Overview

ACTIQ is the only drug approved in the United States for the management of breakthrough cancer pain in opioid tolerant patients. It was approved by the FDA in November 1998 and was launched in the United States in March 1999. Following our acquisition of Anesta Corp. in October 2000, we relaunched ACTIQ in February 2001. In October 2002, we reacquired rights to ACTIQ in twelve countries, principally in Europe, from Elan Pharma International Limited. In 2002, we marketed ACTIQ in the United States through an approximately 60-person field sales and sales management team that detailed the product to pain specialists and oncologists. In early 2003, we increased this team by approximately 30 persons to a total of 90 persons.

ACTIQ uses our proprietary oral transmucosal delivery system (OTS™) to deliver fentanyl citrate, a powerful, Schedule II opioid analgesic. The OTS delivery system consists of a drug matrix that is mounted on a handle. It is designed to achieve absorption of fentanyl through the oral mucosa (the lining of the mouth) and into the bloodstream. Side effects of ACTIQ are typical of opioid products and include somnolence, nausea, vomiting and dizziness. The greatest risk from improper use of ACTIQ, as with all opioid-based products, is the potential for respiratory depression, which can be life threatening.

Breakthrough Cancer Pain

One of the most challenging components of cancer pain is breakthrough pain. Breakthrough pain is a flare of moderate to severe pain that "breaks through" the medication patients use to control their persistent pain. Breakthrough pain may be related to a specific activity, or may occur spontaneously and unpredictably.

Breakthrough cancer pain typically develops rapidly and often reaches maximum intensity in three to five minutes. It has a duration that varies from 30 minutes to several hours and can be extremely painful and debilitating. Cancer patients who suffer from breakthrough pain may suffer a number of episodes every day. Opioid tablets, capsules and elixirs are not optimal to treat breakthrough cancer pain because they typically require 30 minutes or more to produce pain relief. Physicians can attempt to manage breakthrough pain by increasing the dose of the around-the-clock, long-acting opioid analgesic until the patient no longer experiences breakthrough pain. However, this approach frequently takes several days to accomplish and may lead to over-medication and an increase in undesirable side effects such as drowsiness or severe constipation.

Ideal management of breakthrough pain requires rescue medication that has a rapid onset of action and the ability for dosing to be tailored to the individual characteristics of the breakthrough pain episodes, such as intensity and duration. With ACTIQ, a patient places the product between his or her cheek and gum and moves it from side to side. A portion of the fentanyl citrate is absorbed through the mucosal tissues into the blood stream, while the remaining dose is swallowed and absorbed more slowly through the gastro-intestinal tract. Pain relief may begin within 10 to 15 minutes. ACTIQ is available in six dosage strengths to allow individualization of dosing.

Other than ACTIQ, the only currently available treatments that adequately match the onset of pain relief to the onset of breakthrough cancer pain are intravenous or subcutaneous infusions or intramuscular injections of potent opioids. In many settings, infusions or injections are unacceptable because they are invasive, uncomfortable, inconvenient for patients and caregivers, and, in a home setting, are more costly than less invasive methods.

We market ACTIQ under a comprehensive risk management program of educational and safe use messages that inform health care professionals, patients and their families of proper use, storage, handling and disposal of the product.

Intellectual Property Position

We hold an exclusive license to the U.S. patent covering the currently approved pharmaceutical composition and method for administering fentanyl via this composition that is set to expire in May 2005. We also hold patents to an FDA-approved compressed powder formulation that we expect to begin selling in the United States in the second quarter of 2003. These patents expire in September 2006. The FDA could grant us a six-month extension of these patents when we perform a clinical study in pediatric patients. Corresponding patents in foreign countries expire between 2009 and 2010. The loss of patent protection for any of our products, including ACTIQ, could significantly impact our sales.

Other issued patents and pending patent applications in the United States and foreign countries that are owned or licensed by us are directed to various formulation processes of manufacturing the product, methods of using the product and disposal containers required by the FDA to be provided as part of the product. We also hold the rights to the ACTIQ trademark covering pharmaceuticals for oral transmucosal delivery containing fentanyl as the active drug substance.

Manufacturing and Product Supply

At our facility in Salt Lake City, Utah, we manufacture ACTIQ for sale in international markets. In February 2003, the FDA approved our sNDA requesting approval for the movement of production of ACTIQ for the United States from our previous supplier, Abbott Laboratories, to our Salt Lake City facility, and our use of a new compressed powder formulation of ACTIQ in the U.S. market. This formulation is the same formulation that has been sold in Europe for a number of years. We recently expanded our internal manufacturing capacity at our Salt Lake City facility and expect to begin selling the new formulation in the United States in the second quarter of 2003.

Fentanyl, the active ingredient in ACTIQ, is a Schedule II controlled substance under the Controlled Substances Act. Our purchases of fentanyl for use in the production of ACTIQ are subject to quota that are approved by the U.S. Drug Enforcement Administration. Supply disruption could result from delays in obtaining DEA approvals or the receipt of approvals for quantities of fentanyl that are insufficient to meet current or projected product demand. The quota system also limits our ability to build inventories as a method of insuring against possible supply disruptions.

Competition

The market for opioids used in cancer pain is dominated by three products currently marketed for chronic pain: Johnson & Johnson's DURAGESIC® and Purdue Pharmaceuticals' OXYCONTIN® and MS-CONTIN®. Contrasted with ACTIQ, these products have a slower onset of action and a longer duration of action and therefore do not directly compete with ACTIQ. ACTIQ is intended to be used as adjunctive breakthrough pain therapy for patients using long-acting opioids to treat their persistent pain. Cancer pain also is treated with quick-acting invasive (i.e., intravenous, intramuscular and subcutaneous) opioid delivery systems. While these delivery systems effectively match rapid pain relief to the rapid onset of breakthrough cancer pain, these systems generally are more costly, uncomfortable and inconvenient than ACTIQ's OTS delivery system. We are aware that other companies are developing other technologies for rapidly delivering opioids to treat breakthrough pain. If these technologies are successfully developed and approved over the next few years, they could represent significant competition for ACTIQ.

To meet future competitive challenges to ACTIQ, we continue to focus our research efforts on developing improved formulations of ACTIQ with enhanced clinical benefits, including a more rapid onset of action and a sugar-free formulation. In addition to providing significant patient benefit, we believe these efforts could yield enhanced intellectual property protection.

GABITRIL

Overview

GABITRIL is a selective GABA reuptake inhibitor (SGRI) that is approved for use as adjunctive therapy in the treatment of partial seizures in epileptic patients. The FDA approved GABITRIL in September 1997 and it was launched in the United States in 1998 by Abbott. In late 2000, we acquired all U.S. rights to GABITRIL from Abbott in exchange for payments totaling $100 million over five years. We also made an additional payment to Abbott of $10 million when Abbott obtained an extension of the composition patent covering the active drug substance contained in GABITRIL to 2011. In December 2001, we acquired product rights to GABITRIL worldwide, excluding Canada, Latin America and Japan, from Sanofi-Synthelabo and the product inventor, Novo Nordisk A/S. We currently are selling GABITRIL in France, the United Kingdom, Germany, Austria and Switzerland. In 2002, GABITRIL was supported in the United States by our 185-person field sales and sales management and support team that also promoted PROVIGIL. In early 2003, we expanded this sales team to approximately 240 persons.

While applicable laws and regulations prevent us from promoting our products for uses beyond those contained in the approved label, our analysis of prescription data in the United States for GABITRIL indicates that some physicians have elected to prescribe the product to treat indications outside of its currently labeled indication, including generalized anxiety disorder and neuropathic pain.

Epilepsy

Epilepsy is a chronic disorder characterized by seizures that cause sudden, involuntary, time-limited alteration in behavior, including changes in motor activities, autonomic functions, consciousness or sensations, and accompanied by an abnormal electrical discharge in the brain. A partial seizure arises from a disorder emanating from a distinct, identifiable region of the brain and produces a given set of symptoms depending on the area of onset. A general seizure arises from a general dysfunction of biochemical mechanisms throughout the brain and may produce different types of convulsions. Epilepsy usually begins in early childhood, but can appear at any time during an individual's lifespan. It is estimated that more than 1 million adult Americans suffer from epilepsy.

Market expansion strategies

GABA (gamma-amino butyric acid) is an important inhibitory transmitter in the central nervous system and is widely distributed in all regions of the brain. An SGRI increases the amount of available GABA in the brain, which can be useful in treating conditions where increasing GABA in the central nervous system may result in clinical benefit. Based upon the putative mechanism of action of GABITRIL established in animal models, and certain preclinical and clinical study results, we believe GABITRIL may eventually prove effective in treating disorders in addition to epilepsy. Therefore, we initiated pilot studies during 2002 in three areas: generalized anxiety disorder, neuropathic pain and insomnia. The results

of the studies in generalized anxiety disorder and neuropathic pain were analyzed in early 2003 and generally provide support for the potential role of GABITRIL in treating these disorders. As a result, we intend to pursue larger studies in 2003 with GABITRIL in generalized anxiety disorder and post-traumatic stress syndrome. Results from the pilot studies in insomnia are expected later in 2003.

Intellectual Property Position

GABITRIL is our trademark that is used in connection with pharmaceuticals containing tiagabine as the active drug substance. This product is covered by U.S. and foreign patents that are held by Novo-Nordisk A/S and that were licensed in the United States exclusively to Abbott Laboratories. We have an exclusive sublicense from Abbott to these patents in the United States and exclusive licenses from Novo-Nordisk to corresponding foreign patents.

There are three U.S. composition-of-matter patents covering the currently approved product: a patent claiming tiagabine, the active drug substance in GABITRIL; a patent claiming crystalline tiagabine hydrochloride monohydrate and its use as an anti-epileptic agent; and a patent claiming anhydrous crystalline tiagabine hydrochloride and processes for its preparation. These patents currently are set to expire in 2011, 2012 and 2017, respectively. There also is a pharmaceutical composition patent covering the currently approved product and processes for its preparation, which is set to expire in 2016. Supplemental Protection Certificates based upon corresponding foreign patents covering this product are set to expire in 2011.

Manufacturing and Product Supply

Abbott is required to supply us with GABITRIL for the United States until at least October 2005. Outside of the United States, we have an agreement with Sanofi-Synthelabo to supply us with GABITRIL until December 2004. After these dates, we may have to make other arrangements to provide such supply, which could include the manufacture of GABITRIL in-house for the United States, or establishing supply arrangements with third parties. Any such changes will require regulatory approval.

Competition

The pharmaceutical market for the treatment of partial seizures in epileptic patients generally is well served with a number of available therapeutics, several of which are recent entrants to the market. The market is dominated by Pfizer's NEURONTIN® (gabapentin). In addition, several treatments for partial seizures are available in inexpensive generic forms. Growth of pharmaceutical products in this market tends to be slow both because of the number of therapies available and also because physicians are unlikely to change the medication of a patient whose condition is well controlled.

OTHER PRODUCTS

In addition to PROVIGIL, ACTIQ and GABITRIL, we are engaged in the sale and marketing of other of our products and certain third party products in various international markets, principally in France, the United Kingdom and Germany. For the year ended December 31, 2002, aggregate net sales and revenue from these products accounted for approximately 20% of our total

revenues, with the majority of this revenue relating to sales of our own products in France. The following is a summary of certain other products we market and sell.

Product	Country	Indication	Third Party	Contract Expiration
Cephalon Products:				
SPASFON® (phloroglucinol)	France	Biliary/urinary tract spasm and irritable bowel syndrome	n/a	n/a
FONZYLANE® (buflomedil)	France	Cerebral vascular disorders	n/a	n/a
PROXALYOC® (piroxicam)	France	Non-steroid anti-inflammatory	n/a	n/a

PARALYOC® (paracetamol)	France	Analgesic	n/a	n/a
Third Party Products:				
APOKINON® (apomorphine hydrochloride)	France	Levadopa therapy fluctuations in Parkinson's Disease	Laboratoire Aguettant S.A.	2007
OTRASEL® (selegeline hydrochloride)	France	Parkinson's Disease	Elan Pharma International Limited	2015
TEGRETOL® (carbamezipine)	U.K.	Epilepsy	Novartis Pharma AG	2010
RITALIN® (methylphenidate)	U.K.	ADHD	Novartis Pharma AG	2010
LIORESAL® (baclofen)	U.K.	Spasticity	Novartis Pharma AG	2010
ANAFRAIL® (clomipramine hydrochloride)	U.K.	Depression and obsessive compulsive disorder	Novartis Pharma AG	2010
XILOPAR® (selegeline hydrochloride)	Germany	Parkinson's Disease	Elan Pharma International Limited	2015
QUILONUM® (lithium)	Germany	Bipolar disorder	GlaxoSmithKline Inc.	2007

We manufacture certain of our proprietary products at our manufacturing facilities in Mitry-Mory and Nevers, France. We perform warehousing, packaging and distribution activities for France and other export territories from our facilities in Maisons-Alfort, France. We have a sales organization in France numbering approximately 150 persons detailing our proprietary products to office-based and hospital-based physicians, and a sales and marketing organization numbering approximately 50 persons that supports sales of our products and third party products in other European countries. French government efforts to control healthcare costs may result in the rapid growth of generic competition to our proprietary products in France.

Our largest product in terms of product sales in France is SPASFON. SPASFON is an antimuscarinic, antispasmodic muscle relaxant indicated for biliary tract spasms, irritable bowel syndrome, urinary tract spasm and the treatment of certain gynecological-related spasms. The product is sold in a variety of formats, including solid oral tablets, fast-dissolve tablets (LYOC) and suppositories.

In the United Kingdom, we market and sell four neurology products together with PROVIGIL, under an exclusive collaboration arrangement with Novartis Pharma AG established in November 2000. Under this agreement, we exclusively market PROVIGIL, TEGRETOL, RITALIN, ANAFRANIL and LIORESAL. The companies share the earnings from sales of the Novartis products and PROVIGIL in the United Kingdom. We now face competition from generic versions of many of the branded products included in the collaboration. European Union pricing laws also allow the parallel importation of branded drugs between member countries. Due to pricing variations within the European Union, it is possible that our overall margins on our branded drugs could be impacted negatively as a result of the importation of product from relatively lower-margin member countries to relatively higher-margin member countries.

RESEARCH AND DEVELOPMENT

In addition to our clinical programs focused on our marketed products, our research and development efforts focus primarily on two therapeutic areas: neurodegenerative disorders and cancers. Neurodegenerative disorders are characterized by the death of neurons (i.e., the specialized conducting cells of the nervous system) that results in the loss of certain functions such as memory and motor coordination. Cancers are characterized by the uncontrolled proliferation of cells that may form tumors. Our research has focused on an understanding of kinases and the role they play in cellular survival and proliferation. We have coupled this knowledge with a library of active, selective, small molecule inhibitors of kinases that allows us to intervene in these processes. This technology base has resulted in three active clinical programs in the areas of neurology and oncology.

Neurology

A growing body of evidence, substantiated by our own research findings, suggests that neuronal death is caused by a series of biochemical events that are themselves precipitated by the activation of intracellular signaling pathways. Our research,

and that of others, has demonstrated that one of the initial events involved in the cell death process is the activation of the stress-activated protein kinase pathway. Thus, we believe inhibition of this pathway should lead to neuronal survival and result clinically in the inhibition of the progression of neurodegenerative diseases. We have identified targets within this pathway known as mixed lineage kinases (MLK), whose inhibition in preclinical models results in inactivation of the cell death process. We are pursuing the development of certain potent inhibitors of the MLK for the treatment of Parkinson's disease, as described below.

Parkinson's Disease

We have discovered several proprietary compounds that are potent MLK inhibitors and that are also efficacious in preclinical models in preventing neuronal death. We are developing one such MLK inhibitor, CEP-1347, for use as a potential treatment for Parkinson's disease. Parkinson's disease is a progressive disorder of the central nervous system affecting over one million Americans. The primary pathology of the disease is the degeneration of the dopamine neurons in the substantia nigra region of the brain, which results in a slowing of spontaneous movements, gait difficulty, postural instability, rigidity and tremor. In a variety of preclinical models of Parkinson's disease, CEP-1347 demonstrated therapeutic potential in inhibiting the progression of Parkinson's Disease. Specifically, in non-human primate models, CEP-1347 protected against loss of dopamine neurons in the regions of the brain affected by Parkinson's disease and prevented the appearance of the associated behavioral symptoms. Our rights to develop and market CEP-1347 in the United States come from our 1992 collaboration with Kyowa Hakko Kogyo Co., Ltd. We entered into a collaborative agreement with H. Lundbeck A/S, a Danish pharmaceutical company, in 1999 to discover, develop and market in Europe products to treat neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases. This collaboration covers the development and marketing of CEP-1347 and other proprietary small molecules that may be useful in treating these diseases.

In 2002, Cephalon and Lundbeck initiated a North American, randomized, double-blind, placebo-controlled, dose-finding Phase 2/3 clinical trial of CEP-1347 in patients with early stage Parkinson's Disease. The study expects to enroll approximately 800 patients at up to 65 locations in the United States and Canada. The objective of the study is to determine whether or not CEP-1347 may be effective in delaying disability due to progression of Parkinson's Disease. Patients enrolled into the study are expected to be treated for two years and will receive either placebo or CEP-1347. We have a supply agreement with Abbott under which it supplies the key chemical intermediate used for the manufacture of CEP-1347 under contract to Cephalon. Lundbeck uses that intermediate for the manufacture of CEP-1347 for use in clinical trials.

Oncology

In normal tissues, cellular proliferation is balanced by cellular death, and these processes are governed in part by a class of soluble protein molecules (commonly referred to as growth factors) that serve as communication signals between cells. Cancer is a disease characterized by the uncontrolled proliferation of cells, which may be linked to inappropriate signaling from growth factors. Many of these growth factors bind to cell surface receptors (many of which are kinases) and trigger intracellular signals that maintain cell survival or direct the cell to proliferate. Inhibition of these kinases provides a novel therapeutic strategy for treating a variety of oncological disorders without the undesirable side effects associated with traditional chemotherapeutics.

Receptor Tyrosine Kinase Inhibitors

We have synthesized a class of small, orally active molecules that are selective inhibitors of the nerve growth factor receptor tyrosine kinase (trk). Trk may play an important role in the development and propagation of prostate and pancreatic cancers; inhibiting trk antagonizes the "survival" signal elicited by this receptor in such tumors. Our lead compound in this area, CEP-701, is administered orally. We have licensed our rights to develop and market CEP-701 from Kyowa Hakko. We have a supply agreement with Abbott under which it supplies the key chemical intermediate found in CEP-701.

Our scientists have discovered that CEP-701, in addition to its trk activity, is also a potent inhibitor of the flt-3 kinase. Flt-3 kinase has been shown to be mutated in patients suffering from AML who are treatment resistant, which results in a poor prognosis. Thus, inhibition of this kinase may lead to a novel treatment for AML.

We have completed Phase 2 studies with CEP-701 to study its effect in patients refractory to other therapies and suffering from prostate cancer, pancreatic cancer and AML. Our efforts in pancreatic cancer have been halted due to lack of efficacy. In early studies in prostate cancer and AML we observed positive signals from the use of CEP-701, although

the treatment effect seen was not sufficient to justify continued studies as monotherapy in refractory patients. In 2003, we expect to initiate additional studies in earlier stage patients and in combination with other therapies.

Angiogenesis Inhibitors

As cancer cells aggregate and form solid tumors, they secrete growth factors that promote the formation of new blood vessels necessary for providing nutrients to the growing tumor; this process is called angiogenesis. Angiogenesis is promoted by a number of these growth factors but appears to be particularly dependent upon the vascular endothelial growth factor (VEGF). VEGF acts at its receptor kinase to initiate blood vessel growth into the tumor. We believe that inhibition of the receptor kinase for VEGF will result in inhibition of the angiogenesis process thus starving the tumor of needed nutrients. We believe that this approach has potential utility in the treatment of solid tumors.

We have synthesized a number of proprietary, orally active molecules that are potent and selective inhibitors of the VEGF receptor kinase. These molecules have been shown to slow the growth of a variety of tumors in preclinical models. Our lead compound in this area is CEP-7055. We have filed an Investigational New Drug application (IND) and are conducting Phase 1 clinical trials with CEP-7055. In December 2001, we entered into a collaborative agreement with Sanofi-Synthelabo to discover, develop and market worldwide products that inhibit angiogenesis, excluding nervous system and opthalmic disorders. The collaboration covers the development and marketing of CEP-7055 and other proprietary small molecules.

Drug Delivery Technologies

Oral Transmucosal System (OTS)

We are continuing to invest in research and development of our OTS technology platform to expand our position within our current therapeutic areas. For example, we currently are pursuing both sugar free and accelerated delivery formulations of ACTIQ that utilize our OTS technology. In addition, we continue to assess the potential uses of our OTS technology, as well as other proprietary buccal delivery systems, in several therapeutic areas in which we focus.

LYOC Delivery System

We continue to develop our LYOC technology, which is used to create fast-dissolving oral tablets. We currently manufacture and sell several drugs in France using our LYOC technology, including SPASFON LYOC, PARALYOC, PROXALYOC, and are considering other compounds that may be suitable for formulation using this technology.

Neurotrophic Factors

Under a collaboration with Chiron Corporation that was terminated in February 2001, we conducted clinical trials using IGF-I, also known as MYOTROPHIN® (mecasermin) Injection, in patients in North America and Europe suffering from amyotrophic lateral sclerosis (ALS). ALS is a fatal disorder of the nervous system characterized by the chronic, progressive degeneration of motor neurons, which leads to muscle weakness, muscle atrophy and, eventually, to the patient's death. In February 1997, we submitted a New Drug Application (NDA) to the FDA for approval to market MYOTROPHIN in the United States for the treatment of ALS. In May 1998, the FDA issued a letter stating that the NDA was "potentially approvable," under certain conditions. We do not believe those conditions can be met without conducting an additional Phase 3 clinical study, and we have no plans to conduct such a study at this time. However, certain physicians have obtained governmental and non-governmental funding to be used to conduct such a study. We have agreed with these physicians to allow reference to our IND and have agreed to supply MYOTROPHIN in quantities sufficient for them to conduct the study in exchange for the right to use any clinical data generated by such study in support of FDA approval of our pending NDA. These physicians have indicated to us that they expect to commence the study in the first half of 2003; however, if the study does not progress reasonably rapidly, we may be unable to provide quantities of MYOTROPHIN sufficient to complete the study. Even if this additional study is concluded, the results will not be available for several years and may not be sufficient to obtain regulatory approval to market the product.

Other Discovery Research Efforts

Since our inception, we have been engaged in research to discover innovative medicines. To date, we have focused our efforts on neurodegenerative diseases and cancer. This research has resulted in the discovery of compounds that could potentially be useful in treating important clinical conditions beyond those for which we have active development programs. In these and other cases, we often seek to establish collaborative partnerships with companies whose clinical development and marketing capabilities will maximize the value of these discoveries.

In addition to our research programs discussed above, we are pursuing a variety of other innovative discovery research efforts. For example, in June 2002, we announced a multi-year research collaboration with TransTech Pharma, Inc. The

collaboration will utilize TransTech's Translational Technology™, a highly automated and fully integrated proprietary drug discovery process, to discover and develop small molecules for up to three therapeutic targets. Also, in early 2003, we entered into a comprehensive collaboration with MDS Proteomics Inc., a subsidiary of MDS Inc., to utilize MDSP's technologies with the objective of accelerating the clinical development of and broadening the market opportunities for our pipeline of small molecule compounds, including the identification and validation of novel targets for the treatment of CNS disorders.

Scientific and Medical Advisory Board

We maintain a Scientific and Medical Advisory Board consisting of individuals with expertise in neuroscience and oncology research, as well as related fields. Members of the Scientific and Medical Advisory Board advise us on issues concerning long-term scientific planning, research and development, and also periodically evaluate our research programs, clinical development plans and clinical trials. We compensate the members for their services. The current members of our Scientific and Medical Advisory Board are as follows:

Stanley H. Appel, M.D.,
Baylor College of Medicine

Arthur K. Asbury, M.D.,
University of Pennsylvania Medical Center

Robert L. Barchi, M.D., Ph.D.,
University of Pennsylvania Medical Center

Bruce A. Chabner, M.D.,
Massachusetts General Hospital

Stanley Cohen, Ph.D., retired,
Vanderbilt University School of Medicine

Steven T. DeKosky, M.D.,
University of Pittsburgh Medical Center

John T. Isaacs, M.D.,
Johns Hopkins University, Sidney Kimmel Cancer Center

Richard Johnson, M.D.,
Johns Hopkins University School of Medicine

Robert Y. Moore, M.D., Ph.D.,
University of Pittsburgh

Robert H. Roth, Ph.D.,
Yale University School of Medicine

OTHER INTELLECTUAL PROPERTY

We also own issued and pending U.S. patents and applications claiming compositions and/or uses of certain kinase inhibitors, including two novel classes of small molecules referred to as "indolocarbazoles" and "fused pyrrolocarbazoles." We have filed foreign counterparts of these patents in other countries, as appropriate. We also have licensed U.S. and European composition-of-matter and use patents and applications for novel compositions under our collaborative agreement with Kyowa Hakko, including compositions and uses of certain indolocarbazoles for the treatment of pathological conditions of the prostate (including prostate cancer) and for the treatment of neurological disorders. We own issued and pending U.S. and foreign patents and applications claiming compositions and/or uses of inhibitors of certain proteases, including novel classes of small molecules for inhibition of calpain, and novel classes of small molecules for inhibition of the multicatalytic protease.

Through collaborative agreements with researchers at several academic institutions, we have licenses to or the right to license, generally on an exclusive basis, patents and patent applications issued or filed in the United States and certain other countries arising under or related to such collaborations.

CUSTOMERS

Our principal customers are wholesale drug distributors. These customers comprise a significant part of the distribution network for pharmaceutical products in the United States. A small number of large wholesale distributors control a significant share of this network. For the year ended December 31, 2002, our three largest U.S. wholesale drug distributors were Cardinal Health, Inc., McKesson Corporation and AmerisourceBergen Corporation. These three distributors, in the aggregate, accounted for 72% of our total gross product sales. The loss or bankruptcy of any of these customers could have an adverse affect on our results of operation and financial condition.

COMPETITION

We face intense competition and rapid technological change in the pharmaceutical marketplace. Large and small companies, academic institutions, governmental agencies, and other public and private research organizations conduct research, seek patent protection and establish collaborative arrangements for product development in competition with us. Products developed by any of these entities may compete directly with those we develop or sell. In addition, many of the companies and institutions that compete against us have substantially greater capital resources, research and development staffs and facilities than we have, and substantially greater experience in conducting clinical trials, obtaining regulatory approvals and manufacturing and marketing pharmaceutical products. These entities represent significant competition for us. In addition, competitors who are developing products for the treatment of neurological or oncological disorders might succeed in developing technologies and products that are more effective than any that we develop or sell or that would render our technology and products obsolete or noncompetitive. Competition and innovation from these or other sources potentially could negatively affect sales of our products or make them obsolete. Advances in current treatment methods also may adversely affect the market for such products. In addition, we may be at a competitive marketing disadvantage against companies that have broader product lines and whose sales personnel are able to offer more complementary products than we can. Any failure to maintain our competitive position could adversely affect our business and results of operations.

As discussed above, our products face competition in the marketplace. We cannot be sure that we will be able to demonstrate the potential advantages of our products to prescribing physicians and their patients on an absolute basis and/or in comparison to other presently marketed products. We also need to demonstrate to physicians, patients and third party payors that the cost of our products is reasonable and appropriate in the light of their safety and efficacy, the price of competing products and the related health care benefits to the patient.

GOVERNMENT REGULATION

The manufacture and sale of therapeutics are subject to extensive regulation by U.S. and foreign governmental authorities. In particular, pharmaceutical products are subject to rigorous preclinical and clinical trials and other approval requirements as well as other post-approval requirements by the FDA under the Federal Food, Drug, and Cosmetic Act and by analogous agencies in countries outside the United States.

As an initial step in the FDA regulatory approval process, preclinical studies are typically conducted in animals to identify potential safety problems and, in some cases, to evaluate potential efficacy. The results of the preclinical studies are submitted to regulatory authorities as a part of an Investigational New Drug Application (INDA) that is filed with regulatory agencies prior to beginning studies in humans. However, for several of our drug candidates, no animal model exists that is potentially predictive of results in humans. As a result, no in vivo indication of efficacy is available until these drug candidates progress to human clinical trials.

Clinical trials are typically conducted in three sequential phases, although the phases may overlap. Phase 1 typically begins with the initial introduction of the drug into human subjects prior to introduction into patients. In Phase 1, the compound is tested for safety, dosage tolerance, absorption, biodistribution, metabolism, excretion and clinical pharmacology, as well as, if possible, to gain early information on effectiveness. Phase 2 typically involves studies in a

small sample of the intended patient population to assess the efficacy of the drug for a specific indication, determine dose tolerance and the optimal dose range, and to gather additional information relating to safety and potential adverse effects. Phase 3 trials are undertaken to further evaluate clinical safety and efficacy in an expanded patient population, generally at multiple study sites, to determine the overall risk-benefit ratio of the drug and to provide an adequate basis for product labeling. Each trial is conducted in accordance with certain standards under protocols that detail the objectives of the study, the parameters to be used to monitor safety and the efficacy criteria to be evaluated. In the United States, each protocol must be submitted to the FDA as part of the IND. Further, one or more independent Institutional Review Boards must evaluate each clinical study. The Institutional Review Board considers, among other things, ethical factors, the safety of the study, the adequacy of informed consent by human subjects and the possible liability of the institution. Similar procedures and requirements must be fulfilled to conduct studies in other countries. The process of completing clinical trials for a new drug is likely to take a number of years and require the expenditure of substantial resources.

Promising data from preclinical and clinical trials are submitted to the FDA in an NDA for marketing approval and to foreign regulatory authorities under applicable requirements. Preparing an NDA or foreign application involves considerable data collection, verification, analyses and expense, and there can be no assurance that the applicable regulatory authority will accept the application or grant an approval on a timely basis, if at all. The marketing or sale of pharmaceuticals in the United States may not begin without FDA approval. The approval process is affected by a number of factors, including primarily the safety and

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efficacy demonstrated in clinical trials and the severity of the disease. Regulatory authorities may deny an application if, in their sole discretion, they determine that applicable regulatory criteria have not been satisfied or if, in their judgment, additional testing or information is required to ensure the efficacy and safety of the product. One of the conditions for initial marketing approval, as well as continued post-approval marketing, is that a prospective manufacturer's quality control and manufacturing procedures conform to the current Good Manufacturing Practice regulations of the regulatory authority. In complying with these regulations, a manufacturer must continue to expend time, money and effort in the area of production, quality control and quality assurance to ensure full compliance. Manufacturing establishments, both foreign and domestic, also are subject to inspections by or under the authority of the FDA and by other federal, state, local or foreign agencies. Discovery of previously unknown problems with a product or manufacturer may result in restrictions on such product or manufacturer, including withdrawal of the product from the market.

Even after regulatory approval has been obtained, further studies, including Phase 4 post-marketing studies, may be required to provide additional data on safety, to validate surrogate efficacy endpoints, or for other reasons, and the failure of such studies can result in a range of regulatory actions, including withdrawal of the product from the market. Further studies will be required to gain approval for the use of a product as a treatment for clinical indications other than those for which the product was initially approved. Results of post-marketing programs may limit or expand the further marketing of the products. Further, if there are any modifications to the drug, including any change in indication, manufacturing process, labeling or manufacturing facility, it may be necessary to submit an application seeking approval of such changes to the FDA or foreign regulatory authority. Finally, the FDA can place restrictions on approval and marketing utilizing its authority under applicable regulations. For example, ACTIQ was approved subject to restrictions that include mandating compliance with a rigorous Risk Management Program. This program gives the FDA authority to pre-approve promotional materials and permits an expedited market withdrawal procedure if issues arise regarding the safe use of ACTIQ. Moreover, marketed products are subject to continued regulatory oversight by the Office of Medical Policy Division of Drug Marketing, Advertising, and Communications, and the failure to comply with applicable regulations could result in marketing restrictions, financial penalties and/or other sanctions.

Whether or not FDA approval has been obtained, approval of a product by regulatory authorities in foreign countries must be obtained prior to the commencement of commercial sales of the product in such countries. The requirements governing the conduct of clinical trials and product approvals vary widely from country to country, and the time required for approval may be longer or shorter than that required for FDA approval. Although there are procedures for unified filings for most European countries, in general, each country also has its own additional procedures and requirements, especially related to pricing of new pharmaceuticals. Further, the FDA regulates the export of products produced in the United States and, in some circumstances, may prohibit the export even if such products are approved for sale in other countries.

In the United States, the Orphan Drug Act provides incentives to drug manufacturers to develop and manufacture drugs for the treatment of rare diseases, currently defined as diseases that affect fewer than 200,000 individuals in the United States, or for a disease that affects more than 200,000 individuals in the United States, where the sponsor does not realistically anticipate its product becoming profitable. The FDA has granted PROVIGIL orphan drug status for use in treating excessive daytime sleepiness associated with narcolepsy and has designated MYOTROPHIN as an orphan drug for use in treating ALS, because each indication currently affects fewer than 200,000 individuals in the United States. Under the Orphan Drug Act, a manufacturer of a designated orphan product can seek certain tax benefits, and the holder of the first FDA approval of a designated orphan product will be granted a seven-year period of marketing exclusivity for that product for the orphan indication. While the marketing exclusivity of an orphan drug would prevent other sponsors from obtaining approval of the same drug compound for the same indication unless the subsequent sponsors could demonstrate clinical superiority or a market shortage occurs, it would not prevent other sponsors from obtaining approval of the same compound for other indications or the use of other types of drugs for the same use as the orphan drug. Orphan drug designation generally does not confer any special or preferential treatment in the regulatory review process. The U.S. Congress has considered, and may consider in the future, legislation that would restrict the duration or scope of the market exclusivity of an orphan drug and, thus, we cannot be sure that the benefits of the existing statute will remain in effect. Additionally, we cannot be sure that other governmental regulations applicable to our products will not change.

In addition to the market exclusivity period under the Orphan Drug Act, the U.S. Drug Price Competition and Patent Term Restoration Act of 1984 permits a sponsor to apply for a maximum five-year extension of the term of a patent for a period of time following the initial FDA approval of an NDA for a New Chemical Entity (NCE). The statute specifically allows a patent owner acting with due diligence to extend the term of the patent for a period equal to one-half the period of time elapsed between the approval of the IND and the filing of the corresponding NDA, plus the period of time between the filing of the NDA and FDA approval, up to a maximum of five years of patent term extension. Any such extension, however, cannot extend the patent term beyond a maximum term of fourteen years following FDA approval and is subject to other restrictions. Additionally,

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under this statute, five years of marketing exclusivity is granted for the first approval of an NCE. During this period of exclusivity, sponsors generally may not file and the FDA may not approve an abbreviated New Drug Application or a 505 (b)(2) application for a drug product equivalent or identical to the NCE. An ANDA is the application form typically used by manufacturers seeking approval of a generic version of an approved drug. There is also a possibility that Congress will revise the underlying statute in the next few years, which may affect these provisions in ways that we cannot foresee. Additionally, the FDA regulates the labeling, storage, record keeping, advertising and promotion of prescription pharmaceuticals. Drug manufacturing establishments must register with the FDA and list their products with the FDA.

The Controlled Substances Act imposes various registration, record-keeping and reporting requirements, procurement and manufacturing quotas, labeling and packaging requirements, security controls and a restriction on prescription refills on certain pharmaceutical products. A principal factor in determining the particular requirements of this act, if any, applicable to a product is its actual or potential abuse profile. A pharmaceutical product may be listed as a Schedule II, III, IV or V substance, with Schedule II substances considered to present the highest risk of substance abuse and Schedule V substances the lowest. Modafinil, the active drug substance in PROVIGIL, has been scheduled under the Controlled Substances Act as a Schedule IV substance. Schedule IV substances are allowed no more than five prescription refills during a six-month period and are subject to special handling procedures relating to the storage, shipment, inventory control and disposal of the product. Fentanyl, the active ingredient in ACTIQ, is a Schedule II controlled substance. Schedule II substances are subject to even stricter handling and record keeping requirements and prescribing restrictions than Schedule III or IV products. In addition to federal scheduling, both PROVIGIL and ACTIQ are subject to state controlled substance regulation, and may be placed in more restrictive schedules than those determined by the U.S. Drug Enforcement Agency and FDA. However, to date, neither modafinil nor fentanyl has been placed in a more restrictive schedule by any state.

In addition to the statutes and regulations described above, we also are subject to regulation under the Occupational Safety and Health Act, the Environmental Protection Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act and other federal, state and local regulations.

EMPLOYEES

As of December 31, 2002, we had a total of 1,271 full-time employees, of which 706 were employed in the United States and 565 were located at our various facilities in Europe. We believe that we have been successful in attracting skilled and experienced personnel; however, competition for such personnel is intense.

ITEM 2. PROPERTIES

We own our corporate headquarters which are located in West Chester, Pennsylvania and which consist of approximately 160,000 square feet of administrative offices and research facilities. We also lease approximately 52,000 square feet of administrative offices that are near our owned facilities in West Chester. In Salt Lake City, Utah, we house administrative, research, manufacturing and warehousing operations in approximately 123,000 square feet that we lease. We lease office space for our European operations in England, as well as space for our satellite offices in Switzerland and Germany. In France, we own administrative facilities, an executive and research facility, a manufacturing facility, a packaging facility and various warehouses totaling approximately 285,000 square feet. We also lease the site of our other manufacturing facility in France totaling approximately 29,000 square feet. We believe that our current facilities are adequate for our present purposes, although we are seeking additional facilities necessary to support our anticipated growth over the next several years.

ITEM 3. LEGAL PROCEEDINGS

On March 28, 2003, we filed a patent infringement lawsuit in U.S. District Court in New Jersey against Teva Pharmaceuticals USA, Inc., Mylan Pharmaceuticals Inc., Ranbaxy Pharmaceuticals Inc., and Barr Laboratories, Inc. based upon the ANDAs filed by each of these companies seeking FDA approval for a generic equivalent of modafinil. The lawsuit claims infringement of our U.S. Patent No. RE37516, which covers the pharmaceutical compositions and methods of treatment with the form of modafinil contained in PROVIGIL. We intend to vigorously defend the validity, and prevent infringement, of this patent.

We are a party to certain other litigation in the ordinary course of our business, including, among others, U.S. patent interference proceedings, European patent oppositions, and matters alleging employment discrimination, product liability and breach of commercial contract. We are vigorously defending ourselves in all of these actions and do not believe these matters, even if adversely adjudicated or settled, would have a material adverse effect on our financial condition or results of operations.

ITEM 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS

We did not submit any matters to the vote of security holders during the fourth quarter of fiscal 2002.

Executive Officers of the Registrant

The names, ages and positions held by our executive officers as of December 31, 2002 are as follows:

Name	Age	Position
Frank Baldino, Jr., Ph.D.	49	Chairman and Chief Executive Officer
Paul Blake, F.R.C.P.	55	Senior Vice President, Clinical Research and Regulatory Affairs
J. Kevin Buchi	47	Senior Vice President and Chief Financial Officer
Peter E. Grebow, Ph.D.	56	Senior Vice President, Worldwide Business Development
John E. Osborn	45	Senior Vice President, General Counsel and Secretary
Robert P. Roche, Jr.	47	Senior Vice President, Pharmaceutical Operations
Carl A. Savini	53	Senior Vice President, Human Resources
Jeffry L. Vaught, Ph.D.	52	Senior Vice President and President, Research and Development

All executive officers are elected by the Board of Directors to serve in their respective capacities until their successors are elected and qualified or until their earlier resignation or removal.

Dr. Baldino founded Cephalon and has served as Chief Executive Officer and a director since its inception. He was appointed Chairman of the Board of Directors in December 1999. Dr. Baldino received his Ph.D. degree from Temple

University, holds several adjunct academic appointments and is a trustee of Temple University. Dr. Baldino currently serves as a director of Pharmacopeia, Inc., a developer of proprietary technology platforms for pharmaceutical companies, ViroPharma, Inc., a biopharmaceutical company, Acusphere, Inc., a specialty pharmaceutical company, and NicOx S.A., a company engaged in the research, development and commercialization of nitric oxide therapeutics.

Dr. Blake joined Cephalon in March 2001 as Senior Vice President, Clinical Research and Regulatory Affairs. From 1999 to 2001, Dr. Blake served as Chief Medical Officer for MDS Proteomics Inc., a Canadian health and life sciences company. From 1998-99 Dr. Blake served as President and Chief Executive Officer of Proliance Pharmaceuticals, Inc., a drug development company. Prior to that, he spent six years with SmithKline Beecham Pharmaceuticals (currently known as GlaxoSmithKline), most recently as Senior Vice President and Medical Director. Dr. Blake received his medical degree from London University, Royal Free Hospital and completed his clinical training in Internal Medicine and Cardiology. Dr. Blake is a fellow of the Royal College of Physicians (UK), a fellow of the Faculty of Pharmaceutical Medicine and a fellow of the American College of Clinical Pharmacology.

Mr. Buchi joined Cephalon as Controller in March 1991 and held several financial positions with the Company prior to being appointed Senior Vice President and Chief Financial Officer in April 1996. Between 1985 and 1991, Mr. Buchi served in a number of financial positions with E.I. du Pont de Nemours and Company. Since February 2003, Mr. Buchi has served as a member of the board of directors of Lorus Therapeutics Inc., a publicly-traded Canadian biotechnology company. Mr. Buchi received his masters of management degree from the J.L. Kellogg Graduate School of Management, Northwestern University, in 1982.

Dr. Grebow joined Cephalon in January 1991 and served as Senior Vice President, Drug Development prior to holding his current position as Senior Vice President, Business Development. From 1988 to 1990, Dr. Grebow served as Vice President of Drug Development for Rorer Central Research, a division of Rhone-Poulenc Rorer Pharmaceuticals Inc., a pharmaceutical company. Dr. Grebow received his Ph.D. degree in Chemistry from the University of California, Santa Barbara.

Mr. Osborn joined Cephalon in March 1997 as Vice President, Legal Affairs, was appointed Senior Vice President in September 1998, and has served as Senior Vice President, General Counsel and Secretary since January 1999. From 1992 to 1997, Mr. Osborn served in a number of legal positions with The DuPont Merck Pharmaceutical Company. Prior to that, he served in the George H.W. Bush administration with the U.S. Department of State, practiced corporate law with Hale and Dorr in Boston, and clerked for a U.S. Court of Appeals judge. Mr. Osborn received his law degree from the University of Virginia and holds a masters degree in international studies from The Johns Hopkins University. He also is a visiting fellow in politics at Princeton University and is a member of the Council on Foreign Relations.

Mr. Roche joined Cephalon in January 1995 and has served as Senior Vice President, Pharmaceutical Operations since November 2000. Prior to that, he was appointed to Senior Vice President of Sales and Marketing in June 1999 and prior to that as Vice President, Sales and Marketing. Previously, Mr. Roche was Director and Vice President, Worldwide Strategic Product Development, for SmithKline Beecham's central nervous system and gastrointestinal products business, and held senior

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marketing and management positions with that company in the Philippines, Canada and Spain. Mr. Roche graduated from Colgate University and received a master of business administration degree from The Wharton School, University of Pennsylvania.

Mr. Savini joined Cephalon in June 1993 and has served as Senior Vice President, Human Resources since January 2000. Prior to that he served as Director, Human Resources and was appointed Vice President, Human Resources in January 1995. From 1983 to 1993, Mr. Savini was employed by Bristol-Myers Squibb Company and from 1981 to 1983 he was employed by Johnson & Johnson's McNeil Pharmaceuticals. Mr. Savini graduated from Pennsylvania State University and received a master of business administration degree from La Salle College.

Dr. Vaught has been responsible for Cephalon's research operations since joining the Company in August 1991, and currently serves as Senior Vice President and President, Research and Development. Prior to joining Cephalon,

Dr. Vaught was employed by the R. W. Johnson Pharmaceutical Research Institute, a subsidiary of Johnson & Johnson. Dr. Vaught received his Ph.D. degree from the University of Minnesota.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY AND RELATED STOCKHOLDER MATTERS

Our common stock is quoted on the NASDAQ National Market under the symbol "CEPH." The following table sets forth the range of high and low sale prices for the common stock as reported on the NASDAQ National Market for the periods indicated below.

	High	Low
2001		
First Quarter	$ 64.50	$ 36.38
Second Quarter	72.80	39.50
Third Quarter	73.92	43.40
Fourth Quarter	78.40	47.05
2002		
First Quarter	$ 78.88	$ 52.18
Second Quarter	66.97	41.40
Third Quarter	49.00	35.82
Fourth Quarter	59.20	38.36

As of March 14, 2003 there were 620 holders of record of our common stock. On March 14, 2003, the last reported sale price of our common stock as reported on the NASDAQ National Market was $44.10 per share.

We have not paid any dividends on our common stock since our inception and do not anticipate paying any dividends on our common stock in the foreseeable future.

ITEM 6. SELECTED FINANCIAL DATA

In October 2000, we completed a merger with Anesta Corp. under which we acquired all of the outstanding shares of Anesta in a tax-free, stock-for-stock transaction. The merger has been accounted for as a pooling-of-interests and, accordingly, all of our prior period consolidated financial statements have been restated to include the results of operations, financial position, and cash flows of Anesta. Information concerning common stock and per share data has been restated on an equivalent share basis.

On December 28, 2001, we completed the acquisition of the outstanding shares of capital stock of Group Lafon. This acquisition has been accounted for as a purchase and, accordingly, the estimated fair value of assets acquired and liabilities assumed has been recorded as of the date of the acquisition.

Statement of operations data:	Year Ended December 31, 2002	2001	2000	1999	1998
	(In thousands, except per share data)				
Product sales	$ 465,943	$ 226,132	$ 91,637	$ 27,602	$ 921
Other revenues	40,954	35,863	20,153	23,832	15,409
Total revenues	506,897	261,995	111,790	51,434	16,330
Acquired in-process research and development	—	(20,000)	(22,200)	—	—
Debt exchange expense	—	(52,444)	—	—	—
Income tax benefit, net	112,629	—	—	—	—
Income (loss) before cumulative effect of a change in accounting principle	$ 175,062	$ (55,484)	$ (93,744)	$ (79,432)	$ (71,124)
Cumulative effect of a change in accounting principle	(3,534)	—	(7,434)	—	—
Net income (loss)	171,528	(55,484)	(101,178)	(79,432)	(71,124)
Dividends on convertible exchangeable preferred stock	—	(5,664)	(9,063)	(3,398)	—
Net income (loss) applicable to common shares	$ 171,528	$ (61,148)	$ (110,241)	$ (82,830)	$ (71,124)
Basic income (loss) per common share:					
Income (loss) before cumulative effect of a change in accounting principle	$ 3.17	$ (1.27)	$ (2.51)	$ (2.31)	$ (2.15)
Cumulative effect of a change in accounting principle	(.06)	—	(.19)	—	—
	$ 3.11	$ (1.27)	$ (2.70)	$ (2.31)	$ (2.15)
Diluted income (loss) per common share:					
Income (loss) before cumulative effect of a change in accounting principle	$ 2.84	$ (1.27)	$ (2.51)	$ (2.31)	$ (2.15)
Cumulative effect of a change in accounting principle	(.05)	—	(.19)	—	—
	$ 2.79	$ (1.27)	$ (2.70)	$ (2.31)	$ (2.15)
Weighted average number of shares outstanding	55,104	48,292	40,893	35,887	33,129
Weighted average number of shares outstanding — assuming dilution	67,442	48,292	40,893	35,887	33,129

Balance sheet data:	As of December 31, 2002	2001	2000	1999	1998
			(In thousands)		
Cash, cash equivalents and investments	$ 582,688	$ 603,884	$ 97,384	$ 272,340	$ 148,151
Total assets	1,689,090	1,446,408	308,435	312,262	179,802
Long-term debt	860,897	866,589	55,138	15,701	16,596
Accumulated deficit	(405,163)	(576,691)	(515,543)	(405,302)	(322,472)
Stockholders' equity	642,584	398,731	165,193	230,783	137,621

Pro Forma Results

The following data represents pro forma financial results assuming a retroactive adoption of changes in accounting principles.

Statement of operations data:	Year Ended December 31, 2000	1999	1998
	(In thousands, except per share data)		
Total revenues	$ 111,790	$ 44,391	$ 16,163
Net loss	$ (93,744)	$ (90,009)	$ (71,291)

Dividends on convertible exchangeable preferred stock	(9,063)	(3,398)	—
Loss applicable to common shares	$ (102,807)	$ (93,407)	$ (71,291)
Basic and diluted loss per common share	$ (2.51)	$ (2.60)	$ (2.15)
Weighted average number of shares outstanding	40,893	35,887	33,129

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion should be read in conjunction with our audited financial statements, including the related notes, presented in this Annual Report on Form 10-K.

SUBSEQUENT EVENTS

Since the end of our fiscal year, we have announced the following events:

In January 2003, we announced that we had entered into a five-year agreement with MDS Proteomics Inc. (MDSP), a subsidiary of MDS Inc., to utilize MDSP's technologies with the objective of accelerating the clinical development of and broadening the market opportunities for our pipeline of small chemical compounds. MDSP will receive payments upon the successful achievement of specified milestones and will receive royalties on sales of products resulting from the collaboration. As part of the agreement, we purchased from MDSP a $30.0 million 5% convertible note due 2010. The note is convertible into MDSP's common stock at an initial conversion price of $22.00 per share, subject to adjustment if MDSP sells shares of its common stock at a lower price.

On February 5, 2003, we announced that the FDA had accepted an ANDA for a generic form of modafinil, the active ingredient found in PROVIGIL. On March 28, 2003, we filed a patent infringement lawsuit in U.S. District Court in New Jersey against Teva Pharmaceuticals USA, Inc., Mylan Pharmaceuticals Inc., Ranbaxy Pharmaceuticals Inc., and Barr Laboratories, Inc. based upon the ANDAs filed by each of these companies seeking FDA approval for a generic equivalent of modafinil. The lawsuit claims infringement of our U.S. Patent No. RE37516, which covers the pharmaceutical compositions and methods of treatment with the form of modafinil contained in PROVIGIL. We intend to vigorously defend the validity, and prevent infringement, of this patent.

On March 7, 2003, our wholly-owned subsidiary, Cephalon Australia Pty. Limited, formally commenced a takeover bid for SIRTeX Medical Limited (ASX: SRX). SIRTeX markets SIR-Spheres®, a product approved in the United States, Europe, Australia and portions of Asia for the treatment of liver cancer. Under its bid, Cephalon Australia intends to offer A$4.85 cash for each SIRTeX ordinary share including any SIRTeX shares that are issued on the exercise of SIRTeX options. Cephalon Australia also has obtained an option to acquire shares from SIRTeX's largest shareholder representing up to 19.9 percent of the total issued share capital of SIRTeX at a price of A$4.85 per SIRTeX share. The total bid value is approximately US$161.0 million. If successful, we intend to fund the bid price using a portion of our existing cash balance. We believe there are a number of risks inherent in SIRTeX's business, post-acquisition. Specifically, we believe that we will need to significantly increase manufacturing capacity to meet projected demand in the U.S. and European markets over the next few years. Increasing capacity in the pharmaceutical industry is expensive, time consuming and requires approval of appropriate regulatory authorities. Until such expansions are complete, there can be no assurance that product will be available to satisfy anticipated demand for SIR-Spheres. We also believe that substantial investment will be necessary in many other aspects of SIRTeX's business, including sales, marketing and distribution, for us to realize the full potential of its technologies.

CRITICAL ACCOUNTING POLICIES AND ESTIMATES

Management's Discussion and Analysis of Financial Condition and Results of Operations discusses our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the financial statements, and the reported amounts of revenues and expenses during the reporting period. These estimates and assumptions are

developed, and challenged periodically, by management based on historical experience and on various other factors that we believe are reasonable under the circumstances. Actual results may differ from these estimates under different assumptions or conditions.

Our significant accounting policies are described in Note 1 to the consolidated financial statements included in Item 8 of this Form 10-K. The SEC defines critical accounting policies as those that are, in management's view, most important to the portrayal of the company's financial condition and results of operations and most demanding of their judgment. Management considers the following policies to be critical to an understanding of our consolidated financial statements and the uncertainties associated with the complex judgments made by us that could impact our results of operations, financial position and cash flows.

Revenue recognition—Product sales are recognized upon the transfer of ownership and risk of loss for the product to the customer and are recorded net of estimated reserves for contractual allowances, discounts and returns. Contractual allowances result from sales under contracts with managed care organizations and government agencies. We determine the reserve for

contractual allowances by estimating prescriptions to be filled for individuals covered by government agencies and managed care organizations with which we have contracts. We permit product returns with respect to unused pharmaceuticals based on expiration dating of our product. We determine the reserve for product returns by reviewing the history of each product's returns and by estimating the amount of expected future product returns relating to current product sales. We utilize reports from wholesalers and other external, independent sources that produce prescription data. We review this data to monitor product movement through the supply chain to identify remaining inventory in the supply chain that may result in reserves for contractual allowances or returns. To date, product returns have not been material. We review our reserves for contractual allowances, discounts and returns at each reporting period and adjust these reserves as necessary to reflect data available at that time. To the extent we adjust the reserves, the amount of net product sales revenue recognized will fluctuate.

Other revenue, which includes revenues from collaborative agreements, consists primarily of up-front fees, ongoing research and development funding, milestone payments and certain payments under co-promotional or managed services agreements. Non-refundable up-front fees are deferred and amortized to revenue over the related performance period. We estimate our performance period based on the specific terms of each collaborative agreement, but, in practice, our actual performance may vary from our estimate. We adjust the performance periods, if appropriate, based upon available facts and circumstances, though our assessment of such facts and circumstances requires us to use our judgment and experience. We recognize periodic payments for research and development activities over the period that we perform the related activities under the terms of the agreements. Revenue resulting from the achievement of milestone events stipulated in the agreements is recognized when the milestone is achieved. Milestones are based upon the occurrence of a substantive element specified in the contract or as a measure of substantive progress towards completion under the contract.

Payments under co-promotional or managed services agreements are recognized over the period when the products are sold or the promotional activities are performed. The portion of the payments that represent reimbursement of our expenses are recognized as an offset to those expenses in our statement of income.

Inventories—Our inventories are valued at the lower of cost or market, and include the cost of raw materials, labor, overhead and shipping and handling costs. Inventories are valued at standard cost, with variances between standard and actual costs recorded as an adjustment to cost of product sales or, if material, apportioned to inventory and cost of product sales. The majority of our inventories are subject to expiration dating. We regularly evaluate the carrying value of our inventories and when, in our opinion, factors indicate that impairment has occurred, we establish a reserve against the inventories' carrying value. Our determination that a valuation reserve might be required, in addition to the quantification of such reserve, requires us to utilize significant judgment. We base our analysis, in part, on the level of inventories on hand in relation to our estimated forecast of product demand, production requirements over the next 12 months and the expiration dates of raw materials and finished goods. Although we make every effort to ensure the accuracy of forecasts of future product demand, any significant unanticipated decreases in demand could have a material impact on the carrying value of our inventories and our reported operating results. To date, inventory adjustments have not been material.

Valuation of Property and Equipment, Goodwill and Intangible Assets—Our property and equipment has been recorded at cost and is being amortized on a straight-line basis over the estimated useful life of those assets. Our intangible assets (which consist primarily of developed technology, trademarks, and product and marketing rights), are amortized over estimated useful lives which are intended to approximate the estimated pattern of economic benefits generated by the asset. Determining the "estimated pattern of economic benefit" for an intangible asset is a highly subjective and difficult assessment. To the extent that the pattern cannot be reliably determined, a straight line amortization method may be used.

In conjunction with acquisitions of businesses or product rights, we allocate the purchase price based upon the relative fair values of the assets acquired and liabilities assumed. In certain circumstances, fair value may be assigned to purchased in-process technology and expensed immediately.

We regularly assess whether intangibles, long-lived assets and goodwill have been impaired and adjust the carrying values of these assets whenever events or changes in circumstances indicate that some or all of the carrying value of the assets may not be recoverable. Our judgments regarding the existence of impairment indicators are based on legal factors, market conditions and operating performances of our businesses and products. Future events could cause us to conclude that impairment indicators exist and that the carrying values of our property and equipment, intangible assets or goodwill are impaired. Any resulting impairment loss could have a material adverse impact on our financial position and results of operations. No impairment losses have been recorded to date.

We evaluate the recoverability and measure the possible impairment of our goodwill under Statement of Financial Accounting Standards (SFAS) No. 142, "Goodwill and Other Intangible Assets." The impairment test is a two-step process that begins with the estimation of the fair value of the reporting unit. The first step screens for potential impairment, and the second

step measures the amount of the impairment, if any. Our estimate of fair value considers publicly available information regarding the market capitalization of our company, as well as (i) publicly available information regarding comparable publicly-traded companies in the pharmaceutical industry, (ii) the financial projections and future prospects of our business, including our growth opportunities and likely operational improvements, and (iii) comparable sales prices, if available. As part of the first step to assess potential impairment, we compare our estimate of fair value for the company to the book value of our consolidated net assets. If the book value of our consolidated net assets were greater than our estimate of fair value, we would then proceed to the second step to measure the impairment, if any. The second step compares the implied fair value of goodwill with its carrying value. The implied fair value is determined by allocating the fair value of the reporting unit to all of the assets and liabilities of that unit as if the reporting unit had been acquired in a business combination, and the fair value of the reporting unit was the purchase price paid to acquire the reporting unit. The excess of the fair value of the reporting unit over the amounts assigned to its assets and liabilities is the implied fair value of goodwill. If the carrying amount of the reporting unit goodwill is greater than its implied fair value, an impairment loss will be recognized in the amount of the excess.

We performed our annual test of impairment of goodwill as of July 1, 2002. We have only one reporting unit, a pharmaceutical unit, that constitutes our entire business. We compared the fair value of this reporting unit with its carrying value. Our quoted market value at July 1, 2002 was used as the fair value of the reporting unit. Since the fair value of the reporting unit exceeded its carrying value at July 1, 2002, no adjustment to our goodwill for impairment is necessary.

On a quarterly basis, we perform a review of our business to determine if events or changes in circumstances have occurred that could have a material adverse effect on the fair value of our company and its goodwill. If we determine that such events or changes in circumstances have occurred, we would consult with one or more valuation specialists in estimating the impact of these on our estimate of fair value. We believe the estimation methods are reasonable and reflective of common valuation practices.

Income taxes—We have provided for income taxes in accordance with SFAS No. 109, "Accounting for Income Taxes," which requires the recognition of deferred tax assets and liabilities for the expected tax consequences of temporary differences between the tax and financial reporting bases of assets and liabilities.

Prior to 2002, we had a history of losses from our operations, which generated significant international, federal and state net operating loss and tax credit carryforwards. We record a valuation allowance against deferred tax assets if it is more likely than not that they will not be recovered. Based on our profitability for the year ended December 31, 2002 and projected future results, in the fourth quarter of 2002, we concluded that it was more likely than not that we would be able to realize a significant portion of the deferred tax assets, and therefore, we reversed a significant portion of the valuation allowance. As a result, beginning in 2003, we will begin to provide for income taxes at a rate equal to our estimated combined federal and state effective rates. Subsequent adjustments to our estimates of our ability to recover the deferred tax assets could cause our provision for income taxes to vary from period to period.

RECENT ACCOUNTING PRONOUNCEMENTS

On January 1, 2002, we adopted the provisions of SFAS 142, "Goodwill and Other Intangible Assets." SFAS 142 no longer requires the amortization of goodwill; rather, goodwill will be subject to a periodic assessment for impairment by applying a fair-value-based test. In addition, an acquired intangible asset should be separately recognized if the benefit of the intangible asset is obtained through contractual or other legal rights, or if the intangible asset can be sold, transferred, licensed, rented, or exchanged, regardless of the acquirer's intent to do so. Such acquired intangible assets will be amortized over the period in which the economic benefits of the intangible asset are consumed or otherwise used up. The new criteria for recording intangible assets separate from goodwill did not require us to reclassify any of our intangible assets. We have only recorded goodwill related to our acquisition of Group Lafon.

In June 2001, the Financial Accounting Standards Board (FASB) issued SFAS No. 143, "Accounting for Asset Retirement Obligations," which requires recognition of the fair value of liabilities associated with the retirement of long-lived assets when a legal obligation to incur such costs arises as a result of the acquisition, construction, development and/or the normal operation of a long-lived asset. SFAS 143 requires that the fair value of a liability for an asset retirement obligation be recognized in the period in which it is incurred if a reasonable estimate of fair value can be made. The associated asset retirement costs are capitalized as part of the carrying amount of the long-lived asset and subsequently allocated to expense over the asset's useful life. SFAS 143 is effective for fiscal years beginning after December 15, 2002. The adoption of this new standard will not have any impact on our current financial statements.

On January 1, 2002, we adopted SFAS No. 144, "Accounting for the Impairment or Disposal of Long-Lived Assets." This Statement provides new guidance on the recognition of impairment losses on long-lived assets to be held and used or to be disposed of and also broadens the definition of what constitutes a discontinued operation and how the results of a discontinued operation are to be measured and presented. The adoption of this new standard has not had a material impact on our current financial statements.

In April 2002, the FASB issued SFAS No. 145 "Rescission of FASB Statements No. 4, 44 and 64, Amendment of FASB Statement No. 13, and Technical Corrections." This Statement amends or rescinds certain existing authoritative pronouncements including SFAS No. 4, "Reporting Gains and Losses on Extinguishment of Debt," such that the provisions of Accounting Principles Board Opinion (APB) No. 30 "Reporting the Results of Operations-Reporting the Effects of Disposal of a Segment of a Business, and Extraordinary, Unusual and Infrequently Occurring Events and Transactions" must now be followed to determine if the early extinguishment of debt should be classified as an extraordinary item. In addition, any gain or loss on extinguishment of debt that was classified as an extraordinary item in prior periods that does not meet the criteria in APB 30 must be reclassified. SFAS 145 is effective for fiscal years beginning after May 15, 2002. We adopted this new standard effective December 31, 2002 and reclassified all gains and losses on early extinguishment of debt as other income and expense, rather than extraordinary items, in our current financial statements.

In June 2002, the FASB issued SFAS No. 146, "Accounting for Exit or Disposal Activities." This Statement addresses the recognition, measurement and reporting of costs that are associated with exit and disposal activities, including restructuring activities that are currently accounted for pursuant to the guidance in Emerging Issues Task Force Issue No. 94-3, "Liability Recognition for Certain Employee Termination Benefits and Other Costs to Exit an Activity (including Certain Costs Incurred in a Restructuring)." The Statement requires that costs associated with exit or disposal activities be recorded at their fair values when a liability has been incurred. SFAS 146 is effective for disposal activities initiated after December 31, 2002. The adoption of this new standard will not have any impact on our current financial statements.

In December 2002, the FASB issued SFAS No. 148, "Accounting for Stock-Based Compensation-Transition and Disclosure." SFAS 148 amends SFAS 123, "Accounting for Stock-Based Compensation," to provide alternative methods of transition for a voluntary change to the fair value based method of accounting for stock-based employee compensation. In addition, this Statement amends the disclosure requirements of SFAS 123 to require prominent disclosures in both annual and interim financial statements about the method of accounting for stock-based employee compensation and the effect of the method used on reported results. The alternative methods of transition and additional disclosure requirements of SFAS 148 are effective January 1, 2003.

In November 2002, the FASB issued FASB Interpretation (FIN) No. 45, "Guarantor's Accounting and Disclosure Requirements for Guarantees." This Interpretation requires that upon the issuance of a guarantee, the guarantor must recognize a liability for the fair value of the obligation it assumes under that guarantee. FIN 45 is effective for guarantees issued or modified after December 31, 2002. The adoption of this new statement will not have any impact on our current financial statements.

In January 2003, the FASB issued FIN No. 46, "Consolidation of Variable Interest Entities." This Interpretation addresses consolidation of variable interest entities where an enterprise does not have voting control over the entity but has a controlling financial interest in the entity. FIN 46 is effective for all financial statements issued after September 30, 2003. As a result of the adoption of this standard, Cephalon Clinical Partners, L.P. will be consolidated in our financial statements. This consolidation will not have a material impact on our financial statements.

RESULTS OF OPERATIONS

For the year ended December 31, revenues consisted of the following (in thousands):

	2002	2001	2000
Product sales:			
PROVIGIL	$ 196,265	$ 150,305	$ 72,089
ACTIQ	126,725	51,197	15,169
GABITRIL	48,760	24,630	4,379
Group Lafon products	94,193	—	—
Total product sales	465,943	226,132	91,637
Other revenues:			
H. Lundbeck A/S	10,411	11,941	10,395
Novartis Pharma AG	3,564	5,780	—
Sanofi-Synthélabo	20,899	5,052	—
Other	6,080	13,090	9,758
Total other revenues	40,954	35,863	20,153
Total revenues	$ 506,897	$ 261,995	$ 111,790

Year ended December 31, 2002 compared to year ended December 31, 2001

Revenues—Total product sales in 2002 increased 106% over 2001. The increase is attributable to a number of factors including:

- Sales of PROVIGIL increased by 31% compared to last year. This increase was the net result of strong underlying demand for PROVIGIL in the U.S. as evidenced by a 59% increase in prescriptions filled over last year and a 5% price increase effective June 1, 2002. These increases were partially offset by the reduction during 2002 of higher than normal inventory levels which existed at certain wholesalers at the end of 2001 due to significant speculative buying.

- Sales of ACTIQ increased 148% compared to last year. Domestic sales increased 146% driven by a 152% increase in U.S. prescriptions filled. After our merger with Anesta Corp. in October 2000, we established a dedicated sales force for ACTIQ and have made ongoing changes to our marketing approach including hiring additional sales representatives and targeting our marketing efforts to pain specialists, all of which have contributed to sales growth. A domestic price increase of 4.9% effective March 1, 2002 also contributed to higher revenues.

- Sales of GABITRIL increased 98% compared to last year as a result of: (1) a 73% increase in U.S. market demand driven by an expansion of our sales force and marketing efforts during 2002, (2) a 9.8% average U.S. price increase effective March 1, 2002, and (3) the initiation of our European sales efforts, following the December 2001 acquisition of European rights to GABITRIL, which yielded $6.1 million in 2002 sales.

- Product sales generated by Group Lafon, which we acquired on December 28, 2001, were $94.2 million during 2002. The most significant product sales during the year were $47.9 million of SPASFON®, used for biliary/urinary tract spasm and irritable bowel syndrome. Sales of MODIODAL, the trade name for modafinil in France, were $10.9 million for 2002.

Amounts recorded as other revenues consist primarily of amortization of up-front fees, ongoing research and development funding, milestone payments and certain payments under co-promotional or managed services agreements. Total other revenues increased 14% from year to year. The increase is predominantly a result of the recognition of a full year of revenue recorded under our collaboration agreement with Sanofi-Synthelabo which became effective in the fourth quarter of 2001.

Cost of Product Sales—The cost of product sales in 2002 decreased to 16% of product sales from 20% in 2001 principally due to the improvement in PROVIGIL margins as a result of our acquisition of Group Lafon.

Research and Development Expenses—Research and development expenses increased 54% to $128.3 million for 2002 from $83.0 million for 2001. $19.8 million of the increase is the result of research and development expenses incurred at Group Lafon during 2002 for which there are no comparable amounts in 2001. Approximately $15.6 million of this increase is due to higher expenditures on our clinical trials, including Phase 2/3 clinical studies for CEP-1347, studies related to our efforts to expand the label for PROVIGIL and to explore the utility of GABITRIL beyond their respective indications, and increased infrastructure costs to support the growing number of ongoing clinical trials. Approximately $8.0 million of the increase is attributable to expenditures on development costs for compounds that have progressed into later stages of development.

Selling, General and Administrative Expenses—Selling, general and administrative expenses increased 80% to $172.8 million for 2002 from $96.2 million for 2001 primarily as a result of $38.8 million of Group Lafon expenses for which there are no comparable amounts in 2001 and $21.4 million associated with the expansion of both our U.S. field sales force and promotional expenses for our products.

Depreciation and Amortization Expenses—Depreciation and amortization expenses increased to $35.5 million during 2002 from $14.4 million during 2001, of which $11.0 million is attributable to amortization of intangible assets acquired in our acquisition of Group Lafon and $4.8 million is attributable to depreciation for property and equipment acquired from Group Lafon and depreciation from capitalized building improvements at our West Chester and Salt Lake City locations. The remainder of the increase is due to amortization expense associated with the capitalization of various payments in 2002 for additional product rights.

Acquired In-Process Research and Development—In connection with our acquisition of Group Lafon in December 2001, we acquired the rights to certain early stage technologies. Based on an independent appraisal of the assets acquired from Group Lafon, the fair value of these technologies of $20.0 million was recorded as acquired in-process research and development expense in 2001 because, at the date of the acquisition, the technologies acquired had not progressed to a stage where they met technological feasibility and there existed a significant amount of uncertainty as to our ability to complete the development of the technologies and achieve market acceptance within a reasonable timeframe.

In addition, the acquired in-process technologies did not have an alternative future use to us that had reached technological feasibility.

Interest Income—Interest income increased by $1.9 million from 2001 due to higher average investment balances partially offset by lower average rates of return in 2002.

Interest Expense—Interest expense increased by $17.6 million from 2001 due primarily to a full year of interest recorded on the convertible subordinated notes issued in May and December of 2001.

Debt Exchange Expense—In accordance with Statement of Financial Accounting Standards No. 84 "Induced Conversions of Convertible Debt," we recorded a non-cash charge of $52.4 million in the fourth quarter of 2001 associated with the exchange of $217.0 million of our 5.25% convertible notes for our common stock.

Gain (Charge) on Early Extinguishment of Debt—In December 2001, we formed a joint venture with an unaffiliated third party investor to fund additional commercial activities in support of PROVIGIL and GABITRIL in the United States. In exchange for our transfer to the joint venture of certain intellectual property and other rights related to these two products, we received a Class B interest, representing a 50% interest in the joint venture. In exchange for its contribution of $50.0 million in cash to the joint venture, the investor received Class A interests, also representing a 50% interest in the joint venture. We accounted for this transaction by recording the investor's Class A interest of $50.0 million as long-term debt on our balance sheet at December 31, 2001. On March 29, 2002, we acquired the investor's Class A interests and ended the joint venture by the issuance and sale in a private placement of $55.0 million aggregate principal amount of 3.875% convertible subordinated notes due March 2007. The purchase of the unaffiliated third party investor's Class A interests in connection with the termination of the joint venture resulted in the recognition of an extinguishment of debt charge of $7.1 million during the first quarter of 2002.

In May 2001, we paid $24.4 million to Novartis Pharma AG for deferred obligations due to them under our November 2000 collaboration agreement. In connection with this payment, we recorded a gain on the early extinguishment of debt during the second quarter of 2001 of $3.0 million.

Other Expense—Other expense primarily represents the effect of changes in the currency exchange value of the pound Sterling (GBP) and the Euro relative to the settlement of transactions in other currencies, and to an increase in the currency exchange value of the GBP relative to our other foreign operations' currencies that are remeasured into the GBP for financial reporting purposes.

Income Tax Benefit, Net—We recorded a net income tax benefit of $112.6 million in 2002. In light of our expectations for continued profitability, we concluded that it was more likely than not that we would realize a portion of the benefit of the accumulated international, federal and state net operating losses, and federal research and development credits. We reduced the valuation allowance against these deferred tax assets accordingly. The recognition of these deferred tax assets had no impact on our 2002 cash flows. This income tax benefit was partially offset by current year income tax expense primarily associated with our Group Lafon operations.

Cumulative Effect of Changing Inventory Costing Method from FIFO to LIFO—Effective January 1, 2002, we changed our method of valuing domestic inventories from the first-in, first-out, or FIFO method, to the last-in, first-out, or LIFO method. We recognized a charge of $3.5 million in the first quarter of 2002 as the cumulative effect of adopting the LIFO inventory costing

method. The acquisition of Group Lafon's manufacturing operations and the planned expansion of our internal manufacturing capacity for ACTIQ has reduced and is expected to further reduce our reliance on third party manufacturers. The expansion of our internal manufacturing capabilities should allow us to benefit from efficiencies of scale and lead to lower per unit inventory cost. The LIFO method will reflect these expected changes to manufacturing costs on the statement of operations on a timelier basis, resulting in a better matching of current costs of products sold with product revenues. Cost of product sales under the LIFO inventory costing method was $17.9 million lower in 2002 than it would have been under the FIFO method.

Dividends on Convertible Exchangeable Preferred Stock—As of December 31, 2001, there were no shares of preferred stock outstanding and, therefore, no dividends were recorded in 2002.

Year ended December 31, 2001 compared to year ended December 31, 2000

Revenues—Product sales in 2001 increased 147% over 2000. The increase is attributable to a number of factors including:

- Sales of PROVIGIL increased 108% from $72.1 million in 2000 to $150.3 million in 2001. The 2001 sales increase was due to higher sales resulting from increased market acceptance, as well as a 5% domestic price increase that took effect in the second quarter of 2001.

- Sales of ACTIQ increased 238% from $15.2 million in 2000 to $51.2 million in 2001. After our merger with Anesta in October 2000, we established a dedicated sales force for ACTIQ and significantly changed the marketing approach. An average domestic 6.6% price increase in the second quarter of 2001 also contributed to higher recorded sales.

- Sales of GABITRIL increased from $4.4 million in 2000 to $24.6 million in 2001. We acquired all U.S. rights to GABITRIL from Abbott Laboratories during late 2000 and began selling GABITRIL effective January 1, 2001. Prior to 2001, our GABITRIL revenues represented compensation from Abbott under a collaborative agreement where we received a percentage of GABITRIL sales in excess of a base amount. Additionally, an average increase in domestic prices of 10% in the second quarter of 2001 also contributed to the sales increase.

Other revenues increased by $15.7 million, or 78%. This increase was due primarily to revenues recognized under our U.K. joint marketing agreement with Novartis Pharma AG, which we entered into in November 2000, and revenues recognized under our licensing, development and marketing collaboration with Sanofi-Synthélabo, which became effective in the fourth quarter of 2001.

Cost of Product Sales—Cost of product sales rose 153% in 2001 to $44.9 million from $17.8 million in 2000 primarily as a result of the increase in 2001 product sales volumes. Aggregate cost of product sales for all three products remained at 20% of product sales for both 2001 and 2000 due to decreased costs for U.S. production of ACTIQ offset by GABITRIL revenues of $4.4 million in 2000 that did not have corresponding cost of product sales since it was being sold under a collaborative agreement with Abbott.

Research and Development Expenses—Research and development expenses increased 22% in 2001 to $83.0 million from $68.1 million in 2000. The increase is attributable to higher expenditures on clinical trials including infrastructure costs to support the growing number of ongoing clinical trials including Phase 2 clinical studies for CEP-1347 and studies of PROVIGIL related to our efforts to expand the label for PROVIGIL beyond its current indication. In addition, research and development expenses also increased because of regulatory and intellectual property fees.

Selling, General and Administrative Expenses—Selling, general and administrative expenses increased 15% in 2001 to $96.2 million from $83.7 million in 2000. The increase is primarily due to increases in expenditures of $13.8 million associated with the growth of our internal sales force to promote and support PROVIGIL, ACTIQ, and GABITRIL in the United States.

Depreciation and Amortization Expenses—Depreciation and amortization expenses increased to $14.4 million in 2001 from $4.0 million in 2000 primarily due to a full year of amortization expense in 2001 on intangible assets acquired during late 2000 relating to both our acquisition of GABITRIL product rights in the United States and our U.K. joint marketing agreement with Novartis.

Certain Charges—In 2000 we recorded $6.6 million representing the final royalty payment associated with the revenue sharing notes and $13.8 million in merger and integration costs as a result of the merger with Anesta.

Acquired In-Process Research and Development—In connection with our acquisition of Group Lafon in December 2001, we acquired the rights to certain early stage technologies. Based on an independent appraisal of the assets

acquired from Group Lafon, the fair value of these technologies of $20.0 million was recorded as acquired in-process research and development expense in 2001 because, at the date of the acquisition, the technologies acquired had not progressed to a stage where they

met technological feasibility and there existed a significant amount of uncertainty as to our ability to complete the development of the technologies and achieve market acceptance within a reasonable timeframe. In addition, the acquired in-process technologies did not have an alternative future use to us that had reached technological feasibility.

During 2000, we acquired U.S. marketing rights to GABITRIL in a transaction that resulted in us recording $22.2 million as acquired in-process research and development expense. At the acquisition date, we were committed to completing advanced clinical studies for GABITRIL and developing additional uses for the drug. Ongoing and proposed projects included plans to develop GABITRIL for additional indications including the treatment of general anxiety disorder, post traumatic stress disorder, insomnia and other conditions. At the acquisition date, approximately $5.0 million had been incurred toward completion of the in-process research and development projects, and we expected to spend an additional $79.0 million to complete clinical testing and maintain the product. Multiple projects will be initiated in 2003 to support the development of GABITRIL in additional indications. However, development will continue in these areas for a period of two to three years.

Interest Income—Interest income decreased to $12.2 million in 2001 from $16.9 million in 2000 primarily due to $4.0 million of interest income recorded in 2000 associated with the waiver of an interest rate penalty by the Commonwealth of Pennsylvania on a loan used to finance the purchase of our West Chester facilities. The remaining decrease in interest income is due to lower average interest rates in 2001 as compared to 2000, offset in part by higher average investment balances.

Interest Expense—Interest expense increased in 2001 to $20.6 million from $5.2 million in 2000 due to interest on our convertible subordinated notes issued in May and December of 2001, a $1.5 million fee associated with establishing a line of credit for the Group Lafon acquisition and interest recognized on our obligations to Abbott and Novartis. These increases were partially offset by a decrease in interest expense due to the retirement of revenue-sharing notes in the first quarter of 2000.

Debt Exchange Expense—In accordance with Statement of Financial Accounting Standards No. 84 "Induced Conversions of Convertible Debt," we recorded a non-cash charge of $52.4 million in the fourth quarter of 2001 associated with the exchange of $217.0 million of our 5.25% convertible notes for our common stock.

Gain on Early Extinguishment of Debt—In May 2001, we paid $24.4 million to Novartis Pharma AG for deferred obligations due to them under our continuing November 2000 collaboration agreement. In connection with this payment, we recorded a gain on the early extinguishment of debt of $3.0 million.

Other Expense—Other expense represents an increase in currency exchange value of the pound Sterling (GBP) relative to both the U.S. dollar and to our other foreign operations' currencies that are remeasured into the GBP for financial reporting purposes.

Cumulative Effect of a Change in Accounting Principle—We adopted the U.S. Securities and Exchange Commission's Staff Accounting Bulletin No. 101 (SAB 101) on Revenue Recognition and, as a result, we recorded a charge of $7.4 million in the fourth quarter of 2000 to defer upfront license fees associated with our collaborative alliances that were previously recognized in revenues. These payments will be recognized over the performance periods of the alliances.

Dividends on Convertible Exchangeable Preferred Stock—Preferred dividends in 2001 were less than in 2000 due to the conversion during the second and third quarters of 2001 of all outstanding shares of preferred stock into an aggregate of 6,974,998 shares of our common stock. As of December 31, 2001, there were no shares of preferred stock outstanding.

JOINT VENTURE

In December 2001, we formed a joint venture with unaffiliated third party investors to fund additional commercial activities in support of PROVIGIL and GABITRIL in the United States. In exchange for our transfer to the joint venture of certain intellectual property and other rights related to these two products, we received a Class B interest, representing a 50% interest in the joint venture. In exchange for its contribution of $50.0 million in cash to the joint venture, the investors received Class A interests, also representing a 50% interest in the joint venture.

At December 31, 2001, the $50.0 million investors' Class A interest was recorded on our balance sheet as debt, and the joint venture's cash balance of $50.0 million was included in our balance of cash and cash equivalents.

On March 29, 2002, we acquired the investors' Class A interests and ended the joint venture by issuing to the investors, through a private placement, $55.0 million aggregate principal amount of 3.875% convertible subordinated notes due March 2007. The notes are convertible into our common stock, at the option of the holder, at a price of $70.36 per share. The purchase of the investor's Class A interests in the joint venture resulted in the recognition of a charge of $7.1 million on the early extinguishment of debt during the first quarter of 2002.

LIQUIDITY AND CAPITAL RESOURCES

Cash, cash equivalents and investments at December 31, 2002 were $582.7 million, representing 34% of total assets. Working capital was $666.3 million at December 31, 2002.

Net Cash Provided by Operating Activities

Net cash provided by operating activities was $102.6 million for the year ended December 31, 2002 as compared to $12.3 million for 2001. The increase in net cash provided by operating activities is primarily the result of higher net income in 2002.

Net Cash (Used for) Provided by Investing Activities

Net cash used for investing activities was $145.8 million for the year ended December 31, 2002 compared to $475.1 million in 2001. Net cash used for investing activities was higher in 2001 primarily as a result of the 2001 acquisition of Group Lafon, net of cash acquired, for $447.7 million, offset by additional acquisitions of intangible assets during 2002. Specific 2002 intangible asset investments included a payment of $50.0 million for the October 2002 acquisition of ACTIQ marketing rights in certain countries from Elan and a payment of $10.0 million to Abbott pursuant to the extension of the GABITRIL composition of matter patent. Higher property and equipment purchases in 2002 related to the expansion of our manufacturing capacity at our facilities in Salt Lake City, Utah, and France also contributed to the difference.

Net Cash Provided by (Used for) Financing Activities

Net cash used for financing activities was $28.9 million for the year ended December 31, 2002, as compared to net cash provided by financing activities of $974.6 million in 2001. The period-to-period change is primarily the result of net proceeds received from the May 2001 and December 2001 issuances of convertible subordinated notes.

During 2001, we also made dividend payments of $6.8 million on the previously outstanding shares of convertible, exchangeable preferred stock. All outstanding preferred shares were converted during the second and third quarters of 2001 into an aggregate of 6,974,998 shares of our common stock.

Commitments and Contingencies

—Legal Proceedings

On March 28, 2003, we filed a patent infringement lawsuit in U.S. District Court in New Jersey against Teva Pharmaceuticals USA, Inc., Mylan Pharmaceuticals Inc., Ranbaxy Pharmaceuticals Inc., and Barr Laboratories, Inc. based

upon the ANDAs filed by each of these companies seeking FDA approval for a generic equivalent of modafinil. The lawsuit claims infringement of our U.S. Patent No. RE37516, which covers the pharmaceutical compositions and methods of treatment with the form of modafinil contained in PROVIGIL. We intend to vigorously defend the validity, and prevent infringement, of this patent.

We are a party to certain other litigation in the ordinary course of our business, including, among others, U.S. patent interference proceedings, European patent oppositions, and matters alleging employment discrimination, product liability and breach of commercial contract. We are vigorously defending ourselves in all of the actions against us and do not believe these matters, even if adversely adjudicated or settled, would have a material adverse effect on our financial condition or results of operations.

—Standby Letters of Credit

As of December 31, 2002, we had a $0.8 million standby letter of credit outstanding.

—Other Commitments and Contingencies

The following table summarizes our obligations to make future payments under current contracts (in thousands):

	Payments due by period				
Contractual obligations	**Total**	**Less than 1 year**	**1-3 years**	**4-5 years**	**More than 5 years**
Long-term debt	$ 18,543	$ 2,875	$ 4,747	$ 4,511	$ 6,410
Capital lease obligations	2,594	2,053	541	—	—
Operating leases	21,042	5,724	7,381	2,970	4,967
Convertible notes	838,000	—	—	838,000	—
Other long-term liabilities on balance sheet	17,162	10,474	6,688	—	—
Total contractual cash obligations	$ 897,341	$ 21,126	$ 19,357	$ 845,481	$ 11,377

In addition to the above, we have committed to make potential future "milestone" payments to third parties as part of our in-licensing and development programs. Payments under these agreements generally become due and payable only upon the achievement of certain developmental, regulatory and/or commercial milestones. Because the achievement of these milestones is neither probable nor reasonably estimable, we have not recorded a liability on our balance sheet for any such contingencies.

—Cephalon Clinical Partners, L.P.

In August 1992, we exclusively licensed our rights to MYOTROPHIN for human therapeutic use within the United States, Canada and Europe to Cephalon Clinical Partners, L.P. (CCP). A subsidiary of Cephalon is the sole general partner of CCP. We developed MYOTROPHIN on behalf of CCP under a research and development agreement. Under this agreement, CCP granted an exclusive license to manufacture and market MYOTROPHIN for human therapeutic use within the United States, Canada and Europe, and we agreed to make royalty payments equal to a percentage of product sales and a milestone payment of approximately $16.0 million upon regulatory approval. We have a contractual option, but not an obligation, to purchase all of the limited partnership interests of CCP, which is exercisable upon the occurrence of certain events following the first commercial sale of MYOTROPHIN. If, and only if, we decide to exercise this purchase option, we would make an advance payment of approximately $40.3 million in cash or, at our election, approximately $42.4 million in shares of common stock or a combination thereof. If we discontinue development of MYOTROPHIN, or if we do not exercise this purchase option, our license will terminate and all rights to manufacture or market MYOTROPHIN in the United States, Canada and Europe will revert to CCP, which may then commercialize MYOTROPHIN itself or license or assign its rights to a third party. In that event, we would not receive any benefits from such commercialization, license or assignment of rights.

Outlook

Cash, cash equivalents and investments at December 31, 2002 were $582.7 million. We expect to use these funds for working capital and general corporate purposes, including the acquisition of businesses, products, product rights, or technologies, the payment of contractual obligations, including scheduled interest payments on our convertible notes, and/or the purchased, redemption or retirement of our convertible notes. Prior to 2001, we had negative cash flows from operations and used the proceeds of public and private placements of our equity and debt securities to fund operations. We expect that projected increases in sales of our three primary marketed products, PROVIGIL, ACTIQ and GABITRIL, in combination with other revenues, will allow us to continue to generate profits and significant positive cash flows from operations in 2003. At this time, however, we cannot accurately predict the effect of certain developments on future product sales such as the degree of market acceptance and exclusivity of our products, competition, the effectiveness of our sales and marketing efforts and the outcome of our efforts to demonstrate the utility of our products in indications beyond those already included in the FDA approved labels.

Analysis of prescription data for PROVIGIL in the United States indicates physicians have elected to prescribe the product to treat indications outside of its currently labeled indication of excessive daytime sleepiness associated with narcolepsy. Our strategy for PROVIGIL is to broaden the range of clinical uses that are approved by the FDA and European regulatory agencies to include many of its currently prescribed uses. To that end, we have filed an sNDA with the FDA requesting marketing approval of PROVIGIL in the United States for the treatment of excessive sleepiness associated with disorders of sleep and wakefulness in adults. If the FDA does not approve the sNDA, it is not clear what impact, if any, this may have in 2004 and beyond on physicians who currently prescribe PROVIGIL for indications other than narcolepsy. However, without this expanded label, our sales of PROVIGIL in 2004 and beyond may not continue to grow at their current rate.

Continued sales growth of PROVIGIL beyond the December 2005 expiration of orphan drug exclusivity depends, in part, on our maintaining protection on the modafinil particle-size patent. The FDA also could grant us a six-month extension of this exclusivity if we perform an additional clinical study of PROVIGIL in pediatric patients. Our sales of ACTIQ also depend on our existing patent protection, which will begin to expire in the U.S. in May 2005. In February 2003, we announced that the FDA has accepted an ANDA for a generic form of modafinil. On March 28, 2003, we filed a patent infringement lawsuit in U.S. District Court in New Jersey against Teva Pharmaceuticals USA, Inc., Mylan Pharmaceuticals Inc., Ranbaxy Pharmaceuticals Inc., and Barr Laboratories, Inc. based upon the ANDAs filed by each of these companies seeking FDA approval for a generic equivalent of modafinil. The lawsuit claims infringement of our U.S. Patent No. RE37516, which covers the pharmaceutical compositions and methods of treatment with the form of modafinil contained in PROVIGIL. We intend to vigorously defend the validity, and prevent infringement, of this patent. However, these efforts will be expensive and ultimately may be unsuccessful. See "Certain Risks Related to Our Business."

We expect to continue to incur significant expenditures associated with manufacturing, selling and marketing our products and conducting additional clinical studies to explore the utility of these products in treating disorders beyond those currently approved in their respective labels. With respect to PROVIGIL, we plan to conduct pivotal clinical trials in ADHD in 2003. With

respect to GABITRIL, we expect to perform larger studies in at least one clinical area in 2003. We also expect to continue to incur significant expenditures to fund research and development activities, including clinical trials, for our other product candidates and for improved formulations for our existing products. In the future, we may desire to mitigate the risk in our research and development programs by seeking sources of funding for a portion of these expenses through collaborative arrangements with third parties. However, we intend to retain a portion of the commercial rights to these programs and, as a result, we still expect to spend significant funds on our share of the cost of these programs, including the costs of research, preclinical development, clinical research and manufacturing.

We may have significant fluctuations in quarterly results based primarily on the level and timing of:

- product sales and cost of product sales;
- inventory stocking or destocking practices of our large customers;

- achievement and timing of research and development milestones;
- collaboration revenues;
- cost and timing of clinical trials;
- marketing and other expenses; and
- manufacturing or supply disruptions.

We recently expanded our internal manufacturing capacity for ACTIQ at our Salt Lake City facility and plan to move production of ACTIQ for the U.S. market to our Salt Lake City facility beginning in the second quarter of 2003. In February 2003, the FDA approved our sNDA requesting this change. Manufacturing ACTIQ for the U.S. market at our Salt Lake City facility should allow us to benefit from efficiencies of scale and lead to lower cost of product sales for ACTIQ in 2003 and beyond.

In 2001, we completed private placements of $400.0 million of 5.25% convertible subordinated notes due May 2006 and $600.0 million of 2.50% convertible subordinated notes due December 2006. In March 2002, we completed a private placement of $55.0 million of 3.875% convertible notes due March 2007 to acquire all of the joint venture interests of an unaffiliated third party investor. The 5.25% notes, 2.50% notes and 3.875% notes are convertible at the option of the holders into our common stock at per share conversion prices of $74.00, $81.00 and $70.36, respectively. The 5.25% notes and 2.5% notes also are redeemable by us at certain redemption prices beginning in May 2003 and December 2004, respectively. The holders of the 3.875% notes, on March 28, 2005, can elect to require us to redeem all or part of the 3.875% notes at a redemption price of 100% of such principal amount redeemed. In the future, we may agree to exchanges of the notes for shares of our common stock or may determine to use a portion of our existing cash on hand to purchase, redeem or retire all or a portion of the outstanding convertible notes. As of December 31, 2002, there are $838.0 million of convertible notes outstanding. The annual interest payments on the outstanding balance of convertible notes are $26.7 million payable at various dates throughout the year. In early 2003, we entered into an interest rate swap agreement with a financial institution in the aggregate notional amount of $200.0 million. Under the swap, we agreed to pay a variable interest rate on $200.0 million notional amount equal to LIBOR-BBA + .29% (currently 1.65%) in exchange for the financial institution's agreement to pay a fixed rate of 2.5%.

As part of our business strategy, we plan to consider and, as appropriate, make acquisitions of other businesses, products, product rights or technologies. Our cash reserves and other liquid assets may be inadequate to consummate these acquisitions and it may be necessary for us to raise substantial additional funds in the future to complete these transactions. In addition, these acquisitions may result in significant charges to earnings for acquisition and related expenses that may include merger related costs or acquired in-process research and development charges, among others. On March 7, 2003, our wholly-owned subsidiary formally commenced a cash takeover bid of A$4.85 for each outstanding share of SIRTeX Medical Limited. If our bid is successful, the total consideration for the outstanding SIRTeX shares will be approximately $161.0 million, which will be funded using our existing cash balances. To protect against fluctuations in the A$/US$ exchange rate during the bid period, in 2003, we entered into a foreign currency exchange rate hedge that locked in the U.S. dollar value of the bid. If our bid is successful, we would expect to make a substantial investment in many aspects of SIRTeX's business, particularly in the areas of manufacturing, sales, marketing, and distribution.

Based on our current level of operations and projected sales of our products combined with other revenues and interest income, we believe that we will be able to service our existing debt and meet our capital expenditure and working capital requirements for the next several years. However, we cannot be sure that our anticipated revenue growth will be realized or that we will continue to generate significant positive cash flow from operations. We may need to obtain additional funding for our

operational needs, to repay our outstanding indebtedness or for future significant strategic transactions, and we cannot be certain that funding will be available on terms acceptable to us, or at all.

CERTAIN RISKS RELATED TO OUR BUSINESS

You should carefully consider the risks described below, in addition to the other information contained in this report, before making an investment decision. Our business, financial condition or results of operations could be harmed by any of these risks. The risks and uncertainties described below are not the only ones we face. Additional risks not presently known to us or other factors not perceived by us to present significant risks to our business at this time also may impair our business operations.

A significant portion of our revenues is derived from U.S. sales of our three largest products, and our future success will depend on the continued acceptance and growth of these products.

For the year ended December 31, 2002, approximately 80% of our total worldwide net product sales were derived from sales of ACTIQ, GABITRIL and PROVIGIL. We cannot be certain that these products will continue to be accepted in their markets. Specifically, the following factors, among others, could affect the level of market acceptance of ACTIQ, GABITRIL and PROVIGIL, including:

- the perception of the healthcare community of their safety and efficacy, both in an absolute sense and relative to that of competing products;
- the effectiveness of our sales and marketing efforts;
- unfavorable publicity regarding these products or similar products;
- product price relative to other competing drugs or treatments;
- changes in government and other third-party payer reimbursement policies and practices; and
- regulatory developments affecting the manufacture, marketing or use of these products.

Any material adverse developments with respect to the sale or use of ACTIQ, GABITRIL and PROVIGIL could significantly reduce our product revenues and have a material adverse effect on our ability to generate net income and positive net cash flow from operations.

We may be unsuccessful in our efforts to expand the number and scope of authorized uses of PROVIGIL or GABITRIL, which would significantly hamper sales and earnings growth.

The market for the approved indications of two of our three largest products is relatively small. Analysis of prescription data indicates that a significant portion of our product sales is derived from the use of these products outside of their labeled indications. As such, our future success depends on the expansion of the approved indications for PROVIGIL and GABITRIL.

We recently completed clinical studies with PROVIGIL and, in the fourth quarter of 2002, submitted to the FDA a sNDA for an expanded label. While the clinical studies met their primary endpoints, we cannot be sure that we will succeed in obtaining FDA approval to market PROVIGIL for a broader indication than that approved in its current label. If the FDA does not approve the sNDA it is not clear what impact this may have on physicians who currently prescribe PROVIGIL. However, the absence of an expanded label will make it significantly more difficult to maintain or accelerate current rates of growth for PROVIGIL.

We also have initiated pilot studies to examine whether or not GABITRIL is effective and safe when used to treat disorders outside its currently approved use. While the data received from the two pilot studies to date have generally been positive, we will need to conduct additional studies before we can apply to regulatory authorities to expand the authorized uses of this product. We do not know whether these additional studies will demonstrate safety and efficacy, or if they do, whether we will succeed in receiving regulatory approval to market GABITRIL for additional disorders. If the results of some of these additional studies are negative, this could undermine physician and patient comfort with the product, limit its commercial success, and diminish its acceptance. Even if the results of these studies are positive, the impact on sales of GABITRIL may be minimal unless we are able to obtain FDA and foreign medical authority approval to expand the authorized uses of this product. FDA regulations limit our ability to communicate the results of additional clinical studies to patients and physicians without first obtaining regulatory approval for any expanded uses.

We may not be able to maintain adequate protection for our intellectual property or market exclusivity for certain of our products and therefore competitors may develop competing products, which could result in a decrease in sales and market share, cause us to reduce prices to compete successfully and limit our commercial success.

We place considerable importance on obtaining patent protection for new technologies, products and processes. To that end, we file applications for patents covering the compositions or uses of our drug candidates or our proprietary processes. The patent positions of pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal, scientific and factual questions. To date, there has emerged no consistent policy regarding breadth of claims in such companies' patents. Accordingly, the patents and patent applications relating to our products, product candidates and technologies may be challenged, invalidated or circumvented by third parties and might not protect us against competitors with similar products or technology. Patent disputes in our industry are frequent and can preclude commercialization of products. If we ultimately engage in and lose any such disputes, we could be subject to competition or significant liabilities, we could be required to enter into third party licenses or we could be required to cease using the technology or product in dispute. In addition, even if such licenses are available, the terms of any license requested by a third party could be unacceptable to us.

The U.S. composition of matter patent for modafinil expired in 2001. We own U.S. and foreign patent rights that expire between 2014 and 2015 covering pharmaceutical compositions of modafinil and, more specifically, covering certain particle sizes contained in this pharmaceutical composition. Ultimately, these patents might be found invalid if challenged by a third party, or a potential competitor could develop a competing product or product formulation that avoids infringement of these patents. On February 5, 2003, we announced that the FDA had accepted an abbreviated new drug application, or ANDA, for a pharmaceutical product containing modafinil. Any ANDA for modafinil filed with the FDA prior to December 2003 must contain a Paragraph IV certification in which the ANDA applicant certifies that the U.S. particle-size modafinil patent covering PROVIGIL either is invalid or will not be infringed by the ANDA product. On March 28, 2003, we filed a patent infringement lawsuit in U.S. District Court in New Jersey against Teva Pharmaceuticals USA, Inc., Mylan Pharmaceuticals Inc., Ranbaxy Pharmaceuticals Inc., and Barr Laboratories, Inc. based upon the ANDAs filed by each of these companies with the FDA. The lawsuit claims infringement of our U.S. Patent No. RE37516. While we intend to vigorously defend the validity of this patent and prevent infringement, these efforts will be both expensive and time consuming and, ultimately, may not be successful. If an ANDA is approved ultimately, a competitor could begin selling a modafinil-based product upon the expiration of our FDA orphan drug exclusivity, currently in December 2005, which would significantly and negatively impact revenues from PROVIGIL. If we perform an additional clinical study of PROVIGIL in pediatric patients, the FDA could grant us a six-month extension of our orphan drug exclusivity (to June 2006) and particle size patent. However, we cannot be sure that the FDA will grant such extension.

With respect to ACTIQ, we hold an exclusive license to a U.S. patent covering the currently approved pharmaceutical composition and methods for administering fentanyl via this composition that is set to expire in May 2005. We also hold patents to an FDA approved compressed powder formulation that we expect to begin selling in the United States in the second quarter of 2003. These patents expire in September 2006, though the FDA could grant us a six-month extension of these patents if we perform a clinical study in pediatric patients. Corresponding patents in foreign countries are set to expire between 2009 and 2010. The loss of patent protection on ACTIQ, beginning in May 2005 in the United States, could significantly and negatively impact our revenues from the sale of ACTIQ.

We also rely on trade secrets, know-how and continuing technological advancements to support our competitive position. Although we have entered into confidentiality and invention rights agreements with our employees, consultants, advisors and collaborators, these parties could fail to honor such agreements or we could be unable to effectively protect our rights to our unpatented trade secrets and know-how. Moreover, others could independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets and know-how. In addition, many of our scientific and management personnel have been recruited from other biotechnology and pharmaceutical companies where they were conducting research in areas similar to those that we now pursue. As a result, we could be subject to allegations of trade secret violations and other claims.

Manufacturing, supply and distribution problems may create supply disruptions that could result in a reduction of product sales revenue, and damage commercial prospects for our products.

At our two manufacturing facilities in France, we produce the active drug substance modafinil and certain other commercial products. At our U.S. facility in Salt Lake City, Utah, we manufacture ACTIQ for international markets and, beginning in the second quarter of 2003, for the United States. For the remainder of our products, we solely rely on third

parties for product manufacturing. In all cases, we must comply with all applicable regulatory requirements of the FDA and foreign authorities, including current Good Manufacturing Practice regulations. In addition, we must comply with all applicable regulatory requirements of the Drug Enforcement Administration, and analogous foreign authorities for certain products. The facilities used

by us and third parties to manufacture, store and distribute our products are subject to inspection by regulatory authorities at any time to determine compliance with regulations. These regulations are complex, and any failure to comply with them could lead to remedial action, civil and criminal penalties and delays in production or distribution of material.

We rely on third parties to distribute our products, perform customer service activities and accept and process product returns. We also depend upon sole suppliers for active drug substances contained in our products, including our own French plant that manufactures modafinil, Abbott Laboratories to manufacture finished commercial supplies of GABITRIL for the U.S. market and Sanofi-Synthelabo to manufacture GABITRIL for non-U.S. markets. In the second quarter of 2003, we expect to complete the transfer of all manufacturing of ACTIQ for the U.S. market from Abbott to our Salt Lake City facility. We have two qualified manufacturers, Watson Pharmaceuticals, in Copiague, New York and DSM Pharmaceuticals, in Greenville, North Carolina, for finished commercial supplies of PROVIGIL. The process of changing or adding a manufacturer or changing a formulation requires prior FDA and/or European medical authority approval and is very time-consuming. If we are unable to manage this process effectively or if an unforeseen event occurs at any facility, we could face supply disruptions that would result in significant costs and delays, undermine goodwill established with physicians and patients, damage commercial prospects for our products and adversely affect operating results.

As our products are used commercially, unintended side effects, adverse reactions or incidents of misuse may occur that could result in additional regulatory controls and reduced sales of our products.

During research and development, the use of biopharmaceutical products, such as our products, is limited principally to clinical trial patients under controlled conditions and under the care of expert physicians. The widespread commercial use of our products could produce undesirable or unintended side effects that have not been evident in our clinical trials or the relatively limited commercial use to date of our products. In addition, in patients who take multiple medications, drug interactions could occur that can be difficult to predict. Additionally, incidents of product misuse may occur. These events, among others, could result in additional regulatory controls that could limit the circumstances under which the product is prescribed or even lead to the withdrawal of the product from the market. More specifically, ACTIQ has been approved under regulations concerning drugs with certain safety profiles, under which the FDA has established special restrictions to ensure safe use. Any violation of these special restrictions could lead to the imposition of further restrictions or withdrawal of the product from the market.

We face significant product liability risks, which may have a negative effect on our financial performance.

The administration of drugs to humans, whether in clinical trials or commercially, can result in product liability claims whether or not the drugs are actually at fault for causing an injury. Furthermore, our products may cause, or may appear to have caused, adverse side effects (including death) or potentially dangerous drug interactions that we may not learn about or understand fully until the drug has been administered to patients for some time. As our products are used more widely and in patients with varying medical conditions, the likelihood of an adverse drug reaction, unintended side effect or incidence of misuse may increase. Product liability claims can be expensive to defend and may result in large judgments or settlements against us, which could have a negative effect on our financial performance. The costs of product liability insurance have increased dramatically in recent years, and the availability of coverage has decreased. Nevertheless, we maintain product liability insurance in amounts we believe to be commercially reasonable. Any claims could easily exceed our coverage limits. Even if a product liability claim is not successful, the adverse publicity and time and expense of defending such a claim may interfere with our business.

Our activities and products are subject to significant government regulations and approvals, which are often costly and could result in adverse consequences to our business if we fail to comply.

We currently have a number of products that have been approved for sale in the United States, foreign countries or both. All of our approved products are subject to extensive continuing regulations relating to, among other things, testing,

manufacturing, quality control, labeling, and promotion. The failure to comply with any rules and regulations of the FDA or any foreign medical authority, or the post-approval discovery of previously unknown problems relating to our products, could result in, among others:

- fines, recalls or seizures of products;
- total or partial suspension of product sales;
- non-approval of product license applications;
- restrictions on our ability to enter into strategic relationships; and
- criminal prosecution.

It is both costly and time-consuming for us to comply with these regulations. Additionally, incidents of adverse drug reactions, unintended side effects or misuse relating to our products could result in additional regulatory controls or restrictions, or even lead to withdrawal of the product from the market.

With respect to our product candidates and for new therapeutic indications for our existing products, we conduct research, preclinical testing and clinical trials. We cannot market these product candidates or these new indications in the United States or other countries without receiving approval from the FDA or the appropriate foreign medical authority. The approval process is highly uncertain and requires substantial time, effort and financial resources. Ultimately, we may never obtain approval in a timely manner, or at all. Without these required approvals, our ability to substantially grow revenues in the future could be adversely affected.

In addition, because PROVIGIL and ACTIQ contain active ingredients that are controlled substances, we are subject to regulation by the DEA and analogous foreign organizations relating to the manufacture, shipment, sale and use of the applicable products. These regulations also are imposed on prescribing physicians and other third parties, making the storage, transport and use of such products relatively complicated and expensive. With the increased concern for safety by the FDA and the DEA with respect to products containing controlled substances, it is possible that these regulatory agencies could impose additional restrictions on marketing or even withdrawal of regulatory approval for such products. In addition, adverse publicity may bring about rejection of the product by the medical community. If the DEA, FDA or a foreign medical authority withdrew the approval of, or placed additional significant restrictions on the marketing of any of our products, our product sales and ability to promote our products could be substantially affected.

Our product sales and related financial results will fluctuate and these fluctuations may cause our stock price to fall, especially if investors do not anticipate them.

A number of analysts and investors who follow our stock have developed models to attempt to forecast future product sales and expenses and have established earnings expectations based upon those models. These models, in turn, are based in part on estimates of projected revenue and earnings that we disclose publicly. Forecasting future revenues is difficult, especially when there is little commercial history and when the level of market acceptance of our products is uncertain. Forecasting is further complicated by the difficulties in estimating stocking levels at pharmaceutical wholesalers and at retail pharmacies, the timing of purchases by wholesalers and retailers to replenish stock and the frequency and amount of potential product returns. As a result, it is likely that there will be significant fluctuations in revenues, which may not meet with market expectations and which also may adversely affect our stock price. There are a number of other factors that could cause our financial results to fluctuate unexpectedly, including:

- the cost of product sales;
- achievement and timing of research and development milestones;
- collaboration revenues;
-

cost and timing of clinical trials;

- marketing and other expenses; and
- manufacturing or supply disruptions.

We may be unable to service or repay our substantial indebtedness or other contingencies.

As of December 31, 2002, we had $876.3 million of indebtedness outstanding, including $838.0 million outstanding under convertible notes with a conversion price far in excess of our current stock price. Of the indebtedness outstanding, $785.2 million matures in 2006. During 2002 we incurred interest expenses of $38.2 million on our outstanding indebtedness. These factors, among other things, could make it difficult for us to make payments on or refinance our indebtedness or to obtain additional financing in the future, or limit our future flexibility and make us more vulnerable in the event of a downturn in our business. Unless we are able to generate sufficient cash flow from operations to service our indebtedness, we will be required to raise additional funds. Because the financing markets may be unwilling to provide funding to us or may only be willing to provide funding on terms that we would consider unacceptable, we may not have cash available or be able to obtain funding to permit us to meet our debt service or repayment obligations, thus adversely affecting the market price for our securities.

The efforts of government entities and third party payers to contain or reduce the costs of health care may adversely affect our sales and limit the commercial success of our products.

In certain foreign markets, pricing or profitability of pharmaceutical products is subject to various forms of direct and indirect governmental control, including the control over the amount of reimbursements provided to the patient who is prescribed specific pharmaceutical products. For example, we are aware of government efforts in France to limit or eliminate reimbursement for certain of our products, which could impact revenues from our French operations.

In the United States, there have been, and we expect there will continue to be, various proposals to implement similar controls. The commercial success of our products could be limited if federal or state governments adopt any such proposals. In addition, in the United States and elsewhere, sales of pharmaceutical products depend in part on the availability of reimbursement to the consumer from third party payers, such as government and private insurance plans. These third party payers increasingly challenge the prices charged for pharmaceutical products and seek to limit reimbursement levels offered to consumers for such products. These third party payers could focus their cost control efforts on our products, especially with respect to prices of and reimbursement levels for products prescribed outside their labeled indications. In these cases, their efforts could negatively impact our product sales and profitability.

We experience intense competition in our fields of interest, which may adversely affect our business.

Large and small companies, academic institutions, governmental agencies and other public and private research organizations conduct research, seek patent protection and establish collaborative arrangements for product development in competition with us. Products developed by any of these entities may compete directly with those we develop or sell.

The conditions that our products treat, and some of the other disorders for which we are conducting additional studies, are currently treated with several drugs, many of which have been available for a number of years or are available in inexpensive generic forms. With respect to PROVIGIL, there are several other products used for the treatment of narcolepsy in the United States, including methylphenidate products such as RITALIN® by Novartis, and in our other territories, many of which have been available for a number of years and are available in inexpensive generic forms. With respect to ACTIQ, we face competition from inexpensive oral opioid tablets and more expensive but quick-acting invasive (i.e., intravenous, intramuscular and subcutaneous) opioid delivery systems. Other technologies for rapidly delivering opioids to treat breakthrough pain are being developed, at least one of which is in clinical trials. With respect to GABITRIL, there are several products, including NEURONTIN® (gabapentin) by Pfizer, used as adjunctive therapy for the partial seizure market. Some are well-established therapies that have been on the market for several years while others have recently entered the partial seizure marketplace. In addition, several treatments for partial seizures are available in inexpensive generic forms. Thus, we need to demonstrate to physicians, patients and third party payers that the cost of our

products is reasonable and appropriate in the light of their safety and efficacy, the price of competing products and the related health care benefits to the patient.

In addition, many of our competitors have substantially greater capital resources, research and development staffs and facilities than we have, and substantially greater experience in conducting clinical trials, obtaining regulatory approvals and manufacturing and marketing pharmaceutical products. These entities represent significant competition for us. In addition, competitors who are developing products for the treatment of neurological or oncological disorders might succeed in developing technologies and products that are more effective than any that we develop or sell or that would render our technology and products obsolete or noncompetitive. Competition and innovation from these or other sources, including advances in current treatment methods, could potentially affect sales of our products negatively or make our products obsolete. In addition, we may be at a competitive marketing disadvantage against companies that have broader product lines and whose sales personnel are able to offer more complementary products than we can. Any failure to maintain our competitive position could adversely affect our business and results of operations.

We plan to consider and, as appropriate, make acquisitions of technologies, products and businesses, which may subject us to a number of risks and/or result in us experiencing significant charges to earnings that may adversely affect our stock price, operating results and financial condition.

We regularly review potential acquisitions of businesses, products, product rights and technologies that are complementary to our business. As part of that review, we conduct business, legal and financial due diligence with the goal of identifying and evaluating material risks involved in any particular transaction. Despite our efforts, we may be unsuccessful in ascertaining or evaluating all such risks and, as a result, we might not realize the intended advantages of any given acquisition. We also must consolidate and integrate any acquired operations with our business. These integration efforts often take a significant amount of time, place a significant strain on our managerial, operational and financial resources and could prove to be more difficult and

expensive than we predicted. If we fail to realize the expected benefits from an acquisition, whether as a result of unidentified risks, integration difficulties or otherwise, our business, results of operations and financial condition could be adversely affected.

In addition, as a result of acquiring businesses or entering into other significant transactions, we have experienced, and will likely continue to experience, significant charges to earnings for merger and related expenses that may include transaction costs, closure costs or acquired in-process research and development charges. These costs may include substantial fees for investment bankers, attorneys, accountants and other advisers, as well as severance and other closure costs associated with the elimination of duplicate operations and facilities. Our incurrence of these charges could adversely affect our results of operations for particular quarterly or annual periods.

The results and timing of our research and development activities, including future clinical trials are difficult to predict, subject to potential future setbacks and, ultimately, may not result in viable pharmaceutical products, which may adversely affect our business.

In order to sustain our business, we focus substantial resources on the search for new pharmaceutical products. These activities include engaging in discovery research and process development, conducting preclinical and clinical studies and seeking regulatory approval in the United States and abroad. In all of these areas, we have relatively limited resources and compete against larger, multinational pharmaceutical companies. Moreover, even if we undertake these activities in an effective and efficient manner, regulatory approval for the sale of new pharmaceutical products remains highly uncertain because the majority of compounds discovered do not enter clinical studies and the majority of therapeutic candidates fail to show the human safety and efficacy necessary for regulatory approval and successful commercialization.

Preclinical testing and clinical trials must demonstrate that a product candidate is safe and efficacious. The results from preclinical testing and early clinical trials may not be predictive of results obtained in subsequent clinical trials, and these clinical trials may not demonstrate the safety and efficacy necessary to obtain regulatory approval for any product candidates. A number of companies in the biotechnology and pharmaceutical industries have suffered significant setbacks in advanced clinical trials, even after obtaining promising results in earlier trials. For ethical reasons, certain clinical trials

are conducted in patients having the most advanced stages of disease and who have failed treatment with alternative therapies. During the course of treatment, these patients often die or suffer other adverse medical effects for reasons that may not be related to the pharmaceutical agent being tested. Such events can have a negative impact on the statistical analysis of clinical trial results.

The completion of clinical trials of our product candidates may be delayed by many factors, including the rate of enrollment of patients. Neither we nor our collaborators can control the rate at which patients present themselves for enrollment, and the rate of patient enrollment may not be consistent with our expectations or sufficient to enable clinical trials of our product candidates to be completed in a timely manner or at all. In addition, we may not be permitted by regulatory authorities to undertake additional clinical trials for one or more of our product candidates. Even if such trials are conducted, our product candidates may not prove to be safe and efficacious or receive regulatory approvals. Any significant delays in, or termination of, clinical trials of our product candidates could impact our ability to generate product sales from these product candidates in the future.

Our research and development and marketing efforts are often dependent on corporate collaborators and other third parties who may not devote sufficient time, resources and attention to our programs, and which may limit our efforts to develop and market potential products.

Because we have limited resources, we have entered into a number of collaboration agreements with other pharmaceutical companies, including Lundbeck with respect to our research efforts in Parkinson's Disease, and with a number of marketing partners for our products in certain countries outside the United States. In some cases, our collaboration agreements call for our partners to control:

- the supply of bulk or formulated drugs for use in clinical trials or for commercial use;
- the design and execution of clinical studies;
- the process of obtaining regulatory approval to market the product; and/or
- marketing and selling of any approved product.

In each of these areas, our partners may not support fully our research and commercial interests because our program may compete for time, attention and resources with the internal programs of our corporate collaborators. As such, our program may not move forward as effectively, or advance as rapidly, as it might if we had retained complete control of all research, development, regulatory and commercialization decisions. We also rely on some of these collaborators and other third parties for

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the production of compounds and the manufacture and supply of pharmaceutical products. Additionally, we may find it necessary from time to time to seek new or additional partners to assist us in commercializing our products, though we might not be successful in establishing any such new or additional relationships.

The price of our common stock has been and may continue to be highly volatile.

The market price of our common stock is highly volatile, and we expect it to continue to be volatile for the foreseeable future. For example, from January 1, 2002 through March 14, 2003, our common stock traded at a high price of $78.88 and a low price of $36.92. Negative announcements, including, among others:

- adverse regulatory decisions;
- disappointing clinical trial results;
- disputes and other developments concerning patent or other proprietary rights with respect to our products; or

- operating results that fall below the market's expectations

could trigger significant declines in the price of our common stock. In addition, external events, such as news concerning economic conditions, our competitors, changes in government regulations impacting the biotechnology or pharmaceutical industries or the movement of capital into or out of our industry, also are likely to affect the price of our common stock.

A portion of our product sales and certain balance sheet items are subject to exchange rate fluctuations in the normal course of business that could adversely affect our reported results of operations.

Historically, a portion of our product sales has been earned in currencies other than the U.S. dollar. As a result of our acquisition of Group Lafon, the portion of our product sales denominated in the euro and other local currencies has and may continue to increase. For the year ended December 31, 2002, approximately 23% of our product sales were denominated in currencies other than the U.S. dollar. We translate revenue earned from product sales into U.S. dollars at the average exchange rate applicable during the relevant period. A strengthening of the U.S. dollar would, therefore, reduce our earnings. Consequently, fluctuations in the rate of exchange between the U.S. dollar and the euro and other currencies may affect period-to-period comparisons of our operating results. Finally, the balance sheet of our foreign operations will be translated into U.S. dollars at the period-end exchange rate. This latter exposure will result in changes to the translated value of assets and liabilities, with the impact of the translation included as a component of stockholders' equity. Historically, we have not hedged our exposure to these fluctuations in exchange rates.

We are involved, or may become involved in the future, in legal proceedings that, if adversely adjudicated or settled, could materially impact our financial condition.

As a biopharmaceutical company, we are or may become a party to litigation in the ordinary course of our business, including, among others, matters alleging employment discrimination, product liability, patent or other intellectual property rights infringement, patent invalidity or breach of commercial contract. In general, litigation claims can be expensive and time consuming to bring or defend against and could result in settlements or damages that could significantly impact results of operations and financial condition. We currently are vigorously defending ourselves against certain litigation matters. While we currently do not believe that the settlement or adverse adjudication of these lawsuits would materially impact our results of operations or financial condition, the final resolution of these matters and the impact, if any, on our results of operations or financial condition could be material.

Our customer base is highly concentrated.

Our principal customers are wholesale drug distributors. These customers comprise a significant part of the distribution network for pharmaceutical products in the United States. A small number of large wholesale distributors control a significant share of the market. For the year ended December 31, 2002, our three largest U.S. wholesaler customers were Cardinal Health, Inc., McKesson Corporation and AmerisourceBergen Corporation. These three distributors, in the aggregate, accounted for 72% of our total gross product sales. The loss or bankruptcy of any of these customers could materially and adversely affect our results of operations and financial condition.

Our dependence on key executives and scientists could impact the development and management of our business.

We are highly dependent upon our ability to attract and retain qualified scientific, technical and managerial personnel. There is intense competition for qualified personnel in the pharmaceutical and biotechnology industries, and we cannot be sure that we

will be able to continue to attract and retain the qualified personnel necessary for the development and management of our business. Although we do not believe the loss of one individual would materially harm our business, our research and development programs and our business might be harmed by the loss of the services of multiple existing personnel, as well as the failure to recruit additional key scientific, technical and managerial personnel in a timely manner. Much of the know-how we have developed resides in our scientific and technical personnel and is not readily transferable to other personnel. While we have employment agreements with our key executives, we do not ordinarily enter into employment

agreements with our other key scientific, technical and managerial employees. We do not maintain "key man" life insurance on any of our employees.

We may be required to incur significant costs to comply with environmental laws and regulations, and our related compliance may limit any future profitability.

Our research and development activities involve the controlled use of hazardous, infectious and radioactive materials that could be hazardous to human health and safety or the environment. We store these materials, and various wastes resulting from their use, at our facilities pending ultimate use and disposal. We are subject to a variety of federal, state and local laws and regulations governing the use, generation, manufacture, storage, handling and disposal of these materials and wastes, and we may be required to incur significant costs to comply with related existing and future environmental laws and regulations.

While we believe that our safety procedures for handling and disposing of these materials comply with foreign, federal, state and local laws and regulations, we cannot completely eliminate the risk of accidental injury or contamination from these materials. In the event of an accident, we could be held liable for any resulting damages, which could include fines and remedial costs. These damages could require payment by us of significant amounts over a number of years, which would be reflected in our results of operations and financial condition.

Anti-takeover provisions may delay or prevent changes in control of our management or deter a third party from acquiring us, limiting our stockholders' ability to profit from such a transaction.

Our Board of Directors has the authority to issue up to 5,000,000 shares of preferred stock, $0.01 par value, of which 1,000,000 have been reserved for issuance in connection with our stockholder rights plan, and to determine the price, rights, preferences and privileges of those shares without any further vote or action by our stockholders. Our stockholder rights plan could have the effect of making it more difficult for a third party to acquire a majority of our outstanding voting stock.

We are subject to the anti-takeover provisions of Section 203 of the Delaware General Corporation Law, which prohibits us from engaging in a "business combination" with an "interested stockholder" for a period of three years after the date of the transaction in which the person becomes an interested stockholder, unless the business combination is approved in a prescribed manner. The application of Section 203 could have the effect of delaying or preventing a change of control of Cephalon. Section 203, the rights plan, and certain provisions of our certificate of incorporation, our bylaws and Delaware corporate law, may have the effect of deterring hostile takeovers, or delaying or preventing changes in control of our management, including transactions in which stockholders might otherwise receive a premium for their shares over then current market prices.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURE ABOUT MARKET RISK

At December 31, 2002, we did not hold any derivative financial instruments and did not engage in any speculative or derivative trading activities. Therefore, our market risk exposure is limited to changes in interest rates and foreign currency fluctuations. Our exposure to market risk for a change in interest rates relates to our investment portfolio, since all of our outstanding debt is fixed rate. Our investments are classified as short-term and as "available for sale." We do not believe that short-term fluctuations in interest rates would materially affect the value of our securities.

We are exposed to foreign currency exchange risk related to our operations in European subsidiaries that have transactions, assets, and liabilities denominated in foreign currencies that are translated into U.S. dollars for consolidated financial reporting purposes. Historically, we have not hedged any of these foreign currency exchange risks. For the year ended December 31, 2002, an average 10% strengthening of the U.S. dollar relative to the currencies in which our European subsidiaries operate would have resulted in a decrease in reported net sales of $11.1 million and a decrease in reported net income of $0.2 million for that period. This sensitivity analysis of the effects of changes in foreign currency exchange rates does not assume any changes in the level of operations of our European subsidiaries.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

REPORT OF INDEPENDENT ACCOUNTANTS

To the Board of Directors and Shareholders of Cephalon Inc:

In our opinion, the consolidated financial statements listed in the index appearing under Item 15(a)(1) on page 74 present fairly, in all material respects, the financial position of Cephalon Inc. and its subsidiaries at December 31, 2002 and 2001, and the results of their operations and their cash flows for the years then ended in conformity with accounting principles generally accepted in the United States of America. In addition, in our opinion, the financial statement schedule listed in the index appearing under Item 15(a)(2) on page 74 presents fairly, in all material respects, the information set forth therein for the years ended December 31, 2002 and 2001 when read in conjunction with the related consolidated financial statements. These financial statements and the financial statement schedule are the responsibility of the Company's management; our responsibility is to express an opinion on these financial statements and financial statement schedule based on our audits. We conducted our audits of these statements in accordance with auditing standards generally accepted in the United States of America, which require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion. The financial statements and financial statement schedule of Cephalon Inc. as of December 31, 2000 and for the year then ended were audited by other independent accountants who have ceased operations. Those independent accountants expressed an unqualified opinion on those financial statements and financial statement schedule in their reports dated February 11, 2002.

As discussed in Note 1, on January 1, 2002 the Company changed its method of valuing certain inventory and of accounting for business combinations and goodwill.

/s/ PRICEWATERHOUSECOOPERS LLP

Philadelphia, Pennsylvania
March 14, 2003

THE FOLLOWING REPORTS ARE COPIES OF PREVIOUSLY ISSUED REPORTS BY ARTHUR ANDERSEN LLP ("ANDERSEN"). THE REPORTS HAVE NOT BEEN REISSUED BY ANDERSEN NOR HAS ANDERSEN CONSENTED TO THEIR INCLUSION IN THIS ANNUAL REPORT ON FORM 10-K. THE ANDERSEN REPORTS REFER TO THE CONSOLIDATED BALANCE SHEET AS OF DECEMBER 31, 2000 AND THE CONSOLIDATED STATEMENTS OF INCOME, SHAREHOLDERS' INVESTMENT AND CASH FLOWS FOR THE YEAR ENDED DECEMBER 31, 1999 WHICH ARE NO LONGER INCLUDED IN THE ACCOMPANYING FINANCIAL STATEMENTS. SUBSEQUENT TO THE DATE OF THESE REPORTS, THE COMPANY'S CONSOLIDATED BALANCE SHEET AS OF DECEMBER 31, 2001 AND THE RELATED CONSOLIDATED STATEMENTS OF OPERATIONS, OF CASH FLOWS, OF CHANGES IN STOCKHOLDERS' EQUITY AND OF THE RELATED FINANCIAL STATEMENT SCHEDULE FOR THE YEAR ENDED DECEMBER 31, 2001 WERE AUDITED BY OTHER INDEPENDENT ACCOUNTANTS WHOSE REPORT APPEARS ON PAGE 43.

REPORT OF INDEPENDENT PUBLIC ACCOUNTANTS

To Cephalon, Inc.:

We have audited the accompanying consolidated balance sheets of Cephalon, Inc. (a Delaware corporation) and subsidiaries as of December 31, 2001 and 2000, and the related consolidated statements of operations, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2001. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits. We did not audit the financial statements of Anesta Corp., a company acquired during 2000 in a transaction accounted for as a pooling-of-interests, as discussed in Note 2. Such statements are included in the consolidated financial statements of Cephalon, Inc. and reflect total revenues of 13 percent in 1999 of the related consolidated revenues. Those statements were audited by other auditors whose report has been furnished to us, and our opinion, insofar as it relates to amounts included for Anesta Corp., is based solely upon the report of the other auditors.

We conducted our audits in accordance with auditing standards generally accepted in the United States. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits and the report of other auditors provide a reasonable basis for our opinion.

In our opinion, based on our audits and the report of the other auditors, the financial statements referred to above present fairly, in all material respects, the financial position of Cephalon, Inc. and subsidiaries as of December 31, 2001 and 2000, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2001, in conformity with accounting principles generally accepted in the United States.

/s/ ARTHUR ANDERSEN LLP

Philadelphia, Pennsylvania
February 11, 2002 (except with
respect to the matter discussed in Note 3,
as to which the date is March 29, 2002)

REPORT OF INDEPENDENT PUBLIC ACCOUNTANTS

To Cephalon, Inc.:

We have audited, in accordance with auditing standards generally accepted in the United States, the consolidated financial statements of Cephalon, Inc. and subsidiaries and have issued our report thereon dated February 11, 2002 (except with respect to the matter discussed in Note 3, as to which the date is March 29, 2002). Our audit was made for the purpose of forming an opinion on the basic financial statements taken as a whole. The schedule of valuation and qualifying accounts is presented for purposes of complying with the Securities and Exchange Commissions' rules and is not part of the basic financial statements. This schedule has been subject to the auditing procedures applied in the audit of the basic financial statements and, in our opinion based on our audit and the report of other auditors, fairly states in all material respects the financial data required to be set forth therein in relation to the basic financial statements taken as a whole.

/s/ ARTHUR ANDERSEN LLP

Philadelphia, Pennsylvania
February 11, 2002

CEPHALON, INC. AND SUBSIDIARIES CONSOLIDATED BALANCE SHEETS

(In thousands, except share data)

	December 31, 2002	December 31, 2001
ASSETS		
CURRENT ASSETS:		
Cash and cash equivalents	$ 486,097	$ 548,727
Investments	96,591	55,157
Receivables, net	83,130	79,847
Inventory, net	54,299	47,513
Deferred tax asset	56,070	—
Other current assets	9,793	7,872
Total current assets	785,980	739,116
PROPERTY AND EQUIPMENT, net	90,066	64,706
GOODWILL	298,769	301,577
OTHER INTANGIBLE ASSETS, net	351,719	298,269
DEBT ISSUANCE COSTS, net	21,406	26,720
DEFERRED TAX ASSET, net	114,002	—
OTHER ASSETS	27,148	16,020
	$ 1,689,090	$ 1,446,408
LIABILITIES AND STOCKHOLDERS' EQUITY		
CURRENT LIABILITIES:		
Current portion of long-term debt	$ 15,402	$ 32,200
Accounts payable	23,089	24,536
Accrued expenses	80,444	54,025

Current portion of deferred revenues	712	824
Total current liabilities	119,647	111,585
LONG-TERM DEBT	860,897	866,589
DEFERRED REVENUES	1,968	6,042
DEFERRED TAX LIABILITIES	52,666	52,666
OTHER LIABILITIES	11,327	10,795
Total liabilities	1,046,505	1,047,677
COMMITMENTS AND CONTINGENCIES (Note 11)	—	—
STOCKHOLDERS' EQUITY:		
Preferred stock, $.01 par value, 5,000,000 shares authorized, 2,500,000 shares issued, and none outstanding	—	—
Common stock, $.01 par value, 200,000,000 shares authorized, 55,425,841 and 54,909,533 shares issued, 55,152,984 and 54,685,792 shares outstanding	554	549
Additional paid-in capital	1,034,137	982,123
Treasury stock, 272,857 and 223,741 shares outstanding, at cost	(11,989)	(9,523)
Accumulated deficit	(405,163)	(576,691)
Accumulated other comprehensive income	25,046	2,273
Total stockholders' equity	642,585	398,731
	$ 1,689,090	$ 1,446,408

The accompanying notes are an integral part of these consolidated financial statements.

CEPHALON, INC. AND SUBSIDIARIES CONSOLIDATED STATEMENTS OF OPERATIONS

(in thousands, except per share data)

	Year Ended December 31,		
	2002	2001	2000
REVENUES:			
Product sales	$ 465,943	$ 226,132	$ 91,637
Other revenues	40,954	35,863	20,153
	506,897	261,995	111,790
COSTS AND EXPENSES:			
Cost of product sales	74,237	44,946	17,768
Research and development	128,276	83,037	68,063
Selling, general and administrative	172,782	96,179	83,725
Depreciation and amortization	35,457	14,434	4,008
Royalty pre-payment on revenue-sharing notes	—	—	6,600
Merger and integration costs	—	50	13,811
Acquired in-process research and development	—	20,000	22,200
	410,752	258,646	216,175
INCOME (LOSS) FROM OPERATIONS	96,145	3,349	(104,385)
OTHER INCOME AND EXPENSE			
Interest income	14,095	12,170	16,903

Interest expense	(38,215)	(20,630)	(5,189)
Debt exchange expense	—	(52,444)	—
Gain (charge) on early extinguishment of debt	(7,142)	3,016	—
Other expense	(2,450)	(945)	(1,073)
	(33,712)	(58,833)	10,641
INCOME (LOSS) BEFORE INCOME TAXES	62,433	(55,484)	(93,744)
INCOME TAX BENEFIT, NET	112,629	—	—
INCOME (LOSS) BEFORE CUMULATIVE EFFECT OF A CHANGE IN ACCOUNTING PRINCIPLE	175,062	(55,484)	(93,744)
CUMULATIVE EFFECT OF A CHANGE IN ACCOUNTING PRINCIPLE	(3,534)	—	(7,434)
NET INCOME (LOSS)	171,528	(55,484)	(101,178)
DIVIDENDS ON CONVERTIBLE EXCHANGEABLE PREFERRED STOCK	—	(5,664)	(9,063)
NET INCOME (LOSS) APPLICABLE TO COMMON SHARES	$ 171,528	$ (61,148)	$ (110,241)
BASIC INCOME (LOSS) PER COMMON SHARE:			
Income (loss) per common share before cumulative effect of a change in accounting principle	$ 3.17	$ (1.27)	$ (2.51)
Cumulative effect of a change in accounting principle	(0.06)	—	(0.19)
	$ 3.11	$ (1.27)	$ (2.70)
DILUTED INCOME (LOSS) PER COMMON SHARE:			
Income (loss) per common share before cumulative effect of a change in accounting principle	$ 2.84	$ (1.27)	$ (2.51)
Cumulative effect of a change in accounting principle	(0.05)	—	(0.19)
	$ 2.79	$ (1.27)	$ (2.70)
WEIGHTED AVERAGE NUMBER OF COMMON SHARES OUTSTANDING	55,104	48,292	40,893
WEIGHTED AVERAGE NUMBER OF COMMON SHARES OUTSTANDING—ASSUMING DILUTION	67,442	48,292	40,893

The accompanying notes are an integral part of these consolidated financial statements.

CEPHALON, INC. AND SUBSIDIARIES CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY

(In thousands, except share data)

	Comprehensive Income (Loss)	Total	Preferred Stock Shares	Preferred Stock Amount	Common Stock Shares	Common Stock Amount	Additional Paid-in Capital	Treasury Stock Shares	Treasury Stock Amount	Accumulated Deficit	Accumulated Other Comprehensive Income
BALANCE, JANUARY 1, 2000		$ 230,783	2,500,000	$ 25	38,904,174	$ 389	$ 636,395	84,633	$ (1,290)	$ (405,302)	$ 566
Loss	$ (101,178)	(101,178)		—		—	—		—	(101,178)	—
Foreign currency translation gain	1,015										
Unrealized investment losses	(180)										
Other comprehensive income	835	835		—		—	—		—	—	835
Comprehensive loss	$ (100,343)										
Employee stock purchase plan		78		—	5,325	—	78		—	—	—
Stock options exercised		13,615		—	980,999	11	13,604		—	—	—

Stock purchase warrants exercised		26,436		—	2,418,027	24	26,412		—	—	—
Restricted stock award plan		5,625		—	146,725	1	5,624		—	—	—
Employee benefit plan		891		—	22,975	—	891		—	—	—
Dividends declared on convertible preferred stock		(9,063)		—		—	—		—	(9,063)	—
Treasury stock acquired		(2,829)		—		—	—	53,550	(2,829)	—	—
BALANCE, DECEMBER 31, 2000		165,193	2,500,000	25	42,478,225	425	683,004	138,183	(4,119)	(515,543)	1,401
Loss	$ (55,484)	(55,484)		—		—	—		—	(55,484)	—
Foreign currency translation gain	368										
Unrealized investment gains	504										
Other comprehensive income	872	872		—		—	—		—	—	872
Comprehensive loss	$ (54,612)										
Conversion of preferred stock into common stock		—	(2,500,000)	(25)	6,974,998	70	(45)		—	—	—
Issuance of common stock upon conversion of convertible notes		262,590		—	3,691,705	37	262,553		—	—	—
Stock options exercised		25,542		—	1,327,303	13	27,304	32,104	(1,775)	—	—
Stock purchase warrants exercised		2,679		—	265,800	2	2,677		—	—	—
Restricted stock award plan		5,349		—	150,650	2	5,347		—	—	—
Employee benefit plan		1,283		—	20,852	—	1,283		—	—	—
Dividends declared on convertible preferred stock		(5,664)		—		—	—		—	(5,664)	—
Treasury stock acquired		(3,629)		—		—	—	53,454	(3,629)	—	—
BALANCE, DECEMBER 31, 2001		398,731	—	—	54,909,533	549	982,123	223,741	(9,523)	(576,691)	2,273
Income	$ 171,528	171,528		—			—		—	171,528	—
Foreign currency translation gain	20,367										
Unrealized investment gains	2,406										
Other comprehensive income	22,773	22,773		—		—	—		—	—	22,773
Comprehensive income	$ 194,301										
Stock options exercised		5,940		—	347,686	4	6,056	2,055	(120)	—	—
Tax benefit from the exercise of stock options		40,998		—		—	40,998		—	—	—
Restricted stock award plan		2,828		—	129,900	1	2,827		—	—	—
Employee benefit plan		2,133		—	38,722	—	2,133		—	—	—
Treasury stock acquired		(2,346)		—		—	—	47,061	(2,346)	—	—
BALANCE, DECEMBER 31, 2002		$ 642,585	—	$ —	55,425,841	$ 554	$1,034,137	272,857	$(11,989)	$ (405,163)	$ 25,046

The accompanying notes are an integral part of these consolidated financial statements.

CEPHALON, INC. AND SUBSIDIARIES **CONSOLIDATED STATEMENTS OF CASH FLOWS**

(in thousands)

	Year Ended December 31,		
	2002	**2001**	**2000**
CASH FLOWS FROM OPERATING ACTIVITIES:			
Net income (loss)	$ 171,528	$ (55,484)	$ (101,178)
Adjustments to reconcile net income (loss) to net cash provided by (used for) operating activities:			
Deferred income taxes	(170,072)	—	—
Tax benefit from exercise of stock options	40,998	—	—
Cumulative effect of adoption of SAB 101	—	—	7,434
Depreciation and amortization	35,457	14,434	3,945
Amortization of debt issuance costs	11,071	5,158	—
Cumulative effect of changing inventory costing method from FIFO to LIFO	3,534	—	—
Stock-based compensation expense	4,961	6,632	6,516
In-process research and development expense	—	20,000	—
Debt exchange expense	—	52,444	—
Non-cash charge (gain) on early extinguishment of debt	7,142	(3,016)	—
Other	—	181	—
Increase (decrease) in cash due to changes in assets and liabilities, net of effect from acquisition:			
Receivables	3,990	(30,434)	(13,689)
Inventory	(5,821)	(8,918)	(15,903)
Other assets	(16,756)	(7,133)	2,202
Accounts payable, accrued expenses and deferred revenues	18,303	18,484	8,202
Other liabilities	(1,714)	(74)	(4,021)
Net cash provided by (used for) operating activities	102,621	12,274	(106,492)
CASH FLOWS FROM INVESTING ACTIVITIES:			
Purchases of property and equipment	(27,328)	(12,481)	(7,462)
Acquistion of Group Lafon, net of cash acquired	—	(447,717)	—
Acquistion of intangible assets	(79,409)	(21,063)	(56,627)
Sales and maturities (purchases) of investments, net	(39,027)	6,200	186,449
Net cash (used for) provided by investing activities	(145,764)	(475,061)	122,360
CASH FLOWS FROM FINANCING ACTIVITIES:			
Proceeds from exercises of common stock options, warrants and employee stock purchase plan	5,940	28,221	39,448
Payments to acquire treasury stock	(2,346)	(3,629)	(2,829)
Net proceeds from issuance of long-term debt	—	1,009,080	—
Preferred dividends paid	—	(6,797)	(9,063)
Principal payments on and retirements of long-term debt	(32,512)	(52,300)	(32,766)
Net cash (used for) provided by financing activities	(28,918)	974,575	(5,210)
EFFECT OF EXCHANGE RATE CHANGES ON CASH AND CASH EQUIVALENTS	9,431	368	1,015
NET INCREASE (DECREASE) IN CASH AND CASH EQUIVALENTS	(62,630)	512,156	11,673
CASH AND CASH EQUIVALENTS, BEGINNING OF YEAR	548,727	36,571	24,898
CASH AND CASH EQUIVALENTS, END OF YEAR	$ 486,097	$ 548,727	$ 36,571
Supplemental disclosures of cash flow information:			

Cash payments for interest	26,593	14,092	4,352
Non-cash investing and financing activities:			
Capital lease additions	788	360	2,067
Long-term debt	—	—	80,846
Conversion of convertible notes into common stock	—	217,000	—

The accompanying notes are an integral part of those consolidated financial statements.

CEPHALON, INC. AND SUBSIDIARIES NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

(In thousands, except share data)

1. NATURE OF BUSINESS AND SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Business

Cephalon is an international biopharmaceutical company dedicated to the discovery, development and marketing of products to treat sleep disorders, neurological and psychiatric disorders, cancer and pain. In addition to conducting an active research and development program, we market three products in the United States and a number of products in various countries throughout Europe.

Our corporate and research and development headquarters are in West Chester, Pennsylvania, and we have offices in Salt Lake City, Utah, France, the United Kingdom, Germany and Switzerland. We operate manufacturing facilities in France for the production of modafinil, which is the active drug substance in PROVIGIL® (modafinil) tablets [C-IV]. We also operate manufacturing facilities in Salt Lake City, Utah for the production of ACTIQ® (oral transmucosal fentanyl citrate) [C-II] for distribution and sale in the European Union and, beginning in the second quarter of 2003, the United States.

Pervasiveness of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the financial statements and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Principles of Consolidation

The consolidated financial statements include the results of our operations and our wholly owned subsidiaries. Intercompany transactions have been eliminated. In October 2000, we completed a merger with Anesta Corp. in a transaction accounted for as a pooling-of-interests. In December 2001, we acquired all of the outstanding shares of capital stock of Financiere Lafon S.A. and Organisation de Synthese Mondiale Orsymonde S. A. (collectively, Group Lafon) in a transaction accounted for as a purchase. See Note 2.

Foreign Currency

For foreign operating entities with currencies other than the U.S. Dollar, the local currency is the functional currency and we translate asset and liability balances at exchange rates in effect at the end of the period, and income and expense transactions at the average exchange rates in effect during the period. Resulting translation adjustments are reported as a separate component of accumulated other comprehensive income included in stockholders' equity. Gains and losses from foreign currency transactions are included in the consolidated statements of operations.

Statement of Financial Accounting Standards (SFAS) No. 95, "Statement of Cash Flows" requires that the effect of exchange rate changes on cash held in foreign currencies be reported as a separate item in the reconciliation of beginning and ending cash and cash equivalents. All other foreign currency cash flows are reported in the applicable line of the consolidated statement of cash flows using an approximation of the exchange rate in effect at the time of the cash flows.

Cash Equivalents and Investments

Cash equivalents include investments in liquid securities with original maturities of three months or less from the date of purchase. In accordance with SFAS No. 115, "Accounting for Certain Investments in Debt and Equity Securities," we consider our investments to be "available for sale." We classify these investments as short-term and carry them at fair market value. Unrealized gains and losses have been recorded as a separate component of stockholders' equity. All realized gains and losses on our available for sale securities are recognized in results of operations.

Major Customers and Concentration of Credit Risk

Trade accounts receivable included three customers, Cardinal Health, Inc., McKesson Corporation and AmerisourceBergen Corporation, that accounted for 76% and 72%, in the aggregate, of total trade accounts receivable at December 31, 2002 and

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2001, respectively. We sell our products primarily to a limited number of pharmaceutical wholesalers without requiring collateral. These three wholesaler customers accounted for 73%, 92% and 69%, in the aggregate, of our total gross product sales for the years ended December 31, 2002, 2001 and 2000, respectively. We periodically assess the financial strength of these customers and establish allowances for anticipated losses if necessary.

Inventory

Inventory is stated at the lower of cost or market value. Effective January 1, 2002, we began using the last-in, first-out (LIFO) method for our domestic inventories. We use the first-in, first-out (FIFO) method for the majority of our foreign inventories. See Note 6.

Property and Equipment

Property and equipment are recorded at cost and depreciated using the straight-line method over the estimated useful lives of the assets, which range from three to forty years. Property and equipment under capital leases are depreciated or amortized over the shorter of the lease term or the expected useful life of the assets. Expenditures for maintenance and repairs are charged to expense as incurred, while major renewals and betterments are capitalized.

Fair Value of Financial Instruments

The carrying values of cash, cash equivalents, short-term investments, accounts receivable, accounts payable and accrued expenses approximate the respective fair values. The market value of our 2.50% convertible notes was $556.9 million as compared to a carrying value of $600.0 million, and the market value of our 5.25% convertible notes approximated our carrying value of $183.0 million, at December 31, 2002, based on quoted market values. None of our other debt instruments that were outstanding as of December 31, 2002 have readily ascertainable market values; however, management believes that the carrying values approximate the respective fair values.

Goodwill, Intangible Assets and Other Long-Lived Assets

Goodwill represents the excess of purchase price over net assets acquired. In accordance with SFAS No. 142, "Goodwill and Other Intangible Assets" which we adopted on January 1, 2002, goodwill is not amortized; rather, goodwill is subject to a periodic assessment for impairment by applying a fair-value-based test. We have only recorded goodwill related to our acquisition of Group Lafon effective December 28, 2001 and amortization expense related to goodwill for the period December 28, 2001 to December 31, 2001 was immaterial. On January 1, 2002, our transitional impairment test indicated that there was no impairment of goodwill upon our adoption of SFAS 142. In addition, we performed our annual test of impairment of goodwill as of July 1, 2002. We have only one reporting unit, a pharmaceutical unit, that constitutes our entire commercial business, and we compared the fair value of this reporting unit with its carrying value. Our quoted market value at July 1, 2002 was used as the fair value of the reporting unit. Since the fair value of the reporting unit exceeded its carrying value at July 1, 2002, no adjustment to our goodwill for impairment was necessary.

In accordance with SFAS No. 144, "Accounting for the Impairment or Disposal of Long-Lived Assets," we review amortizable assets for impairment on an annual basis or whenever changes in circumstances indicate the carrying value of the asset may not be recoverable. If impairment is indicated, we measure the amount of such impairment by comparing the carrying value of the assets to the present value of the expected future cash flows associated with the use of the asset. Management believes the future cash flows to be received from the long-lived assets will exceed the assets' carrying value, and, accordingly, we have not recognized any impairment losses through December 31, 2002.

Revenue Recognition

Product sales are recognized upon the transfer of ownership and risk of loss for the product to the customer and are recorded net of estimated reserves for contractual allowances, discounts and returns. Contractual allowances result from sales under contracts with managed care organizations and government agencies.

Other revenue, which includes revenues from collaborative agreements, consists primarily of up-front fees, ongoing research and development funding, milestone payments and payments under co-promotional or managed services agreements.

Non-refundable up-front fees are deferred and amortized to revenue over the related performance period. We estimate our performance period based on the specific terms of each collaborative agreement. We adjust the performance periods, if appropriate, based upon available facts and circumstances. We recognize periodic payments over the period that we perform the related activities under the terms of the agreements. Revenue resulting from the achievement of milestone events stipulated in the agreements is recognized when the milestone is achieved. Milestones are based upon the occurrence of a substantive element specified in the contract or as a measure of substantive progress towards completion under the contract.

Reimbursement rates of research and development activities under collaborative agreements vary according to the terms of the individual agreements. Costs incurred related to collaborative agreements and reflected in our operating expenses approximated $44.0 million, $21.8 million and $15.5 million for the years ended December 31, 2002, 2001 and 2000, respectively.

Payments under co-promotional or managed services agreements are recognized when the products are sold or the promotional activities are performed. The portion of the payments that represents reimbursement of our expenses is recognized as an offset to those expenses in our statement of income.

As of December 31, 2002, we have recorded $2.7 million of deferred revenues of which $0.7 million is classified as current. These deferred revenues will be recognized over future periods in accordance with the revenue recognition policies described above.

Research and Development

All research and development costs are charged to expense as incurred.

Acquired In-Process Research and Development

Purchased in-process research and development represents the estimated fair value assigned to research and development projects acquired in a purchase business combination that have not been completed at the date of acquisition and which have no future alternative use. Accordingly, these costs are charged to expense as of the acquisition date.

Other Comprehensive Income (Loss)

We follow SFAS No. 130, "Reporting Comprehensive Income." This statement requires the classification of items of other comprehensive income (loss) by their nature and disclosure of the accumulated balance of other comprehensive income (loss), separately within the equity section of the balance sheet. The balance in accumulated other comprehensive income due to foreign currency translation adjustments was $21.9 million and $1.5 million as of December 31, 2002 and

2001, respectively. The balance in accumulated other comprehensive income due to unrealized investment gains was $3.2 million and $0.8 million as of December 31, 2002 and 2001, respectively.

Earnings Per Share

We compute income (loss) per common share in accordance with SFAS No. 128, "Earnings Per Share." Basic income (loss) per common share is computed based on the weighted average number of common shares outstanding during the period. Diluted income (loss) per common share is computed based on the weighted average shares outstanding and the dilutive impact of common stock equivalents outstanding during the period. The dilutive effect of employee stock options and restricted stock awards is measured using the treasury stock method. The dilutive effect of convertible notes is measured using the "if-converted" method. Common stock equivalents are not included in periods where there is a loss, as they are anti-dilutive.

The following is a reconciliation of net income (loss) and weighted average common shares outstanding for purposes of calculating basic and diluted income (loss) per common share:

	Year ended December 31,		
	2002	2001	2000
Basic income (loss) per share computation:			
Numerator:			
Income (loss) before cumulative effect of a change in accounting principle	$ 175,062	$ (55,484)	$ (93,744)
Cumulative effect of a change in accounting principle	(3,534)	—	(7,434)
Net income (loss)	171,528	(55,484)	(101,178)
Dividends on convertible exchangeable preferred stock	—	(5,664)	(9,063)
Net income (loss) used for basic income (loss) per common share	$ 171,528	$ (61,148)	$ (110,241)
Denominator:			
Weighted average shares used for basic income (loss) per common share	55,104,000	48,292,000	40,893,000
Basic income (loss) per common share:			
Income (loss) per common share before cumulative effect of a change in accounting principle	$ 3.17	$ (1.27)	$ (2.51)
Cumulative effect of a change in accounting principle	(0.06)	—	(0.19)
	$ 3.11	$ (1.27)	$ (2.70)
Diluted income (loss) per share computation:			
Numerator:			
Income (loss) before cumulative effect of a change in accounting principle	$ 175,062	$ (55,484)	$ (93,744)
Cumulative effect of a change in accounting principle	(3,534)	—	(7,434)
Net income (loss)	171,528	(55,484)	(101,178)
Dividends on convertible exchangeable preferred stock	—	(5,664)	(9,063)
Net income (loss) used for basic income (loss) per common share	171,528	(61,148)	(110,241)
Add: interest on convertible notes (net of tax)	16,259	—	—
Net income (loss) used for diluted income (loss) per common share	$ 187,787	$ (61,148)	$ (110,241)
Denominator:			
Weighted average shares used for basic income (loss) per common share	55,104,000	48,292,000	40,893,000
Effect of dilutive securities:			
Convertible notes	10,466,000	—	—
Employee stock options and restricted stock awards	1,872,000	—	—
Weighted average shares used for diluted income (loss) per common share	67,442,000	48,292,000	40,893,000
Diluted income (loss) per common share:			
Income (loss) per common share before cumulative effect of a change in accounting principle	$ 2.84	$ (1.27)	$ (2.51)
Cumulative effect of a change in accounting principle	(0.05)	—	(0.19)
	$ 2.79	$ (1.27)	$ (2.70)

The weighted average shares used in the calculation of diluted income per common share excludes 2,331,000 shares relating to outstanding employee stock options for the year ended December 31, 2002 as the inclusion of such shares would be anti-dilutive.

Stock-based Compensation

We account for stock-based compensation in accordance with the provisions of Accounting Principles Board Opinion (APB) No. 25, "Accounting for Stock Issued to Employees," and related interpretations. Accordingly, compensation cost is not required to be recognized for options granted to employees and directors at the then fair market value. We follow the disclosure-only provisions of SFAS No. 123, "Accounting for Stock-Based Compensation."

Income Taxes

We account for income taxes using the liability method under SFAS No. 109, "Accounting for Income Taxes." This method generally provides that deferred tax assets and liabilities be recognized for temporary differences between the financial reporting basis and the tax basis of the assets and liabilities and expected benefits of utilizing net operating loss and tax credit carryforwards. We record a valuation allowance for certain temporary differences for which it is more likely than not that we will not generate future tax benefits. The impact on deferred taxes of changes in tax rates and laws, if any, are applied to the years during which temporary differences are expected to be settled and reflected in the consolidated financial statements in the period of enactment.

Reclassifications

Certain reclassifications of prior year amounts have been made to conform to the current year presentation.

Recent Accounting Pronouncements

On January 1, 2002, we adopted the provisions of SFAS No. 142, "Goodwill and Other Intangible Assets." SFAS 142 no longer requires the amortization of goodwill; rather, goodwill will be subject to a periodic assessment for impairment by applying a fair-value-based test. In addition, an acquired intangible asset should be separately recognized if the benefit of the intangible asset is obtained through contractual or other legal rights, or if the intangible asset can be sold, transferred, licensed, rented, or exchanged, regardless of the acquirer's intent to do so. Such acquired intangible assets will be amortized over the period in which the economic benefits of the intangible asset are consumed or otherwise used up. The new criteria for recording intangible assets separate from goodwill did not require us to reclassify any of our intangible assets. We have only recorded goodwill related to our acquisition of Group Lafon.

In June 2001, the Financial Accounting Standards Board (FASB) issued SFAS No. 143, "Accounting for Asset Retirement Obligations," which requires recognition of the fair value of liabilities associated with the retirement of long-lived assets when a legal obligation to incur such costs arises as a result of the acquisition, construction, development and/or the normal operation of a long-lived asset. SFAS 143 requires that the fair value of a liability for an asset retirement obligation be recognized in the period in which it is incurred if a reasonable estimate of fair value can be made. The associated asset retirement costs are capitalized as part of the carrying amount of the long-lived asset and subsequently allocated to expense over the asset's useful life. SFAS 143 is effective for fiscal years beginning after December 15, 2002. The adoption of this new standard will not have any impact on our current financial statements.

On January 1, 2002, we adopted SFAS No. 144, "Accounting for the Impairment or Disposal of Long-Lived Assets." This Statement provides new guidance on the recognition of impairment losses on long-lived assets to be held and used or to be disposed of and also broadens the definition of what constitutes a discontinued operation and how the results of a discontinued operation are to be measured and presented. The adoption of this new standard has not had a material impact on our current financial statements.

CEPHALON, INC. AND SUBSIDIARIES NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

(In thousands, except share data)

In April 2002, the FASB issued SFAS No. 145 "Rescission of FASB Statements No. 4, 44 and 64, Amendment of FASB Statement No. 13, and Technical Corrections." This Statement amends or rescinds certain existing authoritative pronouncements including SFAS No. 4, "Reporting Gains and Losses on Extinguishment of Debt," such that the provisions of APB No. 30 "Reporting the Results of Operations-Reporting the Effects of Disposal of a Segment of a Business, and Extraordinary, Unusual and Infrequently Occurring Events and Transactions" must now be followed to determine if the early extinguishment of debt should be classified as an extraordinary item. In addition, any gain or loss on extinguishment of debt that was classified as an extraordinary item in prior periods that does not meet the criteria in APB 30 must be reclassified. SFAS 145 is effective for fiscal years beginning after May 15, 2002. We adopted this new standard effective December 31, 2002 and reclassified all gains and losses on early extinguishment of debt as other income and expense, rather than extraordinary items, in our current financial statements.

In June 2002, the FASB issued SFAS No. 146, "Accounting for Exit or Disposal Activities." This Statement addresses the recognition, measurement and reporting of costs that are associated with exit and disposal activities, including restructuring activities that are currently accounted for pursuant to the guidance in Emerging Issues Task Force Issue No. 94-3, "Liability Recognition for Certain Employee Termination Benefits and Other Costs to Exit an Activity (including Certain Costs Incurred in a Restructuring)." The Statement requires that costs associated with exit or disposal activities be recorded at their fair values when a liability has been incurred. SFAS 146 is effective for disposal activities initiated after December 31, 2002. The adoption of this new standard will not have any impact on our current financial statements.

In December 2002, the FASB issued SFAS No. 148, "Accounting for Stock-Based Compensation-Transition and Disclosure." SFAS 148 amends SFAS 123, "Accounting for Stock-Based Compensation," to provide alternative methods of transition for a voluntary change to the fair value based method of accounting for stock-based employee compensation. In addition, this Statement amends the disclosure requirements of SFAS 123 to require prominent disclosures in both annual and interim financial statements about the method of accounting for stock-based employee compensation and the effect of the method used on reported results. The alternative methods of transition and additional disclosure requirements of SFAS 148 are effective January 1, 2003.

In November 2002, the FASB issued FASB Interpretation (FIN) No. 45, "Guarantor's Accounting and Disclosure Requirements for Guarantees." This Interpretation requires that upon the issuance of a guarantee, the guarantor must recognize a liability for the fair value of the obligation it assumes under that guarantee. FIN 45 is effective for guarantees issued or modified after December 31, 2002. The adoption of this new statement will not have any impact on our current financial statements.

In January 2003, the FASB issued FIN No. 46, "Consolidation of Variable Interest Entities." This Interpretation addresses consolidation of variable interest entities where an enterprise does not have voting control over the entity but has a controlling financial interest in the entity. FIN 46 is effective for all financial statements issued after September 30, 2003. As a result of the adoption of this standard, Cephalon Clinical Partners, L.P. will be consolidated in our financial statements. This consolidation will not have a material impact on our financial statements. See Note 11.

2. MERGERS AND ACQUISITIONS

Anesta Corp.

On October 10, 2000, we completed a merger with Anesta Corp. under which we acquired all of the outstanding shares of Anesta in a tax-free, stock-for-stock transaction. The merger was accounted for as a pooling-of-interests and, accordingly, all of our consolidated financial statements prior to the merger date were restated to include the results of operations, financial position, and cash flows of Anesta. In connection with the merger, we recorded merger and integration costs of $13.8 million in the fourth quarter of 2000.

Group Lafon

On December 28, 2001, we completed our acquisition of the outstanding shares of capital stock of Group Lafon. The results of operations for Group Lafon have not been included in our consolidated statements in 2001 since operations between the acquisition date and December 31, 2001 were immaterial.

The purchase price of $454.2 million was funded in part by the proceeds of our December 11, 2001 offering of $600.0 million of 2.50% convertible subordinated notes. Of the purchase price, $450.0 million was paid in cash to the sellers with the remainder primarily representing transaction costs of the acquisition and severance payments to certain Group Lafon employees. The purchase accounting for the acquisition was finalized effective December 31, 2002 and resulted in a $2.8 million decrease in the amount of goodwill originally recorded at the date of acquisition.

At December 31, 2001, $4.9 million was recorded as a net accrual for transaction costs in our consolidated balance sheet. All such amounts were paid in 2002.

The following table summarizes the fair values of assets acquired and liabilities assumed at the date of acquisition.

	At December 31, 2002
Current assets	$ 63,407
Property, plant and equipment	25,281
Intangible assets	148,000
Acquired in-process research and development	20,000
Goodwill	298,769
Other assets	4,898
Total assets acquired	560,355
Current liabilities	(38,148)
Deferred tax liabilities	(52,666)
Other liabilities	(15,349)
Total liabilities assumed	(106,163)
Net assets acquired	$ 454,192

Of the $148.0 million of acquired intangible assets, $16.0 million was assigned to trademarks and tradenames with an estimated useful life of 15 years with the remaining $132.0 million assigned to developed technology for existing pharmaceutical products with a weighted average estimated useful life of approximately 14 years. The $298.8 million of goodwill was assigned to the pharmaceutical segment. None of this goodwill is expected to be deductible for income tax purposes.

In accordance with SFAS 142, goodwill is not amortized, but is subject to a periodic assessment for impairment by applying a fair-value-based test. We performed our annual test of impairment of goodwill as of July 1, 2002. We have only one reporting unit, a pharmaceutical unit, that constitutes our entire commercial business, and we compared the fair value of this reporting unit with its carrying value. Our quoted market value at July 1, 2002 was used as the fair value of the reporting unit. Since the fair value of the reporting unit exceeded its carrying value at July 1, 2002, no adjustment to our goodwill for impairment was necessary.

In connection with the acquisition of Group Lafon, we allocated approximately $20.0 million of the purchase price to in-process research and development projects. This allocation represented the estimated fair value based on risk-adjusted cash flows related to the incomplete research and development projects. At the date of acquisition, the development of these projects had not yet reached technological feasibility, and the research and development in progress had no alternative future uses. Accordingly, these costs were charged to expense as of the acquisition date.

At the acquisition date, Group Lafon had spent approximately $10.0 million on the in-process research and development projects ongoing research and development initiatives, including next-generation MODIODAL drug delivery technologies; a Phase IV clinical trial for FONZYLANE; CRL 41789, an anti-depressant drug candidate ready for Phase II clinical trials; and several other ongoing research and development projects. During 2002, the CRL 41789 study was

discontinued while work was continued on the MODIODAL and FONZYLANE studies. We still expect that the completion dates for the development work are in the time-frame of 2004 through 2006 and at which time we expect to begin benefiting from these developed technologies. The estimated revenues for the remaining in-process projects are expected to peak within 10-12 years of acquisition.

In determining the purchase price allocation, management considered present value calculations of income, an analysis of project accomplishments and remaining outstanding items, an assessment of overall contributions, as well as project risks. The value assigned to purchased in-process technology was determined by independent appraisal by estimating the costs to develop the acquired technology into commercially viable products, estimating the resulting net cash flows from the projects, and discounting the net cash flows to their present value. The revenue projections used to value the in-process research and development were, in some cases, reduced based on the probability of success in developing a new drug, and considered the relevant market sizes and growth factors, expected trends in technology, and the nature and expected timing of new product introductions by us and our competitors. The resulting net cash flows from such projects are based on management's estimates of cost of sales, operating expenses, and income taxes from such projects.

The rates utilized to discount the net cash flows to their present value were based on estimated cost of capital calculations. Due to the nature of the forecast and the risks associated with the projected growth and profitability of the developmental projects, discount rates ranging from 25 to 40 percent were considered appropriate for the in-process research and development. These discount rates were commensurate with the projects' stage of development and the uncertainties in the economic estimates described above.

If these projects are not successfully developed, the sales and profitability of the combined company may be adversely affected in future periods. Additionally, the value of other acquired intangible assets may become impaired. We believed that the foregoing assumptions used in the in-process research and development analysis were reasonable at the time of the acquisition. We cannot be sure, however, that the underlying assumptions used to estimate expected project sales, development costs or profitability, or the events associated with such projects, will transpire as estimated.

The following unaudited pro forma information shows the results of the our operations for the years ended December 31, 2001 and 2000 as though the acquisition had occurred as of the beginning of the years presented:

	For the years ended December 31,	
	2001	2000
Total revenues	$ 364,691	$ 217,678
Net loss before cumulative effect of accounting change	$ (73,333)	$ (106,371)
Net loss	$ (73,333)	$ (113,805)
Basic and diluted net loss per common share:		
Before cumulative effect of accounting change	$ (1.52)	$ (2.60)
Net loss	$ (1.52)	$ (2.78)

The pro forma results have been prepared for comparative purposes only and are not necessarily indicative of the actual results of operations had the acquisition taken place as of the beginning of the periods presented, or the results that may occur in the future. Furthermore, the pro forma results do not give effect to all cost savings or incremental costs that may occur as a result of the integration and consolidation of the acquisition.

3. JOINT VENTURE

In December 2001, we formed a joint venture with unaffiliated third party investors to fund additional commercial activities in support of PROVIGIL and GABITRIL in the United States. In exchange for our transfer to the joint venture of certain intellectual property and other rights related to these two products, we received a Class B interest, representing a 50% interest in the joint venture. In exchange for a contribution of $50.0 million in cash to the joint venture, the investors received Class A interests, also representing a 50% interest in the joint venture. As of December 31, 2001, the $50.0 million investors' Class A interest was recorded on our balance sheet as long-term debt, and the joint venture's cash balance of $50.0 million was included in our balance of cash and cash equivalents.

On March 29, 2002, we acquired the investors' Class A interests and ended the joint venture by issuing to the investors, through a private placement, $55.0 million aggregate principal amount of 3.875% convertible subordinated notes due March 2007. See Note 10.

The purchase of the investor's Class A interests in the joint venture resulted in the recognition of a charge of $7.1 million on the early extinguishment of debt during the first quarter of 2002. The following table summarizes the calculation of this charge:

Carrying value of the debt as of December 31, 2001	$ 50,000
Interest accreted during the first quarter 2002 at 20%	2,500
Carrying value of the debt as of March 29, 2002	52,500
Less: unamortized joint venture formation costs as of March 29, 2002	(4,642)
	47,858
Fair value of subordinated notes issued on March 29, 2002	(55,000)
Charge on early extinguishment of debt	$ (7,142)

In addition, our statement of operations for the year ended December 31, 2002 included certain charges related to the operations of the joint venture, as follows:

Selling, general and administrative expenses	$ 3,508
Interest expense	3,163
Interest income	(190)
Total	$ 6,481

4. CASH, CASH EQUIVALENTS AND INVESTMENTS

At December 31, cash, cash equivalents and investments consisted of the following:

	2002	2001
Cash and cash equivalents:		
Demand deposits	$ 486,097	$ 4,364
Repurchase agreements	—	155,817
U.S. government agency obligations	—	79,985
Commercial paper	—	245,158
Asset-backed securities	—	4,636
Bonds	—	58,767
	486,097	548,727
Short-term investments (at market value):		
U.S. government agency obligations	4,994	8,076
Commercial paper	—	17,135
Asset-backed securities	65,796	2,878
Bonds	25,801	26,068
Certificates of deposit	—	1,000
	96,591	55,157
	$ 582,688	$ 603,884

The contractual maturities of our investments in cash, cash equivalents, and investments at December 31, 2002 are as follows:

(In thousands, except share data)

Less than one year	$ 497,547
Greater than one year but less than two years	51,740
Greater than two years but less than three years	33,401
	$ 582,688

Some of our lease agreements contain covenants that obligate us to maintain a minimum balance in unrestricted cash and investments of $30.0 million or deliver to the lessor an irrevocable letter of credit in the amount of the then outstanding balance

due on all equipment leased under the agreements. At December 31, 2002, the balance due under these lease agreements was $1.4 million.

5. RECEIVABLES

At December 31, receivables consisted of the following:

	2002	2001
Trade receivables	$ 63,659	$ 40,790
Receivables from collaborations	12,321	16,438
Other receivables	12,251	24,950
	88,231	82,178
Less reserve for sales discounts, returns and allowances	(5,101)	(2,331)
	$ 83,130	$ 79,847

At December 31, inventory consisted of the following:

	2002	2001
Raw material	$ 28,628	$ 19,666
Work-in-process	2,448	7,632
Finished goods	23,223	20,215
	$ 54,299	$ 47,513

Effective January 1, 2002, we changed our method of valuing domestic inventories from the first-in, first-out, or FIFO method, to the last-in, first-out, or LIFO method. We recognized a charge of $3.5 million in the first quarter of 2002 as the cumulative effect of adopting the LIFO inventory costing method. The acquisition of Group Lafon's manufacturing operations and the expansion of our internal manufacturing capacity for ACTIQ has reduced our reliance on third party manufacturers and sharpened management's focus on minimizing the cost of manufacturing products. Consistent with this goal, the LIFO method reflects current changes to manufacturing costs on the statement of operations on a more timely basis, resulting in a better matching of currents costs of products sold with product revenues.

Cost of product sales under the LIFO inventory costing method was $17.9 million lower in 2002 than it would have been under the FIFO method. If we had adopted LIFO effective January 1, 2000, the effect on our statement of operations for 2000 and 2001 would have been immaterial.

7. PROPERTY AND EQUIPMENT

At December 31, property and equipment consisted of the following:

	Estimated Useful Lives	2002	2001
Land and improvements	—	$ 4,612	$ 3,370
Buildings and improvements	10-40 years	54,556	39,554
Laboratory, machinery and other equipment	3-10 years	45,335	36,099
Construction in progress	—	18,686	6,736
		123,189	85,759
Less accumulated depreciation and amortization		(33,123)	(21,053)
		$ 90,066	$ 64,706

Depreciation and amortization expense was $7.8 million, $3.0 million, and $2.3 million for the years ended December 31, 2002, 2001 and 2000, respectively.

8. OTHER INTANGIBLE ASSETS, NET

At December 31, other intangible assets consisted of the following:

	2002	2001
Developed technology acquired from Lafon	$ 132,000	$ 132,000
Trademarks/tradenames acquired from Lafon	16,000	16,000
GABITRIL product rights	110,749	92,648
Novartis product rights	41,641	41,641
ACTIQ marketing rights	75,465	29,114
Modafinil marketing rights	7,906	—
Other	12,377	—
	396,138	311,403
Less accumulated amortization	(44,419)	(13,134)
	$ 351,719	$ 298,269

Other intangible assets are amortized over their estimated useful economic life using the straight line method. Amortization expense was $27.7 million, $11.5 million, and $1.7 million for the years ended December 31, 2002, 2001 and 2000, respectively. Estimated amortization expense of intangible assets for each of the next five years is approximately $32.8 million.

9. ACCRUED EXPENSES

At December 31, accrued expenses consisted of the following:

	2002	2001
Accrued compensation and benefits	$ 14,433	$ 9,042
Accrued income taxes	13,242	—
Accrued professional and consulting fees	7,476	3,384
Accrued clinical trial fees and related expenses	7,065	8,397
Accrued license fees and royalties	7,985	9,199
Accrued merger and integration expenses	—	6,413
Accrued contractual sales allowances	6,145	4,655
Accrued interest	2,900	2,789
Other accrued expenses	21,198	10,146
	$ 80,444	$ 54,025

10. LONG-TERM DEBT

At December 31, long-term debt consisted of the following:

	2002	2001
Capital lease obligations	$ 2,594	$ 2,852
Mortgage and building improvement loans	10,940	12,085
Joint venture (See Note 3)	—	50,000
Convertible subordinated notes	838,000	783,000
Notes payable/other	7,603	13,460
Due to Abbott Laboratories	17,162	37,392
Total debt	876,299	898,789
Less current portion	(15,402)	(32,200)
Total long-term debt	$ 860,897	$ 866,589

Aggregate maturities of long-term debt are as follows:

2003	$ 15,402
2004	9,277
2005	2,699
2006	785,223
2007	57,288
2008 and thereafter	6,410
	$ 876,299

Capital Lease Obligations

We currently lease certain property and laboratory, production and computer equipment with a cost of $6.8 million. Under the terms of certain of the lease agreements, we must maintain a minimum balance in unrestricted cash and investments of $30.0 million or deliver to the lessor an irrevocable letter of credit in the amount of the then outstanding balance due on all equipment leased under the agreements. At December 31, 2002, the balance due under these lease agreements was $1.4 million. Our lease agreements provide us with an option to purchase the leased equipment at the conclusion of the lease.

Mortgage and Building Improvement Loans

In March 1995, we purchased the buildings housing our administrative offices and research facilities in West Chester, Pennsylvania for $11.0 million. We financed the purchase through the assumption of an existing $6.9 million first mortgage and from $11.6 million in state funding provided by the Commonwealth of Pennsylvania. The first mortgage has a 15-year term with an annual interest rate of 9.625%. The state funding has a 15-year term with an annual interest rate of 2%. The state loans contained a provision that would have allowed the rate on the loans to be increased to prime plus 2% if we did not meet targets for hiring new employees in Pennsylvania by the end of 1999. We were accruing interest at this higher rate over the life of the loan. Although we did not meet the hiring target, in April 2000, we and the Commonwealth reached an agreement under which the Commonwealth waived the interest penalty. As a result, we recognized interest income in 2000 for the interest differential of $4.0 million that was previously accrued. The loans require annual aggregate principal and interest payments of $1.8 million. The loans are secured by the buildings and by all our equipment located in Pennsylvania that is otherwise unsecured.

In November 2002, the Pennsylvania Industrial Development Board (PIDA) authorized the write-off of the outstanding principal balance of a loan granted by PIDA in 1995, contingent upon the commencement of construction of a new headquarters facility in the Commonwealth of Pennsylvania no later than June 30, 2004, unless an extension is approved by the PIDA Board. Until the earlier of the commencement of actual and direct construction of a headquarters facility or June 30, 2004 (or later date if extended), no further interest will accrue on the outstanding balance and no payments are required by PIDA. If the above contingency is not met, interest and principal payments will proceed with the amortization schedule previously established in the original loan agreement. The outstanding loan balance of $5.3 million at December 31, 2002 is reflected in our balance sheets as a long-term liability.

Subordinated Convertible Notes

In the second quarter of 2001, we completed a private placement of $400.0 million of 5.25% convertible subordinated notes due May 2006. Debt issuance costs of $14.4 million have been capitalized in other assets and are being amortized over the term of the notes. Interest on the notes is payable each May 1 and November 1. The notes are convertible, at the holder's option, into our common stock at a conversion price of $74.00 per share, subject to adjustment in certain circumstances. We may redeem the notes on or after May 5, 2003. Prior to that date, we may redeem the notes if our common stock price exceeds 150% of the conversion price for a specified period of time. Upon early redemption, we are required to pay interest that would have been due up through May 5, 2003. During the fourth quarter of 2001, certain note holders approached us, and we

agreed, to exchange $217.0 million of these outstanding notes into 3,691,705 shares of our common stock. We recognized debt exchange expense of $52.4 million in the fourth quarter of 2001 relating to these early exchanges in accordance with SFAS No. 84, "Induced Conversion of Convertible Debt."

In December 2001, we completed a private placement of $600.0 million of 2.50% convertible subordinated notes due December 2006. Debt issuance costs of $21.3 million have been capitalized in other assets and are being amortized over the term of the notes. Interest on the notes is payable each June 15 and December 15, beginning June 15, 2002. The notes are convertible into our common stock at a conversion price of $81.00 per share, subject to adjustment in certain circumstances. We may redeem the notes on or after December 20, 2004.

In March 2002, we issued and sold $55.0 million of aggregate principal in a private placement of 3.875% convertible notes due March 2007. These notes were issued in connection with our purchase of the investor's Class A interests in the joint venture and sold to the purchaser in a transaction exempt from registration requirements of the Securities Act of 1933, as amended, because the offer and sale of the notes did not involve a public offering. Interest on the notes is payable at a rate of 3.875% per year on each of April 15 and October 15. The notes also are convertible into our common stock, at the option of the holders, at a price of $70.36 per share, subject to adjustment upon certain events. The holders of these notes may elect to require us to redeem the notes on March 28, 2005 at a redemption price equal to 100% of the principal amount of notes submitted for redemption, plus accrued and unpaid interest. In certain other circumstances, at the option of the holders, we may be required to repurchase the notes at 100% of the principal amount of the notes submitted for repurchase, plus accrued and unpaid interest.

Notes Payable/Other

In December 2001, we acquired Group Lafon, which included the assumption of $13.5 million of notes payable, bank debt and outstanding amounts under lines of credit. At December 31, 2002, $7.6 million is outstanding with fixed and variable interest rates ranging from 4.2% to 6.0%, such amounts are payable through 2011.

Due to Abbott Laboratories

In March 2000, we purchased the U.S. marketing rights to ACTIQ from Abbott Laboratories for $29.2 million. At December 31, 2002, $3.6 million is outstanding and payable through 2005.

In October 2000, we agreed to purchase the product rights to market and sell GABITRIL in the United States from Abbott for $100.0 million due through 2004, of which $40.0 million was paid immediately. We recorded $54.2 million of

debt which represented the net present value of the remaining $60.0 million obligation, based on an incremental borrowing rate of 7.5%. We made payments of $24.0 million in 2001 and $21.0 million in 2002. At December 31, 2002, $13.6 million is outstanding and payable through 2004.

Due to Novartis Pharma AG

In November 2000, we entered into a collaboration agreement with Novartis to consolidate the sales and marketing efforts of four Novartis CNS products with PROVIGIL in the United Kingdom. In connection with this agreement, we agreed to pay Novartis approximately $45.0 million, of which approximately $15.0 million was paid immediately and approximately $30.0 million was due in various installments through 2002. We recognized $26.7 million at December 31, 2000 as the net present value of the remaining payments based on an incremental borrowing rate of 7.5%. In May 2001, we paid $24.4 million to Novartis to satisfy our outstanding obligation and recorded a gain on the early extinguishment of debt of $3.0 million.

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11. COMMITMENTS AND CONTINGENCIES

Leases

We lease certain of our offices and automobiles under operating leases in the U.S. and Europe that expire at various times through 2018. Lease expense under all operating leases totaled $4.3 million, $3.3 million, and $2.2 million in 2002, 2001, and 2000, respectively. Estimated lease expense for each of the next five years is as follows:

2003	$ 5,724
2004	4,592
2005	2,789
2006	1,747
2007	1,223
2008 and thereafter	4,967
	$ 21,042

Cephalon Clinical Partners, L.P.

In August 1992, we exclusively licensed our rights to MYOTROPHIN for human therapeutic use within the United States, Canada and Europe to Cephalon Clinical Partners, L.P. (CCP). Development and clinical testing of MYOTROPHIN is performed on behalf of CCP under a research and development agreement with CCP.

CCP has granted us an exclusive license to manufacture and market MYOTROPHIN for human therapeutic use within the United States, Canada and Europe in return for royalty payments equal to a percentage of product sales and a milestone payment of approximately $16.0 million that will be made if MYOTROPHIN receives regulatory approval.

We have a contractual option, but not an obligation, to purchase all of the limited partnership interests of CCP, which is exercisable upon the occurrence of certain events following the first commercial sale of MYOTROPHIN. If, and only if, we decide to exercise this purchase option, we would make an advance payment of approximately $40.3 million in cash or, at our election, approximately $42.4 million in shares of common stock or a combination thereof. Should we discontinue development of MYOTROPHIN, or if we do not exercise this purchase option, our license will terminate and all rights to manufacture or market MYOTROPHIN in the United States, Canada and Europe will revert to CCP, which may then commercialize MYOTROPHIN itself or license or assign its rights to a third party. In that event, we would not receive any benefits from such commercialization, license or assignment of rights.

Legal Proceedings

On March 28, 2003, we filed a patent infringement lawsuit in U.S. District Court in New Jersey against Teva Pharmaceuticals USA, Inc., Mylan Pharmaceuticals Inc., Ranbaxy Pharmaceuticals Inc., and Barr Laboratories, Inc. based upon the ANDAs filed by each of these companies seeking FDA approval for a generic equivalent of modafinil. The lawsuit claims infringement of our U.S. Patent No. RE37516, which covers the pharmaceutical compositions and methods of treatment with the form of modafinil contained in PROVIGIL. We intend to vigorously defend the validity, and prevent infringement, of this patent.

We are a party to certain other litigation in the ordinary course of our business, including, among others, U.S. patent interference proceedings, European patent oppositions, and matters alleging employment discrimination, product liability and breach of commercial contract. We are vigorously defending ourselves in all of these actions and do not believe these matters, even if adversely adjudicated or settled, would have a material adverse effect on our financial condition or results of operations.

12. STOCKHOLDERS' EQUITY

Convertible Exchangeable Preferred Stock

During the third quarter of 1999, we completed a private offering to institutional investors of 2,500,000 shares of convertible exchangeable preferred stock at $50 per share. Dividends on the preferred stock were payable quarterly and were cumulative at the annual rate of $3.625 per share. We recognized $5.7 million and $9.1 million of preferred dividends in 2001

and 2000, respectively. The preferred stock was convertible into an aggregate of approximately 6,975,000 shares of our common stock at a conversion price of $17.92 per share, subject to adjustment in certain circumstances.

In May 2001, the holders of 2,344,586 shares of the 2,500,000 shares outstanding of our convertible exchangeable preferred stock converted their preferred shares into an aggregate of 6,541,394 shares of our common stock. As an inducement to the holders to convert their preferred stock prior to August 2001, when we were initially permitted to redeem the preferred stock, we agreed to pay immediately all dividends accrued through the date of conversion as well as all dividends that would have accrued on the converted shares through the August 2001 redemption date. In the second quarter of 2001, we recorded an additional $1.1 million of dividend expense associated with the early conversion. In September 2001, the remaining 155,414 shares of our convertible exchangeable preferred stock were converted into an aggregate of 433,604 shares of our common stock.

Equity Compensation Plans

We have established equity compensation plans for our employees, directors and certain other individuals. All grants and terms are authorized by the Compensation Committee of our Board of Directors. We may grant non-qualified stock options under the 1995 Equity Compensation Plan and the 2000 Equity Compensation Plan, and also may grant incentive stock options and restricted stock awards under 1995 Plan. The options and restricted stock awards generally become exercisable or vest ratably over four years from the grant date, and the options must be exercised within ten years of the grant date.

The following tables summarize the aggregate option activity under the plans for the years ended December 31:

	2002		2001		2000	
	Shares	Weighted Average Exercise Price	Shares	Weighted Average Exercise Price	Shares	Weighted Average Exercise Price
Outstanding, January 1,	5,607,595	$ 45.36	5,253,730	$ 28.44	4,601,272	$ 17.07
Granted	2,497,200	51.88	2,035,100	70.32	1,796,200	49.69

Exercised	(347,686)	17.43	(1,339,380)	19.71	(945,023)	15.16
Canceled	(180,168)	50.98	(341,855)	31.88	(198,719)	22.76
Outstanding, December 31,	7,576,941 $	48.52	5,607,595 $	45.36	5,253,730 $	28.44
Exercisable at end of year	2,829,136 $	35.16	1,937,125 $	22.91	2,360,358 $	17.95
Weighted average fair value of options granted during the year	$	23.79	$	41.78	$	40.60

CEPHALON, INC. AND SUBSIDIARIES NOTES TO CONSOLIDATED FINANCIAL STATEMENTS **(Continued)**

(In thousands, except share data)

The fair value of the options granted during 2002, 2001 and 2000 were estimated on the date of grant using the Black-Scholes option-pricing model based on the following assumptions:

	2002	2001	2000
Risk free interest rate	3.30%	4.89%	5.04%
Expected life	6 years	6 years	6 years
Expected volatility	43%	59%	103%
Expected dividend yield	0%	0%	0%

	Options Outstanding			Options Exercisable	
Range of Exercise Price	Shares	Weighted Average Remaining Contractual Life (yrs)	Weighted Average Exercise Price	Shares	Weighted Average Exercise Price
$ 6.00-$14.99	859,225	5.3	$ 9.21	838,575	$ 9.18
$15.00-$29.99	785,169	6.1	24.20	645,441	23.72
$30.00-$50.99	298,622	7.0	38.33	136,345	31.16
$51.00-$59.99	3,643,200	9.1	51.92	723,250	52.48
$60.00-$71.96	1,990,725	8.9	70.40	485,525	70.59
	7,576,941	8.0	$ 48.52	2,829,136	$ 35.16

In 2002, the 1995 and 2000 Equity Compensation Plans were amended to increase the number of shares subject to the annual grants awarded under all of the plans by 1,200,000 and 1,700,000 shares, respectively. At December 31, 2002, 869,484 shares were available for future grants under all of the plans.

During 2002, 2001, and 2000, we received net proceeds of $5.9 million, $25.5 million, and $13.6 million, respectively, from the exercise of stock options. During 2002 and 2001, some stock options were exercised by tendering mature shares as consideration for the exercise price, resulting in the recording of treasury stock of $0.1 million and $1.8 million, respectively.

The following table summarizes restricted stock award activity for the years ended December 31:

	2002	2001	2000
Outstanding, January 1,	268,875	446,850	496,700
Granted	—	—	119,200
Vested	(129,900)	(150,650)	(146,725)
Canceled	(5,700)	(27,325)	(22,325)
Outstanding, December 31,	133,275	268,875	446,850
Compensation expense recognized	$ 2,828	$ 5,349	$ 5,625

We have opted to disclose only the provisions of SFAS No. 123, "Accounting for Stock-Based Compensation," as they pertain to financial statement recognition of compensation expense attributable to option grants. As such, no compensation cost has been recognized for our stock option plans. If we had elected to recognize compensation cost based on the fair value of

stock options as prescribed by SFAS 123, the pro forma income (loss) and income (loss) per share amounts would have been as follows:

	Year ended December 31,		
	2002	2001	2000
As reported			
Income (loss) applicable to common shares	$ 171,528	$ (61,148)	$ (110,241)
Basic income (loss) per share	$ 3.11	$ (1.27)	$ (2.70)
Diluted income (loss) per share	$ 2.79	$ (1.27)	$ (2.70)
Pro forma			
Income (loss) applicable to common shares	$ 136,868	$ (98,450)	$ (118,234)
Basic income (loss) per share	$ 2.48	$ (2.04)	$ (2.89)
Diluted income (loss) per share	$ 2.03	$ (2.04)	$ (2.89)

Warrants

The following table summarizes warrant activity for the years ended December 31:

	2001	2000
Outstanding, January 1,	265,800	2,779,000
Granted	—	—
Exercised	(265,800)	(2,513,200)
Expired	—	—
Outstanding, December 31,	—	265,800

At December 31, 2001, no warrants to purchase common stock remained outstanding and no warrants were issued during 2002.

Qualified Savings and Investment Plan

We have a profit sharing plan pursuant to section 401(k) of the Internal Revenue Code whereby eligible employees may contribute up to 15% of their annual salary to the plan, subject to statutory maximums. The plan provides for discretionary matching contributions by us in cash or a combination of cash and shares of our common stock. Our contribution for the years 2000 through 2002 was 100% of the first 6% of employee salaries contributed in the ratio of 50% cash and 50% Cephalon stock. We contributed $3.6 million, $3.0 million, and $1.8 million, in cash and common stock to the plan for the years 2002, 2001, and 2000, respectively. Prior to the merger (see Note 2), Anesta had a 401(k) Plan whereby eligible employees were able to contribute up to 25% of their annual salary to the plan. Anesta had the option of making discretionary contributions equal to 25% of participant contributions up to 6% of participant compensation. Anesta contributed $58,000 for the year 2000.

Employee Stock Purchase Plan

In November 1993, Anesta adopted the Employee Stock Purchase Plan authorizing the issuance of 250,000 shares pursuant to purchase rights granted to employees of Anesta. Participants could elect to use up to 10% of their compensation to purchase Anesta's common stock at the end of each year at a price equal to 85% of the lower of the

beginning or ending stock price in the plan period. This plan terminated in October 2000 upon the merger of Cephalon and Anesta (see Note 2).

Pro forma Aggregate Conversions or Exercises

At December 31, 2002, the conversion or exercise of all outstanding options and convertible subordinated notes into shares of Cephalon common stock in accordance with their terms would increase the outstanding number of shares of common stock by approximately 18,240,000 shares, or 33%.

Preferred Share Purchase Rights

In November 1993, our Board of Directors declared a dividend distribution of one right for each outstanding share of common stock. In addition, a right attaches to and trades with each new issue of our common stock. Each right entitles each registered holder, upon the occurrence of certain events, to purchase from us a unit consisting of one one-hundredth of a share of our Series A Junior Participating Preferred Stock, or a combination of securities and assets of equivalent value, at a purchase price of $90.00 per unit, subject to adjustment.

13. INCOME TAXES

The components of total income (loss) from operations before income taxes and the cumulative effect of a change in accounting principle were:

	2002	2001	2000
United States	$ 70,562	$ (34,589)	$ (88,042)
Foreign	(8,129)	(20,895)	(5,702)
Total	$ 62,433	$ (55,484)	$ (93,744)

The components of the provision (benefit) for income taxes are as follows:

	2002	2001	2000
Current taxes:			
United States	$ 19,997	$ —	$ —
Foreign	13,041	—	—
State	1,067	—	—
	34,105	—	—
Deferred taxes:			
United States	9,224	(19,004)	(32,828)
Foreign	2,138	(5,949)	(1,711)
State	3,182	(19,657)	(8,214)
	14,544	(44,610)	(42,753)
Change in valuation allowance	(161,278)	44,610	42,753
	(146,734)	—	—
Total	$ (112,629)	$ —	$ —

A reconciliation of the United States Federal statutory rate to our effective tax rate is as follows:

	2002	2001	2000

(In thousands, except share data)

U.S. Federal statutory rate—expense (benefit)	35.0%	(35.0)%	(35.0)%
Non-deductible expenses	6.8	1.7	0.5
Debt conversion expense	—	33.1	—
Revision of prior years' estimates	—	(27.1)	(7.4)
State income taxes, net of U.S. federal tax benefit	1.7	—	—
Tax rate differential on foreign income	13.6	2.2	0.3
Change in valuation allowance	(236.5)	25.4	41.6
Other	(1.0)	(0.3)	—
Consolidated effective tax rate	(180.4)%	—%	—%

The tax benefits associated with employee exercises of non-qualified stock options and disqualifying dispositions of stock acquired with incentive stock options reduce taxes payable. A tax benefit of $5.2 million associated with the exercise of employee stock options was recorded to additional paid-in capital in 2002. The 2002 tax benefit from the reduction in the valuation allowance also includes a portion attributable to all prior years' tax benefits associated with the exercise of employee stock options, the tax benefits of which were previously not likely to be realized. Consequently, $35.8 million of the reduction in the valuation allowance was recognized as an increase to additional paid-in capital.

Net unremitted deficit of foreign subsidiaries at December 31, 2002 amounted to approximately $28 million. To the extent a subsidiary has unremitted earnings, such amounts have been included in the consolidated financial statements without giving effect to deferred taxes since it is management's intent to reinvest such earnings in foreign operations.

Deferred income taxes reflect the tax effects of temporary differences between the bases of assets and liabilities recognized for financial reporting purposes and tax purposes, and net operating loss and tax credit carryforwards. Significant components of net deferred tax assets and deferred tax liabilities as of December 31 are as follows:

	2002	2001
Net operating loss carryforwards	$ 120,610	$ 140,536
Capitalized research and development expenditures	52,479	69,505
Research and development tax credits	17,354	12,833
Acquired product rights and intangible assets	11,921	7,544
Reserves and accrued expenses	6,072	2,776
Deferred revenue	1,028	2,783
Other, net	5,376	5,901
Total deferred tax assets	214,840	241,878
Valuation allowance	(44,768)	(241,878)
Net deferred tax assets	$ 170,072	$ —
Deferred tax liabilities:		
Purchase accounting adjustments for foreign acquisition	$ 52,666	$ 52,666
Other	173	173
Total deferred tax liabilities	$ 52,839	$ 52,839

Other deferred tax liabilities are classified as accrued expenses in the accompanying balance sheets. At December 31, 2002, we had net operating loss carryforwards for U.S. federal income tax purposes of approximately $306.7 million that will begin to expire in 2003, and state net operating losses of approximately $256 million that will expire in varying years starting in 2003. We also have international net operating loss carryforwards of approximately $2.2 million with indefinite expiration dates. The net operating loss carryforwards differ from the accumulated deficit principally due to differences in the recognition of certain research and development expenses for financial and federal income tax reporting. Federal research tax credits of $17.3 million are available to offset future tax liabilities, and begin to expire in 2003. The amount of U.S. federal net operating loss carryforwards which can be utilized in any one period will be limited by federal income tax regulations since a change in ownership as defined in Section 382 of the Internal Revenue Code occurred in the prior years. We do not believe that such limitation will have a material adverse impact on the utilization of the net operating loss carryforwards, but we do believe it will affect utilization of tax credit carryforwards.

In the fourth quarter of 2002, we determined that all of our domestic net operating loss carryforwards, portions of international operating loss carryforwards, and certain other deferred tax assets were more likely than not to be recovered. The remaining valuation allowance of $44.8 million at December 31, 2002 relates to certain tax credits, international operating loss carryforwards and temporary differences that we believe are not likely to be recovered.

14. SELECTED CONSOLIDATED QUARTERLY FINANCIAL DATA (UNAUDITED)

	2002 Quarter Ended			
	December 31,	September 30,	June 30,	March 31,
Statement of Operations Data:				
Total revenues	$ 144,306	$ 130,363	$ 120,727	$ 111,501
Income before cumulative effect of a change in accounting principle	139,994	19,976	14,429	663
Cumulative effect of a change in accounting principle	—	—	—	(3,534)
Net income (loss) applicable to common shares	$ 139,994	$ 19,976	$ 14,429	$ (2,871)
Basic income (loss) per common share:				
Income per common share before cumulative effect of a change in accounting principle	$ 2.53	$ 0.36	$ 0.26	$ 0.01
Cumulative effect of a change in accounting principle	—	—	—	(0.06)
	$ 2.53	$ 0.36	$ 0.26	$ (0.05)
Weighted average number of shares outstanding	55,250,000	55,128,000	55,071,000	54,963,000
Diluted income (loss) per common share:				
Income per common share before cumulative effect of a change in accounting principle	$ 2.13	$ 0.35	$ 0.25	$ 0.01
Cumulative effect of a change in accounting principle	—	—	—	(0.06)
	$ 2.13	$ 0.35	$ 0.25	$ (0.05)
Weighted average number of shares outstanding-assuming dilution	67,619,000	56,730,000	57,033,000	54,963,000

	2001 Quarter Ended			
	December 31,	September 30,	June 30,	March 31,
Statement of Operations Data:				
Total revenues	$ 74,902	$ 83,822	$ 56,199	$ 47,072
Net income (loss)	(64,545)	21,577	(2,974)	(9,542)
Dividends on convertible exchangeable preferred stock	—	(70)	(3,328)	(2,266)
Net income (loss) applicable to common shares	$ (64,545)	$ 21,507	$ (6,302)	$ (11,808)
Basic income (loss) per common share	$ (1.23)	$ 0.43	$ (0.13)	$ (0.28)

Weighted average number of shares outstanding	52,422,000	50,269,000	47,725,000	42,732,000
Diluted income (loss) per common share	$ (1.23)	$ 0.40	$ (0.13)	$ (0.28)
Weighted average number of shares outstanding-assuming dilution	52,422,000	53,412,000	47,725,000	42,732,000

15. SEGMENT AND SUBSIDIARY INFORMATION

On December 28, 2001, we completed our acquisition of Group Lafon. As a result, we now have significant sales, manufacturing, and research operations conducted by several subsidiaries located in Europe. Prior to 2002, our European operations were immaterial.

Although we now have significant European operations, we have determined that all of our operations have similar economic characteristics and may be aggregated with our United States operations into a single operational segment for reporting purposes. Summarized revenue and long-lived asset information by geographic region is provided below:

Revenues for the year ended December 31:

	2002
United States	$ 395,738
Europe	111,159
Total	$ 506,897

Long-lived assets:

	At December 31,	
	2002	2001
United States	$ 383,768	$ 206,697
Europe	519,342	500,595
Total	$ 903,110	$ 707,292

16. SUBSEQUENT EVENTS

In January 2003, we announced that we had entered into a five-year agreement with MDS Proteomics Inc. (MDSP), a subsidiary of MDS Inc., to utilize MDSP's technologies with the objective of accelerating the clinical development of and broadening the market opportunities for our pipeline of small chemical compounds. MDSP will receive payments upon the successful achievement of specified milestones and will receive royalties on sales of products resulting from the collaboration. As part of the agreement, we purchased from MDSP a $30.0 million 5% convertible note due 2010. The note is convertible into MDSP's common stock at an initial conversion price of $22.00 per share, subject to adjustment if MDSP sells shares of its common stock at a lower price.

On February 5, 2003, we announced that the FDA had accepted an abbreviated new drug application (ANDA) for a generic form of modafinil, the active ingredient in PROVIGIL. On March 28, 2003, we filed a patent infringement lawsuit in U.S. District Court in New Jersey against Teva Pharmaceuticals USA, Inc., Mylan Pharmaceuticals Inc., Ranbaxy Pharmaceuticals Inc., and Barr Laboratories, Inc. based upon the ANDAs filed by each of these companies seeking FDA approval for a generic equivalent of modafinil. The lawsuit claims infringement of our U.S. Patent No. RE37516, which covers the pharmaceutical compositions and methods of treatment with the form of modafinil contained in PROVIGIL. We intend to vigorously defend the validity, and prevent infringement, of this patent.

On March 7, 2003, our wholly-owned subsidiary, Cephalon Australia Pty. Limited, formally commenced a takeover bid for SIRTeX Medical Limited (ASX: SRX). SIRTeX markets SIR-Spheres®, a product approved in the United States, Europe, Australia and portions of Asia for the treatment of certain types of liver cancer. Under its bid, Cephalon Australia intends to offer A$4.85 cash for each SIRTeX ordinary share including any SIRTeX shares that are issued on the exercise of SIRTeX options. Cephalon Australia also has obtained an option to acquire shares from SIRTeX's largest shareholder representing up to 19.9 percent of the total issued share capital of SIRTeX at a price of A$4.85 per SIRTeX share. The total bid value is approximately US$161 million. If successful, we intend to fund the bid price using a portion of our existing cash and investment balance.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

PART III

ITEM 10. DIRECTORS AND EXECUTIVE OFFICERS OF THE REGISTRANT

Directors

The information required by Item 10 is incorporated herein by reference to the information contained under the caption "Proposal 1—Election of Directors" in our definitive proxy statement related to the 2003 annual meeting of stockholders.

Executive Officers

The information concerning our executive officers required by this Item 10 in provided under the caption "Executive Officers of the Registrant" in Part I hereof.

Section 16(a) Beneficial Ownership Reporting Compliance

The information concerning Section 16(a) Beneficial Ownership Reporting Compliance by our directors and executive officers is incorporated by reference to the information contained under the caption "Section 16(a) Beneficial Ownership Reporting Compliance" in our definitive proxy statement related to the 2003 annual meeting of stockholders.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this Item 11 is incorporated by reference to the information contained in our definitive proxy statement for the 2003 annual meeting of stockholders.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by Item 12 is incorporated by reference to the information contained in our definitive proxy statement for the 2003 annual meeting of stockholders.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS

The information required by Item 13 is incorporated by reference to the information contained in our definitive proxy statement for the 2003 annual meeting of stockholders.

ITEM 14. CONTROLS AND PROCEDURES

We maintain a set of disclosure controls and procedures that are designed to ensure that information required to be disclosed by us in the reports filed by us under the Securities Exchange Act of 1934, as amended ("Exchange Act") is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. Within the 90 days prior to the filing date of this report, we carried out an evaluation, under the supervision and with the participation of our management, including our Chairman and Chief Executive Officer and Senior Vice President and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures (as defined in Exchange Act Rule 13a-14(c)). Based on that evaluation, our Chairman and Chief Executive Officer and Senior Vice President and Chief Financial Officer concluded that our disclosure controls and procedures are effective. A controls system, no matter how well designed and operated, cannot provide absolute assurance that the objectives of the controls system are met, and no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within any company have been detected.

There have been no significant changes in our internal controls or other factors that could significantly affect those controls subsequent to the date of their evaluation, including any corrective actions with regard to significant deficiencies and material weaknesses.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES AND REPORTS ON FORM 8-K

(a)DOCUMENTS FILED AS PART OF THIS REPORT

The following is a list of our consolidated financial statements and our subsidiaries and supplementary data included in this report under Item 8 of Part II hereof:

1. FINANCIAL STATEMENTS AND SUPPLEMENTAL DATA

Reports of Independent Public Accountants.

Consolidated Balance Sheets as of December 31, 2002 and 2001.

Consolidated Statements of Operations for the years ended December 31, 2002, 2001 and 2000.

Consolidated Statements of Stockholders' Equity for the years ended December 31, 2002, 2001 and 2000.

Consolidated Statements of Cash Flows for the years ended December 31, 2002, 2001 and 2000.

Notes to Consolidated Financial Statements.

2. FINANCIAL STATEMENT SCHEDULES

Schedule II—Valuation and Qualifying Accounts

Schedules, other than those listed above, are omitted because they are not applicable or are not required, or because the required information is included in the consolidated financial statements or notes thereto.

(b)REPORTS ON FORM 8-K

During the fiscal quarter ended December 31, 2002, we filed Current Reports on Form 8-K as follows:

- On October 4, 2002, we filed a Form 8-K that included a press release dated October 3, 2002 announcing that we had reacquired rights to our cancer pain product ACTIQ® (oral transmucosal fentanyl citrate) [C-II] in 12 countries, principally in Europe, from Elan Pharma International Limited, a subsidiary of Elan

Corporation, plc.

- On October 31, 2002, we filed a Form 8-K that included a press release dated October 23, 2002 announcing results of our clinical study evaluating PROVIGIL(R) (modafinil) C-IV in patients with shift work sleep disorder.

(c)EXHIBITS

The following is a list of exhibits filed as part of this annual report on Form 10-K. Where so indicated by footnote, exhibits that were previously filed are incorporated by reference. For exhibits incorporated by reference, the location of the exhibit in the previous filing is indicated.

Exhibit No.	Description
3.1(a)	Restated Certificate of Incorporation, as amended, filed as Exhibit 3.1 to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 1996.
3.1(b)	Certificate of Amendment of Restated Certificate of Incorporation, filed as Exhibit 3.1 to the Company's Quarterly Report on Form 10-Q for the period ending June 30, 2002.
3.2	Bylaws of the Registrant, as amended and restated, filed as Exhibit 3.2 to the Company's Quarterly Report on Form 10-Q for the period ending June 30, 2002.
4.1	Specimen copy of stock certificate for shares of Common Stock of the Registrant, filed as Exhibit 4.1 to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 1993.
4.2(a)	Amended and Restated Rights Agreement, dated as of January 1, 1999 between Cephalon, Inc. and StockTrans, Inc. as Rights Agent, filed as Exhibit 1 to the Company's Form 8-A/A (12G) filed January 20, 1999.

4.2(b)	First Amendment to Amended and Restated Rights Agreement, dated July 31, 2000 between Cephalon, Inc. and StockTrans, Inc. as Rights Agent, filed as Exhibit 1 to the Company's Form 8-A/12G filed on August 2, 2000.
4.3(a)	Specimen Preferred Stock Certificate of Cephalon, Inc., filed as Exhibit 4.1 to the Company's Registration Statement on Form S-3 (Registration No. 333-88985) filed October 14, 1999.
4.3(b)	Certificate of the Powers, Designations, Preferences and Rights of the $3.625 Convertible Exchangeable Preferred Stock filed August 17, 1999, filed as Exhibit 4.2 to the Company's Registration Statement on Form S-3 (Registration No. 333-88985) filed October 14, 1999.
4.3(c)	Indenture, dated as of August 18, 1999 between Cephalon, Inc. and State Street Bank and Trust Company, as Trustee, filed as Exhibit 4.3 to the Company's Registration Statement on Form S-3 (Registration No. 333-88985) filed October 14, 1999.
4.3(d)	Form of Series A Warrant to purchasers of Units including a limited partnership interest in Cephalon Clinical Partners, L.P., filed as Exhibit 10.4 to the Company's Registration Statement on Form S-3 (Registration No. 333-56816) filed on January 7, 1993.
4.3(e)	Form of Series B Warrant to purchasers of Units including a limited partnership interest in Cephalon Clinical Partners, L.P., filed as Exhibit 10.5 to the Company's Registration Statement on Form S-3 (Registration No. 333-56816) filed on January 7, 1993.
4.3(f)	Incentive Warrant to purchase 115,050 shares of Common Stock of Cephalon, Inc. issues to PaineWebber Incorporated, filed as Exhibit 10.6 to the Company's Registration Statement on Form S-3 (Registration No. 333-56816) filed on January 7, 1993.
4.3(g)	Fund Warrant to purchase 19,950 shares of Common Stock of Cephalon, Inc. issued to PaineWebber R&D Partners III, L.P., filed as Exhibit 10.7 to the

	Company's Registration Statement on Form S-3 (Registration No. 333-56816) filed on January 7, 1993.
4.4(a)	Indenture, dated as of May 7, 2001 between Cephalon, Inc. and State Street Bank and Trust Company, as Trustee, filed as Exhibit 4.1 to the Company's Registration Statement on Form S-3 (Registration No. 333-62234) filed June 4, 2001.
4.4(b)	Registration Rights Agreement, dated May 7, 2001 between Cephalon, Inc. and Robertson Stephens, Inc., Adams, Harkness & Hill, Inc., Banc of America Securities LLC, CIBC World Markets Corp., SG Cowen Securities Corporation, UBS Warburg LLC, and U.S. Bancorp Piper Jaffray Inc., as Purchasers, filed as Exhibit 4.2 to the Company's Registration Statement on Form S-3 (Registration No. 333-62234) filed June 4, 2001.
4.5(a)	Indenture, dated as of December 11, 2001 between Cephalon, Inc. and State Street Bank and Trust Company, as Trustee, filed as Exhibit 4.1 to the Company's Registration Statement on Form S-3 (Registration No. 333-82788) filed on February 14, 2002.
4.5(b)	Registration Rights Agreement, dated as of December 11, 2001 between Cephalon, Inc. and Credit Suisse First Boston Corporation, Robertson Stephens, Inc., CIBC World Markets Corp., SG Cowen Securities Corporation, UBS Warburg LLC, U.S. Bancorp Piper Jaffray Inc., Adams Harkness & Hill, Inc. and Banc of America Securities, as the Initial Purchasers, filed as Exhibit 4.2 to the Company Registration Statement on Form S-3 (Registration No. 333-82788) filed on February 14, 2002.
4.6(a)	Form of $3^{7}/_{8}$% Convertible Promissory Note Due March 29, 2007, filed as Exhibit 4.1 to the Company's Quarterly Report on Form 10-Q for the period ended March 31, 2002.
4.6(b)	Registration Rights Agreement between Cephalon, Inc. and Anthem Investors, LLC dated March 29, 2002, filed as Exhibit 4.2 to the Company's Quarterly Report on Form 10-Q for the period ended March 31, 2002.
10.1	Letter agreement, dated March 22, 1995 between Cephalon, Inc. and the Salk Institute for Biotechnology Industrial Associates, Inc., filed as Exhibit 99.1 to the Company's Registration Statement on Amendment No. 1 to Form S-3 (Registration No. 33-93964) filed on June 30, 1995.
†10.2(a)	Executive Severance Agreement between Frank Baldino, Jr. and Cephalon, Inc. dated July 25, 2002, filed as Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q for the period ending June 30, 2002.
†10.2(b)	Form of Executive Severance Agreement between Certain Executives and Cephalon, Inc. dated July 25, 2002, filed as Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q for the period ending June 30, 2002.
†10.3(a)	Consulting Agreement dated October 1, 2001 between Cephalon, Inc. and Martyn D. Greenacre, filed as Exhibit 10.18 to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2001.

†10.3(b)	Amendment to Consulting Agreement between Cephalon, Inc. and Martyn D. Greenacre dated April 1, 2002, filed as Exhibit 10.18(b) to the Company's Quarterly Report on Form 10-Q for the period ended June 30, 2002.
*†10.3(c)	Second Amendment to Consulting Agreement between Cephalon, Inc. and Martyn D. Greenacre dated December 10, 2002.
10.4(a)	License Agreement, dated May 15, 1992 between Cephalon, Inc. and Kyowa Hakko Kogyo Co., Ltd., filed as Exhibit 10.6 to the Transition Report on Form 10-K for transition period January 1, 1991 to December 31, 1991, as amended by Amendment No. 1 filed on September 4, 1992 on Form 8.
10.4(b)	Letter agreement, dated March 6, 1995 amending the License Agreement between Cephalon, Inc. and Kyowa Hakko Kogyo Co., Ltd., filed as Exhibit 10.4(b) to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 1994.
10.4(c)	

	Letter agreement, dated May 11, 1999 amending the License Agreement between Cephalon, Inc. and Kyowa Hakko Kogyo Co., Ltd., filed as Exhibit 10.4(c) to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 1999. (1)
†10.5(a)	Cephalon, Inc. Amended and Restated 1987 Stock Option Plan, filed as Exhibit 10.7 to the Transition Report on Form 10-K for transition period January 1, 1991 to December 31, 1991, as amended by Amendment No. 1 filed on September 4, 1992.
†10.5(b)	Cephalon, Inc. Equity Compensation Plan, as amended and restated, effective as of February 1, 2002, filed as Exhibit 99.1 to the Company's Registration Statement on Form S-8 (Registration No. 333-89230) filed on May 28, 2002.
†10.5(c)	Cephalon, Inc. Non-Qualified Deferred Compensation Plan, filed as Exhibit 10.6 (b) to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 1993.
†10.5(d)	Cephalon, Inc. 2000 Equity Compensation Plan for Employees and Key Advisors, as amended and restated, effective as of May 15, 2002, filed as Exhibit 99.1 to the Company's Registration Statement on Form S-8 (Registration No. 333-89228) filed on May 28, 2002.
10.6(a)	Amended and Restated Agreement of Limited Partnership, dated as of June 22, 1992 by and among Cephalon Development Corporation, as general partner, and each of the limited partners of Cephalon Clinical Partners, L.P., filed as Exhibit 10.1 to the Company's Registration Statement on Form S-3 (Registration No. 33-56816) on January 7, 1993.
10.6(b)	Amended and Restated Product Development Agreement, dated as of August 11, 1992 between Cephalon, Inc. and Cephalon Clinical Partners, L.P., filed as Exhibit 10.2 to the Company's Registration Statement on Form S-3 (Registration No. 33-56816) filed on January 7, 1993.
10.6(c)	Purchase Agreement, dated as of August 11, 1992 by and between Cephalon, Inc. and each of the limited partners of Cephalon Clinical Partners, L.P., filed as Exhibit 10.3 to the Company's Registration Statement on Form S-3 (Registration No. 33-56816) filed on January 7, 1993.
10.6(d)	Pledge Agreement, dated as of August 11, 1992 by and between Cephalon, Inc. and Cephalon Clinical Partners, L.P., filed as Exhibit 10.8 to the Company's Registration Statement on Form S-3 (Registration No. 33-56816) filed on January 7, 1993.
10.6(e)	Promissory Note, dated as of August 11, 1992 issued by Cephalon Clinical Partners, L.P. to Cephalon, Inc., filed as Exhibit 10.9 to the Company's Registration Statement on Form S-3 (Registration No. 33-56816) filed on January 7, 1993.
10.6(f)	Form of Promissory Note, issued by each of the limited partners of Cephalon Clinical partners, L.P. to Cephalon Clinical Partners, L.P., filed as Exhibit 10.10 to the Company's Registration Statement on Form S-3 (Registration No. 33-56816) filed on January 7, 1993.
10.7	Supply, Distribution and License Agreement, dated as of July 27, 1993 between Kyowa Hakko Kogyo Co., Ltd. and Cephalon, Inc., filed as Exhibit 10.3 to the Company's Registration Statement on Form S-3 (Registration No. 33-73896) filed on January 10, 1994. (1)
10.8	Toll Manufacturing and Packaging Agreement, dated February 24, 1998 between Cephalon, Inc. and Circa Pharmaceuticals, Inc. (now Watson Pharmaceuticals), filed as Exhibit 10.12 to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 1998. (1)

10.9(a)	GABITRIL Product Agreement, dated October 31, 2000 between Cephalon, Inc. and Abbott Laboratories, filed as Exhibit 10.13(b) to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2000. (1)
10.9(b)	

	Toll Manufacturing and Packaging Agreement, dated October 31, 2000 between Cephalon, Inc. and Abbott Laboratories, filed as Exhibit 10.13(c) to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2000. (1)
10.10	Joint Research, Development and License Agreement, dated May 28, 1999 between Cephalon, Inc. and H. Lundbeck A/S, filed as Exhibit 10.14 to the Company's Quarterly Report on Form 10-Q for the period ended June 30, 1999. (1)
10.11(a)	Managed Services Agreement, dated November 27, 2000 between Cephalon (UK) Limited and Novartis Pharmaceuticals UK Limited, filed as Exhibit 10.17(a) to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2000. (1)
10.11(b)	License Agreement, dated November 27, 2000 between Cephalon, Inc. and Novartis AG, filed as Exhibit 10.17(b) to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2000. (1)
10.11(c)	Collaboration Agreement, dated November 27, 2000 between Cephalon, Inc. and Novartis AG, filed as Exhibit 10.17(c) to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2000. (1)
10.11(d)	Distribution Agreement, dated November 27, 2000 between Cephalon, Inc. and Novartis AG, filed as Exhibit 10.17(d) to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2000. (1)
10.12(a)	Agreement and Plan of Merger, dated July 14, 2000 by and among Cephalon, Inc., Anesta Corp. and C Merger Sub, Inc., filed as Exhibit 99.1 to the Company's Current Report on Form 8-K filed July 21, 2000.
10.12(b)	Distribution, License and Supply Agreement, dated December 7, 1999, between Anesta Corp. and Elan Pharma International Limited, filed as Exhibit 10.18 to Anesta Corp.'s Annual Report on Form 10-K for the fiscal year ended December 31, 1999. (1)
10.12(c)	Intellectual Property Sale, Amendment and Termination Agreement dated October 2, 2002, amending the Distribution, License and Supply Agreement, dated as of December 7, 1999, and as amended from time to time thereafter, by and between Anesta Corp. and Elan Pharma International Limited, filed as Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q for the period ending September 30, 2002.
10.12(d)	Termination and Asset Sale and Purchase Agreement, dated March 13, 2000 between Abbott Laboratories, Inc. and Anesta Corp., filed as Exhibit 10.19 to Anesta Corp.'s Quarterly Report on Form 10-Q for the period ending March 31, 2000. (1)
10.12(e)	Technology License Agreement, dated September 16, 1985, as amended through December 3, 1993 between Anesta Corp. and the University of Utah Research Foundation, filed as Exhibit 10.6 to Anesta Corp.'s Registration Statement on Form S-1 (File No. 33-72608) filed May 31, 1996. (1)
10.12(f)	Wiley Post Plaza Lease, dated December 7, 1994 between Anesta Corp. and Asset Management Services, filed as Exhibit 10.13 to Anesta Corp.'s Annual Report on Form 10-K (File No. 0-23160) for the fiscal year ended December 31, 1994.
10.13(a)	Toll Manufacturing and Packaging Agreement, dated August 24, 1999 between Cephalon, Inc. and Catalytica Pharmaceuticals, Inc. (now DSM Pharmaceuticals, Inc.), filed as Exhibit 10.16(a) to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2001. (1)
10.13(b)	Amendment No. 1 to the Toll Manufacturing and Packaging Agreement, dated July 3, 2001 between Cephalon, Inc. and Catalytica Pharmaceuticals, Inc. (now DSM Pharmaceuticals, Inc.), filed as Exhibit 10.16(b) to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2001. (1)
10.13(c)	Amendment No. 2 to Toll Manufacturing and Packaging Agreement, dated October 9, 2001 between Cephalon, Inc. and Catalytica Pharmaceuticals, Inc. (now DSM Pharmaceuticals, Inc.), filed as Exhibit 10.16(c) to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2001. (1)
*10.13(d)	Amendment No. 3 to Toll Manufacturing and Packaging Agreement, dated June 21, 2002 between Cephalon, Inc. and DSM Pharmaceuticals, Inc. (2)
*10.14(a)	

	5% Secured Convertible Note due January 7, 2010 by MDS Proteomics Inc. in favor of Cephalon, Inc.
*10.14(b)	Security Agreement dated January 7, 2003 between MDS Proteomics Inc. and Cephalon, Inc.

*21	List of Subsidiaries
*23.1	Consent of Pricewaterhouse Coopers LLP
*23.2	Information Regarding Arthur Andersen Consent.
*99.1	Certification Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
*99.2	Certification Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

* Filed herewith.

† Compensation plans and arrangements for executives and others.

(1) Portions of the Exhibit have been omitted and have been filed separately pursuant to an application for confidential treatment granted by the Securities and Exchange Commission.

(2) Portions of the Exhibit have been omitted and have been filed separately pursuant to an application for confidential treatment filed with the Securities and Exchange Commission pursuant to Rule 24b-2 under the Securities Exchange Act of 1934, as amended.

CEPHALON, INC. AND SUBSIDIARIES

SCHEDULE II—VALUATION AND QUALIFYING ACCOUNTS

(In thousands)

Year Ended December 31,	Balance at Beginning of the Year	Additions (Deductions)(1)	Additions(2)	Other Deductions	Balance at End of the Year
Reserve for sales discounts, returns and allowances:					
2002	$ 2,331	$ 12,243	$ —	$ 9,473	$ 5,101
2001	$ 1,136	$ 6,663	$ 160	$ 5,628	$ 2,331
2000	$ 5,843	$ (2,491)	$ —	$ 2,216	$ 1,136
Reserve for inventories:					
2002	$ 1,188	$ 2,609	$ —	$ —	$ 3,797
2001	$ —	$ 3	$ 1,185	$ —	$ 1,188
2000	$ —	$ —	$ —	$ —	$ —

(1) Amounts represent charges and reductions to expenses and revenue.

(2) Amounts represent additions from the acquisition of Group Lafon.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: March 31, 2003

CEPHALON, INC.

By: /s/ FRANK BALDINO, JR.

Frank Baldino, Jr., Ph.D.
Chairman and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ FRANK BALDINO, JR. **Frank Baldino, Jr., Ph.D.**	Chairman and Chief Executive Officer (Principal executive officer)	March 31, 2003
/s/ J. KEVIN BUCHI **J. Kevin Buchi**	Sr. Vice President and Chief Financial Officer (Principal financial and accounting officer)	March 31, 2003
/s/ WILLIAM P. EGAN **William P. Egan**	Director	March 31, 2003
/s/ ROBERT J. FEENEY **Robert J. Feeney, Ph.D.**	Director	March 31, 2003
Martyn D. Greenacre	Director	
/s/ CHARLES A. SANDERS **Charles A. Sanders, M.D.**	Director	March 31, 2003
Gail R. Wilensky, Ph.D.	Director	
/s/ HORST WITZEL **Horst Witzel, Dr.-Ing.**	Director	March 31, 2003

CERTIFICATIONS

I, Frank Baldino, Jr., certify that:

1. I have reviewed this annual report on Form 10-K of Cephalon, Inc.;

2. Based on my knowledge, this annual report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this annual report;

3. Based on my knowledge, the financial statements, and other financial information included in this annual report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this annual report;

4. The registrant's other certifying officers and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-14 and 15d-14) for the registrant and have:

   a) designed such disclosure controls and procedures to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this annual report is being prepared;

   b) evaluated the effectiveness of the registrant's disclosure controls and procedures as of a date within 90 days prior to the filing date of this annual report (the "Evaluation Date"); and

   c) presented in this annual report our conclusions about the effectiveness of the disclosure controls and procedures based on our evaluation as of the Evaluation Date;

5. The registrant's other certifying officers and I have disclosed, based on our most recent evaluation, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) all significant deficiencies in the design or operation of internal controls which could adversely affect the registrant's ability to record, process, summarize and report financial data and have identified for the registrant's auditors any material weaknesses in internal controls; and

   b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal controls; and

6. The registrant's other certifying officers and I have indicated in this annual report whether there were significant changes in internal controls or in other factors that could significantly affect internal controls subsequent to the date of our most recent evaluation, including any corrective actions with regard to significant deficiencies and material weaknesses.

Date: March 31, 2003

/s/ Frank Baldino, Jr.

Frank Baldino, Jr., Ph.D.
Chairman and Chief Executive Officer

I, J. Kevin Buchi, certify that:

1. I have reviewed this annual report on Form 10-K of Cephalon, Inc.;

2. Based on my knowledge, this annual report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this annual report;

3. Based on my knowledge, the financial statements, and other financial information included in this annual report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this annual report;

4. The registrant's other certifying officers and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-14 and 15d-14) for the registrant and have:

   a) designed such disclosure controls and procedures to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this annual report is being prepared;

   b) evaluated the effectiveness of the registrant's disclosure controls and procedures as of a date within 90 days prior to the filing date of this annual report (the "Evaluation Date"); and

   c) presented in this annual report our conclusions about the effectiveness of the disclosure controls and procedures based on our evaluation as of the Evaluation Date;

5. The registrant's other certifying officers and I have disclosed, based on our most recent evaluation, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) all significant deficiencies in the design or operation of internal controls which could adversely affect the registrant's ability to record, process, summarize and report financial data and have identified for the registrant's auditors any material weaknesses in internal controls; and

   b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal controls; and

6. The registrant's other certifying officers and I have indicated in this annual report whether there were significant changes in internal controls or in other factors that could significantly affect internal controls subsequent to the date of our most recent evaluation, including any corrective actions with regard to significant deficiencies and material weaknesses.

Date: March 31, 2003

/s/ J. Kevin Buchi

J. Kevin Buchi
Senior Vice President and Chief Financial Officer

QuickLinks

EXHIBIT 80

U.S. Department of Justice

United States Attorney

Eastern District of Pennsylvania

615 Chestnut Street
Suite 1250
Philadelphia, Pennsylvania 19106-4476
(215) 861-8200

For Immediate Release

September 29, 2008

PHARMACEUTICAL COMPANY CEPHALON TO PAY $425 MILLION FOR OFF-LABEL DRUG MARKETING

PHILADELPHIA - United States Attorney General Michael B. Mukasey and Acting United States Attorney Laurie Magid today announced the filing of a criminal information[1] against, and a civil settlement with, the pharmaceutical company Cephalon, headquartered in West Chester, PA, for the off-label marketing of three of its drugs. Joining Magid in today's announcement were FDA Special Agent-in-Charge Kim Rice, Special Agent-in-Charge of the Office of Inspector General for the Department of Health and Human Services Philadelphia Patrick Doyle, Special Agent-in-Charge of United States Postal Service Office of Inspector General Elizabeth Farcht.

The information alleges that from approximately January 2001 through at least 2006, Cephalon promoted the drugs Actiq, Gabitril, and Provigil for uses other than what the federal Food and Drug Administration approved. The company is charged with one count of Distribution of Misbranded Drugs: Inadequate Directions for Use, a misdemeanor offense.

Under the provisions of the Food, Drug and Cosmetic Act, a company must specify the intended uses of a product in its new drug application to the FDA. Before approving a drug, the FDA must determine that the drug is safe and effective for the use proposed by the company. Once approved, the drug may not be marketed or promoted for so-called "off label" uses - meaning any use not specified in an application and approved by FDA.

The FDA approved Actiq, a fentanyl product manufactured as a lollipop, for use only in opioid-tolerant cancer patients (meaning those patients for whom morphine-based painkillers are no longer effective). The drug is a strong and highly addictive narcotic, with significant potential for abuse. From 2001 through at least 2006, Cephalon was allegedly promoting the drug for non-cancer patients to use for such maladies as migraines, sickle-cell pain crises, injuries, and in anticipation of changing wound dressings or radiation therapy. Cephalon also promoted Actiq for use in patients who were not yet opioid-tolerant, and for whom it could have life-threatening

[1]An Indictment or Information is an accusation. A defendant is presumed innocent unless and until proven guilty.

results.

The FDA approved Gabitril for use as an anti-epilepsy drug in the treatment of partial seizures. From 2001 to 2005, Cephalon allegedly promoted Gabitril as a remedy for anxiety, insomnia, and pain. In 2005, following reports of seizures in patients taking Gabitril who did not have epilepsy, the FDA required Cephalon to send a warning letter to doctors advising them of the connection between off-label Gabitril use and risk of seizures. The company then ceased promotion of the drug.

The FDA first approved Provigil to treat excessive daytime sleepiness associated with narcolepsy, then expanded the label to include treatment of excessive sleepiness associated with sleep apnea, and shift work sleep disorder. From 2001 through 2006, Cephalon allegedly promoted Provigil as a non-stimulant drug for the treatment of sleepiness, tiredness, decreased activity, lack of energy, and fatigue. In 2002, the FDA sent Cephalon a letter instructing the company not to continue to promote Provigil off-label. The company ignored the FDA's letter.

Defendant Cephalon undertook its off-label promotional practices using a variety of techniques. It trained its sales force to disregard the restrictions of the FDA-approved label, and to promote the drugs for off-label uses. For example, the Actiq label stated that the drug was for "opioid tolerant cancer patients with breakthrough cancer pain, to be prescribed by oncologist or pain specialists familiar with opioids." Using the mantra "pain is pain," Cephalon instructed the Actiq sales representatives to focus on physicians other than oncologists, including general practitioners, and to promote the drug for many uses other than breakthrough cancer pain. In the case of Gabitril, which had been approved for use for epilepsy, Cephalon told the sales force to visit not just neurologists, but also psychiatrists, and to promote the drug for anxiety and other psychiatric indications. Cephalon also structured its sales quota and bonuses in such a way that sales representatives could reach their sales goals only if they promoted and sold the drugs for off-label uses.

"These are potentially harmful drugs that were being peddled as if they were, in the case of Actiq, actual lollipops instead of a potent pain medication intended for a specific class of patients," said Magid. "This company subverted the very process put in place to protect the public from harm, and put patients' health at risk for nothing more than boosting its bottom line. People have an absolute right to their doctors' best medical judgement. They need to know the recommendations a doctor makes are not influenced by sales tactics designed to convince the doctor that the drug being prescribed is safe for uses beyond what the FDA has approved."

Defendant Cephalon employed sales representatives and retained medical professionals to speak to doctors about off-label uses of Actiq, Gabitril, and Provigil. The company funded continuing medical education programs, through millions of dollars in grants, to promote off-label uses of its drugs, in violation of the FDA's requirements.

In a plea agreement with the United States, Cephalon agrees to pay $50 million to resolve this information, of which $40 million will be applied to a criminal fine, and $10 million will be applied as substitute assets to satisfy the forfeiture obligation.

In a separate civil settlement among Cephalon, the United States and various states, executed contemporaneously with this guilty plea agreement, Cephalon will pay $375 million, plus interest, to resolve False Claims Act claims by the United States Medicaid and Medicare Trust Funds and other federal programs and agencies, including Tricare, the Federal Employees Health Benefit program, the Postal Worker's Compensation Program, the Federal Employees Compensation Act Program, the Energy Employees Occupational Illness Compensation Program, Department of Veterans Affairs, Defense Logistics Agency, Bureau of Prisons, and the Public Health Service Entities. The state Medicaid programs and the District of Columbia will share $116 million of the civil settlement.

"This settlement is further evidence of the Department's willingness to prosecute cases involving violations of the FDCA and to recover taxpayer dollars used to pay for drugs sold as a result of illegal marketing campaigns," said Assistant Attorney General Gregory Katsas.

"Today's settlement demonstrates the government's continued scrutiny of sales and marketing practices by pharmaceutical companies that put profits ahead of the public health," said Special Agent-in-Charge Kim Rice of FDA's Office of Criminal Investigations. "The FDA will continue to seek this kind of criminal resolution and stiff sanctions when pharmaceutical companies undermine the drug approval process by promoting drugs for uses for which they have not been proven to be safe and effective."

"This case should serve as still another warning to all those who break the law in order to improve their profits," said Patrick Doyle, head of the Philadelphia Regional Office of the Department of Health and Human Services Office of Inspector General (OIG). "OIG, working with our law enforcement partners, will pursue and bring to justice those who would steal from vulnerable beneficiaries and the taxpayers."

The civil settlement also resolves four qui tam ("whistle blower") actions filed in the Eastern District of Pennsylvania: United States of America ex rel. Lucia Paccione v. Cephalon, Inc., Civil Action No. 03-6268; United States of America and the States of California, Delaware, Florida, Hawaii, Illinois, Louisiana, Massachusetts, Nevada, New Hampshire, New Mexico, Texas, Tennessee and Virginia and the District of Columbia ex rel. Joseph Piacentile v. Cephalon, Inc., Civil Action No. 03-6277; United States of America; the States of California, Delaware, Florida, Hawaii, Illinois, Massachusetts, Nevada, New Mexico, Tennessee, Texas, Virginia, the District of Columbia, and New York; ex rel. Bruce Boise v. Cephalon, Inc., Civil Action No. 04-4401 and United States of America ex rel. Michael Makalusky v. Cephalon, Inc.,

Civil Action No. 05-1904. Three of those cases were filed by former Cephalon sales representatives who were disturbed by the company's off-label marketing practices. The relators will receive $46,469,978 from the federal share of the settlement amount.

United States Postal Service Office of Inspector General Special Agent- in-Charge Elizabeth A. Farcht stated, "These types of investigations are an important part of the Postal Service Office of Inspector General's mission to prevent and detect fraud, waste, and misconduct in the Postal Service, and to promote the integrity and efficiency of postal programs. This includes federal programs that the postal service participates in or contributes to such as the federal workers' compensation program, under which these drugs were paid for by the postal service. Drugs promoted off-label can lead to potential safety issues and unnecessary, inflated program costs for the Postal Service and others."

As part of the resolution of these allegations, the HHS Office of Inspector General and Cephalon have entered into a five-year Corporate Integrity Agreement. The Agreement requires that Cephalon send doctors a letter advising of this resolution, and give them a means to report questionable conduct of sales representatives; that it post payments to doctors on its web site; and that its Board and top management regularly certify that the company has an effective compliance program and is in compliance with all applicable requirements.

The case was investigated by the Food and Drug Administration's Office of Criminal Investigation, the Department of Health and Human Services' Office of the Inspector General, the Postal Service Office of the Inspector General, and the Office of Personnel Management Office of Inspector General. The case was prepared by Assistant United States Attorney Marilyn May and Assistant United States Attorney Cathy Votaw, together with Jeffrey Steger of the Department of Justice Office of Consumer Litigation.

Assistance was provided by Laura Pawlowski from the FDA Office of Chief Counsel, as well as representatives of the National Association of Medicaid Fraud Control Units, headed by Charles William Gambrell, Jr., Director South Carolina Medicaid Fraud Control Unit, and the Connecticut Attorney General's Office. The Corporate Integrity Agreement was negotiated by Mary Riordan and Maame Gyamfi in the Office of General Counsel, Office of Inspector General, Department of Health and Human Services. The Department of Justice acknowledges Cephalon's cooperation with the investigation and resolution of this case.

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http://www.usdoj.gov/usao/pae

EXHIBIT 81

1 of 1 DOCUMENT

The Wall Street Journal

November 21, 2006 Tuesday

SECTION: Pg. B1

LENGTH: 1481 words

HEADLINE: Cephalon Used Improper Tactics to Sell Drug, Probe Finds

BYLINE: By John Carreyrou

BODY:

FROM SETTING unrealistically high sales quotas to pushing larger prescriptions at higher doses, drug maker Cephalon Inc. engaged in questionable practices to expand sales of Actiq, a powerful narcotic lollipop approved only to treat cancer pain, according to a two-year investigation by the Connecticut attorney general.

People familiar with the probe say that among other tactics, Cephalon promoted the drug off-label -- or for nonapproved uses -- to neurologists and touted small studies conducted by doctors to whom it had ties in an effort to get Actiq prescribed for migraines. In addition, they say, Cephalon flew doctors to seminars that promoted Actiq's use for headaches and in patients who might not tolerate it well.

Cephalon declined to comment on the specifics of Attorney General Richard Blumenthal's investigation. Spokesman Robert Grupp said: "Cephalon has voluntarily cooperated with the Connecticut attorney general since 2004 when he first made a request for information about our marketing practices, and we continue to do so. Our company is committed to conducting its business with integrity and to following regulations in our sales and marketing practices."

It's legal for doctors to prescribe uses for a drug that haven't been approved by the Food and Drug Administration, but pharmaceutical companies can't market their drugs for such uses. In the case of Actiq, the agency also requires that

Cephalon abide by a strict risk-management program to control the drug's distribution and usage.

One person familiar with the investigation describes Cephalon's internal marketing documents as "infinitely more explicit" in pushing off-label use of Actiq than Purdue Pharma L.P. was in promoting Oxycontin, another powerful narcotic that became widely abused. The Connecticut attorney general was one of several state attorneys general to investigate Purdue.

Mr. Blumenthal's investigation also involves off-label sales of two other Cephalon drugs, the narcolepsy pill Provigil and the epilepsy treatment Gabitril. Cephalon is also being investigated by the U.S. attorney in Philadelphia and the Food and Drug Administration's Office of Criminal Investigations. Like Mr. Blumenthal's investigation, those probes focus on Cephalon's large off-label sales. The U.S. attorney and the FDA declined to comment.

Mr. Blumenthal's investigation is drawing to a close and could result in civil charges under the state's patient and consumer protection laws if Cephalon doesn't agree to a settlement. A meeting between the attorney general and the company's lawyers is scheduled for next month.

If Cephalon opts to settle the case out of court, Mr. Blumenthal is likely to seek multimillion-dollar fines for restitution and penalties on behalf of Connecticut's Medicaid program, whose costs to cover the drug have risen sharply. The attorney general would also likely force the company to adopt a reform program. "We want them to change the way they do business," Mr. Blumenthal says.

Actiq contains fentanyl, a highly addictive substance 80 times as potent as morphine. Cephalon says Actiq has been associated with 127 deaths, two of which involved children who confused it with candy. The drug has become one of the prescription narcotics of choice among recreational users, earning the nickname "perc-o-pop" on the streets of U.S. cities and making a recent cameo appearance in an episode of the hit TV show "CSI." In the first nine months of this year, Actiq sales reached $471 million.

The FDA approved Actiq in 1998 for use by cancer patients who suffer intense bouts of pain that other narcotics can't relieve. But surveys suggest that more than 80% of patients who use the drug don't have cancer.

The trigger for Mr. Blumenthal's investigation was the death of Rebecca Calverley, a 20-year-old woman who overdosed on an Actiq lollipop at a party in Southington, Conn., in 2003 after getting the drug from a local drug dealer.

Mr. Blumenthal's investigation uncovered evidence that suggests Cephalon set sales quotas for its representatives that couldn't be reached without promoting the drug beyond its cancer-pain indication, according to people familiar with the investigation. Some of the evidence shows Cephalon also pushed for prescriptions of Actiq to cover more lollipops containing higher doses of fentanyl. Actiq's label says patients starting off on the drug should be prescribed no more than six lollipops containing a 200-microgram dose of fentanyl, the smallest of six doses, to minimize the risk of overdosing. Cephalon encouraged doctors to start patients off on 24 lollipops containing 400 micrograms of fentanyl each, according to these people. The higher dose costs more and brings in more revenue.

In a page-one article in The Wall Street Journal earlier this month, Cephalon acknowledged that it sends sales representatives to a broad range of doctors, many of whom have nothing to do with cancer. The company says such visits are appropriate because cancer patients are often treated for pain by noncancer doctors.

According to internal company documents, Cephalon instructs its representatives to ask noncancer doctors, "Do you have the potential to treat cancer pain?" Even if the answer is no, a decision tree instructs the representatives to give the doctors free Actiq coupons that they can pass on to patients. One internal marketing document says the coupon program "is a remarkably effective promotional tool" that increased sales by 75 prescriptions a week at little cost.

Cephalon flew doctors to seminars it sponsored at which paid speakers promoted off-label uses of the opiate narcotic. At a New York seminar attended by 33 doctors in September 2003, one of the topics discussed was "Opioid

use in headache." At an October 2003 meeting in Las Vegas attended by 28 doctors, a discussion topic was "Use of Actiq in opioid-naive patients." Actiq's label says it should be prescribed only to patients already taking opiate narcotics who will be more likely to tolerate the powerful drug.

Mr. Grupp declined to comment on the seminars. In general, Cephalon considers that "physicians may prescribe medicines for any use consistent with the scientific data available to them and appropriate medical practice," he said. "The decision to prescribe 'off label' is theirs and theirs alone."

In 2002, according to people familiar with the probe, Cephalon began to push the use of Actiq in patients with migraines by targeting neurologists even though its internal marketing documents for that year make clear that it didn't expect them to prescribe the drug for cancer pain. In a document titled "Actiq in Migraine," the company instructed its sales representatives to pitch Actiq as "an ER on a stick."

Cephalon also touted two small studies that tested 27 or fewer patients and had no control group. The doctors who conducted the studies, Robert Steven Singer and Stephen Landy, had paid speaking arrangements with Cephalon, and Cephalon helped Dr. Landy with the study he conducted, according to the people close to Mr. Blumenthal's probe.

Dr. Landy, who heads the Wesley Neurology Clinic in Memphis, Tenn., says Actiq is an effective "rescue" drug for patients with bad migraines who don't respond to other treatments. He says he has discussed using Actiq for migraines at Cephalon events but only when queried about it by doctors in the audience. Dr. Landy won't say how much Cephalon paid him for speaking. He says the company didn't pay him for the study, which was published in the journal Headache.

Dr. Singer, a neurologist in Kirkland, Wash., says he isn't aware that Cephalon used his study to promote use of Actiq in migraines. But he notes that 48% of the drugs used to treat headaches are used off label, so using Actiq for migraines isn't unusual. He declines to say how much Cephalon paid him to speak.

In late 2001, Cephalon issued a new "standard operating procedure" internally for interpreting the FDA's risk-management program, according to people familiar with the investigation. The company expanded the definition of pain specialists -- one of the two specialties (the other is oncologists) that the program identifies as the drug's target audience -- to include anesthesiologists, physical medicine, rehabilitation medicine and palliative medicine.

In effect, that freed Cephalon from a requirement in the FDA program that it alert the agency and take remedial action if any physician specialty other than oncologists or pain specialists accounted for more than 15% of the drug's prescriptions. Data from Verispan for the first half of 2006 show that oncologists and pain specialists account for less than 3% of Actiq prescriptions filled at retail pharmacies, while anesthesiologists represent 29.5% of prescriptions.

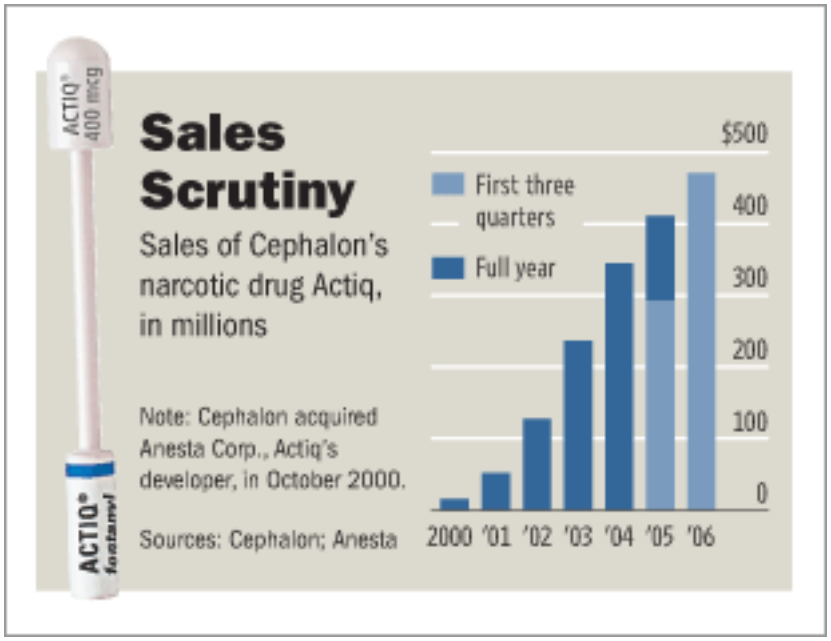

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EXHIBIT 82

Seeking Alpha

Cephalon Q1 2007 Earnings Call Transcript

May. 1.07 | About: Cephalon, Inc. (CEPH)

Cephalon, Inc. (NASDAQ:CEPH)

Q1 2007 Earnings Call

May 1, 2007 5:00 pm ET

Executives

Chip Merritt - Senior Director of IR

Frank Baldino - CEO

Bob Roche - EVP of Worldwide Pharmaceutical Operations

Kevin Buchi - CFO

Lesley Russell - EVP of Worldwide Medical & Regulatory Operations

John Osborn - General Counsel

Analysts

Eric Schmidt - Cowen & Co.

Ronnie Gal - Sanford Bernstein

Jim Dawson - Buckingham Research Group

Annabel Samimy - UBS

Brett Holley - CIBC World Markets

Dave Windley - Jeffries & Co.

Michael Rockefeller - Morgan Stanley

Jim Birchenough - Lehman Brothers

Adam Greene - J.P. Morgan

Corey Davis - Natexis

Operator

Good day, everyone and welcome to the Cephalon First Quarter 2007 Earnings Announcement. Today's call is being recorded. At this time for opening remarks and introductions, I would like to turn the call over to Mr. Chip Merritt, Senior Director of Investor Relations for Cephalon. Please go ahead, sir.

Chip Merritt

Thank you. Today we will review Cephalon's financial performance for the first quarter of 2007. Before we begin let me remind you that certain statements on this call maybe forward-looking and are subject to risks and uncertainties associated with the Company's business.

These statements may concern among other things guidance as to future revenues and earnings, operations, transactions, prospects, intellectual property, litigation, development of pharmaceutical products, clinical trials, and potential approval of our product candidates.

The Company also may discuss certain non-GAAP financial measures within the meaning of Regulation G during today's call. The information required by Regulation G is available in the newsroom section of our website at www.cephalon.com.

Additional information and risk factors affecting the Company's business and financial prospects and factors that would cause Cephalon's actual performance to vary from our current expectations is available in the Company's current Form 10K on file with the SEC. During the call, we will update full year 2007 guidance and provide second quarter guidance.

Please note that guidance remains in effect unless the Company provides subsequent modifications or updates. Our earnings press release is available on the Internet at www.cephalon.com. Investors with further questions should contact me at 610-738-6376. This conference call is being webcast via the Cephalon homepage and will be archived for one week after the call.

Speaking on today's call will be Dr. Frank Baldino, Chief Executive Officer, Bob Roche, Worldwide Pharmaceutical Operations, and Kevin Buchi, Chief Financial Officer. Also joining us on the call today are Dr. Lesley Russell, Worldwide Medical and Regulatory Operations, and John Osborn, General Counsel. Following remarks by Frank, Bob, and Kevin we will be pleased to answer your questions. Now, Frank Baldino.

EXHIBIT 83

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Search Archive

Drugs

Public Health Advisory: Important Information for the Safe Use of Fentora (fentanyl buccal tablets)

9/26/2007

FDA is issuing this public health advisory to alert patients, caregivers, and healthcare professionals to important information on the safe use of Fentora, a narcotic medicine for treating pain in cancer patients who are opioid-tolerant. FDA has received reports of death and life-threatening side effects in patients who have taken Fentora. The reports indicate that:

- there have been patients who should not have been prescribed this medicine (deaths occurred in patients who did not have cancer and/or were not opioid tolerant);
- patients were prescribed the wrong Fentora dose;
- patients took too many Fentora doses; and
- healthcare professionals substituted Fentora for another fentanyl-containing product that is not equal to Fentora.

Fentora contains fentanyl, a very potent narcotic (opioid) pain medicine. It is only approved for breakthrough cancer pain in patients who are *opioid-tolerant*, meaning those patients who take a regular, daily, around-the-clock narcotic pain medicine. Patients who take narcotic pain medications every day, around-the-clock develop *tolerance*, meaning they are more resistant to the dangerous side effects of narcotic pain medicines than patients who only occasionally take these medicines. For patients who are not opioid-tolerant, the amount of fentanyl in Fentora is large enough to cause dangerous side effects, such as respiratory depression (severe trouble breathing) and death. Patients should ask their doctor if they are opioid-tolerant before taking Fentora.

FDA is highlighting the following important safety information on Fentora:

- **Fentora should only be used for breakthrough pain in opioid-tolerant patients with cancer.**
  - Fentora should not be used to treat any type of short-term pain including headaches or migraines, postoperative pain, or pain due to injury.
  - Fentora should not be used by patients who only take narcotic pain medications occasionally.
- **The dosage strength of fentanyl in Fentora is NOT equal to the same dosage strength of fentanyl in other fentanyl-containing products.**
  - Healthcare professionals **must not directly substitute Fentora for other fentanyl medicines**, including Actiq.
  - Doctors must select the Fentora dose carefully for each patient.
- **Patients who take Fentora and their caregivers must understand how to use it safely and follow the directions exactly.** Directions for taking Fentora are provided in the Medication Guide for patients.
- **Healthcare professionals who prescribe Fentora and patients who use Fentora and their caregivers should be aware of the signs of fentanyl overdose.** Signs of fentanyl overdose include trouble breathing or shallow breathing; tiredness, extreme sleepiness or sedation; inability to think, talk or walk normally; and feeling faint, dizzy or confused. If these signs occur, patients or their caregivers should get medical attention right away.

The Fentora product label and Medication Guide for patients are being updated to add new safety information. In addition, Cephalon, the manufacturer of Fentora, issued "Dear Healthcare Professional" and "Dear Doctor" letters which are available at the MedWatch web site. FDA will provide updates as new information is available.

Related Information

- Safe Use of Fentora (fentanyl buccal tablets) - Overview[1] [ARCHIVED]
  Podcast - September 27, 2007
- Safe Use of Fentora (fentanyl buccal tablets) - Full Version[2] [ARCHIVED]
  Podcast - September 27, 2007

Page Last Updated: 08/16/2013
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U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Contact FDA

Links on this page:

1. /Drugs/DrugSafety/DrugSafetyPodcasts/ucm078489.htm
2. /Drugs/DrugSafety/DrugSafetyPodcasts/ucm078493.htm

EXHIBIT 84

FENTORA® (fentanyl buccal tablet) CII

United States Food and Drug Administration

Joint Meeting of Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees

May 6, 2008

FENTORA® (fentanyl buccal tablet) CII Regulatory History and Overview

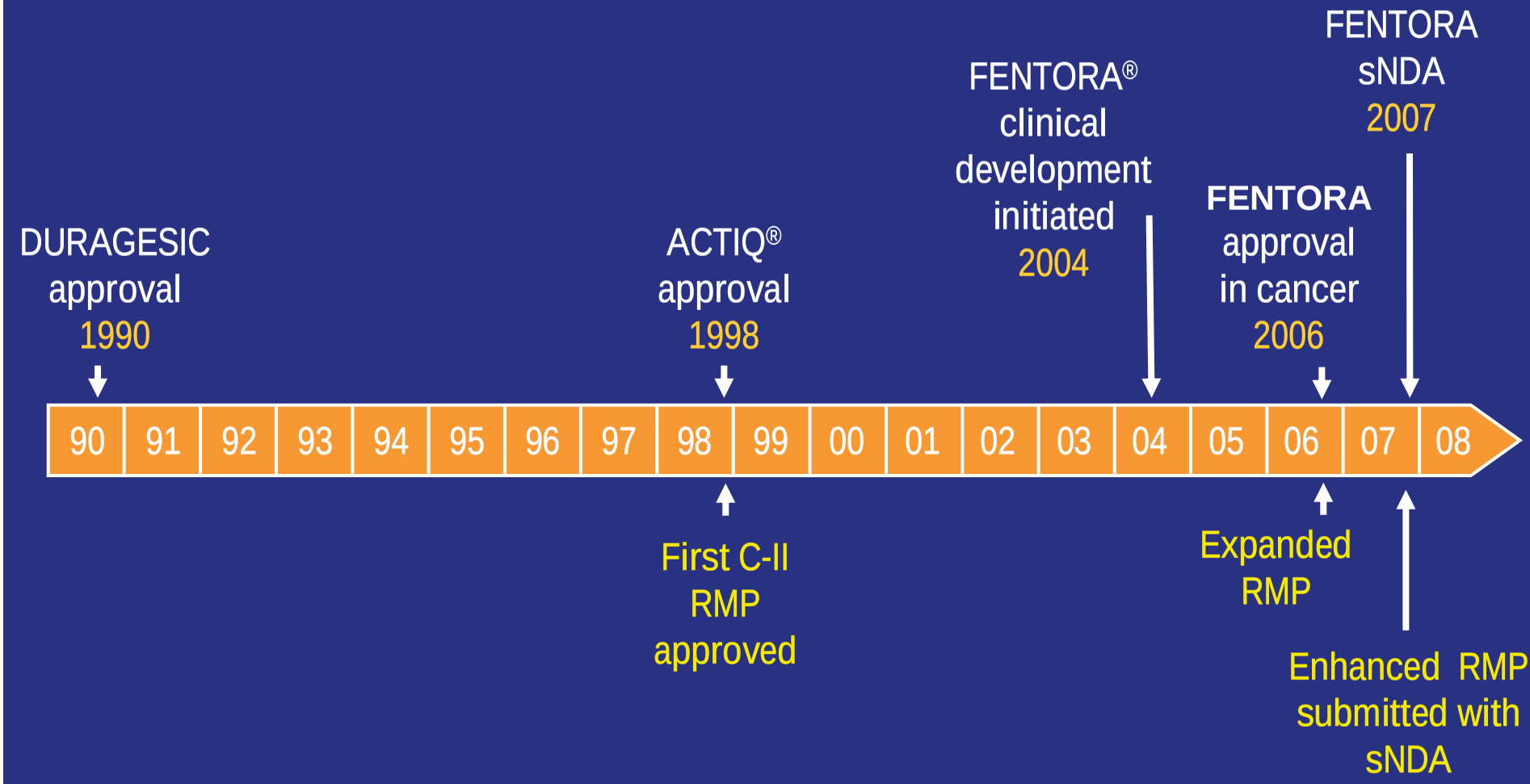
Eric A. Floyd, PhD

Vice President, Worldwide Head Regulatory Affairs
Cephalon, Inc.

Proposed Indication

FENTORA® is an opioid analgesic indicated for the management of breakthrough pain in patients who are taking around-the-clock opioid medications for their underlying persistent pain

Regulatory History



The Questions We Face Today

- Need for expanded indication
- The safe use of FENTORA® in the expanded patient population
- Manage the risks of overdose, abuse, and diversion

Overview of FENTORA® RiskMAP Strategy

- Registration system
  - Prevent risk of overdose
- Controlled growth via controlled launch
  - Mitigate the risks of abuse and diversion
- Extensive surveillance

Agenda for Presentation

Medical Need/ Breakthrough Pain	**Perry G. Fine, MD** **Professor of Anesthesiology** **Pain Research Center** **University of Utah, Salt Lake City**
Efficacy **Mitigating Risk of Abuse and Diversion**	**John Messina, PharmD** **Senior Director, Clinical Research** **Cephalon, Inc.**
Clinical and Postmarketing Safety **Mitigating Risk of Overdose**	**Juergen Schmider, MD, PhD** **Corporate Safety Officer and Vice President** **Global Pharmacovigilance and Epidemiology** **Cephalon, Inc.**
Closing Remarks	**Lesley Russell, MBChB, MRCP** **Executive Vice President and Chief Medical Officer** **Cephalon, Inc.**

Consultants

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Aaron M. Gilson, PhD
U of Wisconsin, School of Medicine and Public Health

Howard Heit, MD, FACP, FASAM
Georgetown University

Robert N. Jamison, PhD
Harvard Medical School

Sidney H. Schnoll, MD, PhD
Pinney Associates

Addressing Treatment Needs of Patients With Breakthrough Pain: Optimizing Benefit and Minimizing Risk

Perry G. Fine, MD

Professor of Anesthesiology
Pain Research Center
University of Utah, Salt Lake City

Breakthrough Pain in Patients With Chronic Pain Is a Highly Relevant Clinical Problem

Opioids and Chronic Pain

- Opioid therapy is a component of comprehensive pain care for patients with chronic cancer and noncancer pain that is poorly responsive to other therapies
- Chronic pain has 2 components
  - Persistent pain
  - Breakthrough pain
    - In opioid-tolerant patients

Inclusion of Breakthrough Pain Within Prescribing Information

OXYCONTIN **(oxycodone HCl controlled-release)**	**…Patients should be advised to report episodes of breakthrough pain…** **…Patients who experience breakthrough pain may require dosage adjustment or rescue medication…**
AVINZA **(morphine sulfate extended-release)**	**…Is of most benefit when a constant level of opioid analgesia is used as a platform from which breakthrough pain is managed…** **…In the event that breakthrough pain occurs, AVINZA may be supplemented with a small dose…of a short-acting analgesic…**
DURAGESIC **(fentanyl transdermal system)**	**…Some patients still may require periodic supplemental doses of other short-acting analgesics for breakthrough pain…**

Breakthrough Pain—Definition

- Breakthrough pain (BTP) is typically defined as a transitory exacerbation of pain that occurs on a background of otherwise controlled chronic pain[a]
- Patients entering the FENTORA® clinical program
  - Had chronic pain of ≥ 3 months' duration
  - Were opioid tolerant
    - Taking ≥ 60 mg of oral morphine/day, or an equianalgesic dose of another opioid for ≥ 7 days prior to enrollment

[a] Portenoy RK, et al. *Pain*. 1990;41:273-281.

Breakthrough Pain Is Similar in Cancer and Noncancer Patients

Characteristic	Patients with cancer BTP n = 63	Patients with noncancer BTP n = 228
Prevalence	64%	74%
Frequency (median)	4 episodes/day	2 episodes/day
Onset to peak intensity	43% in 3 minutes	46% in 5 minutes
Duration (median)	30 minutes	60 minutes

Portenoy RK, et al. *J Pain*. 2006;7:583-591.
Portenoy RK, et al. *Pain*. 1990;41:273-281.

Cancer and Noncancer Chronic Pain Share Common Features

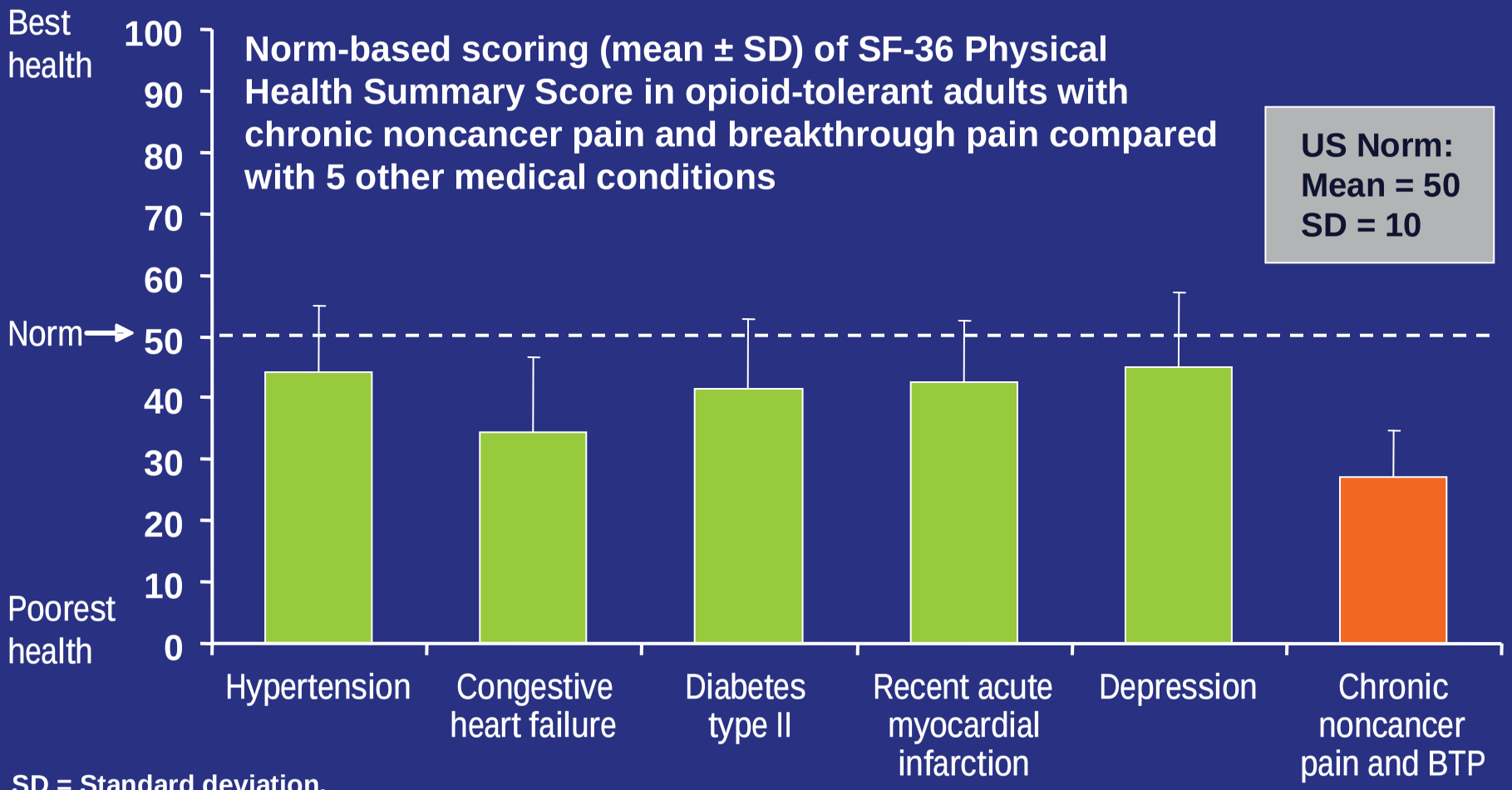
- The final pathways that lead to the perception of pain are common to chronic cancer and noncancer pain conditions

BTP pathophysiology	Cancer-related BTP n = 63	Noncancer-related BTP n = 228
Nociceptive somatic	33%	38%
Nociceptive visceral	20%	4%
Neuropathic	27%	18%
Mixed	20%	40%

Portenoy RK, et al. *J Pain*. 2006;7:583-591.
Portenoy RK, et al. *Pain*. 1990;41:273-281.

No Medications Approved for the Management of Chronic Noncancer Breakthrough Pain

Quality of Life in Opioid-Tolerant Patients With Chronic Pain and Breakthrough Pain



SD = Standard deviation.

Chronic noncancer pain and breakthrough pain group, n = 941 patients entering FENTORA® clinical studies

Norm-based data for the 5 other medical conditions taken from Ware JE, et al. *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Boston, MA: Health Assessment Lab, 1994.

Evidence Supporting the Need for Effective Treatment of BTP in Opioid-Tolerant Patients With Chronic Noncancer Pain

Survey data

- 74% of patients with BTP
- 68% using short-acting opioids
- 65% reported inconsistent efficacy

Prescription data

- > 80% of FENTORA® is prescribed for noncancer BTP

Clinical trial data

At study entry

- All patients on short-acting opioids

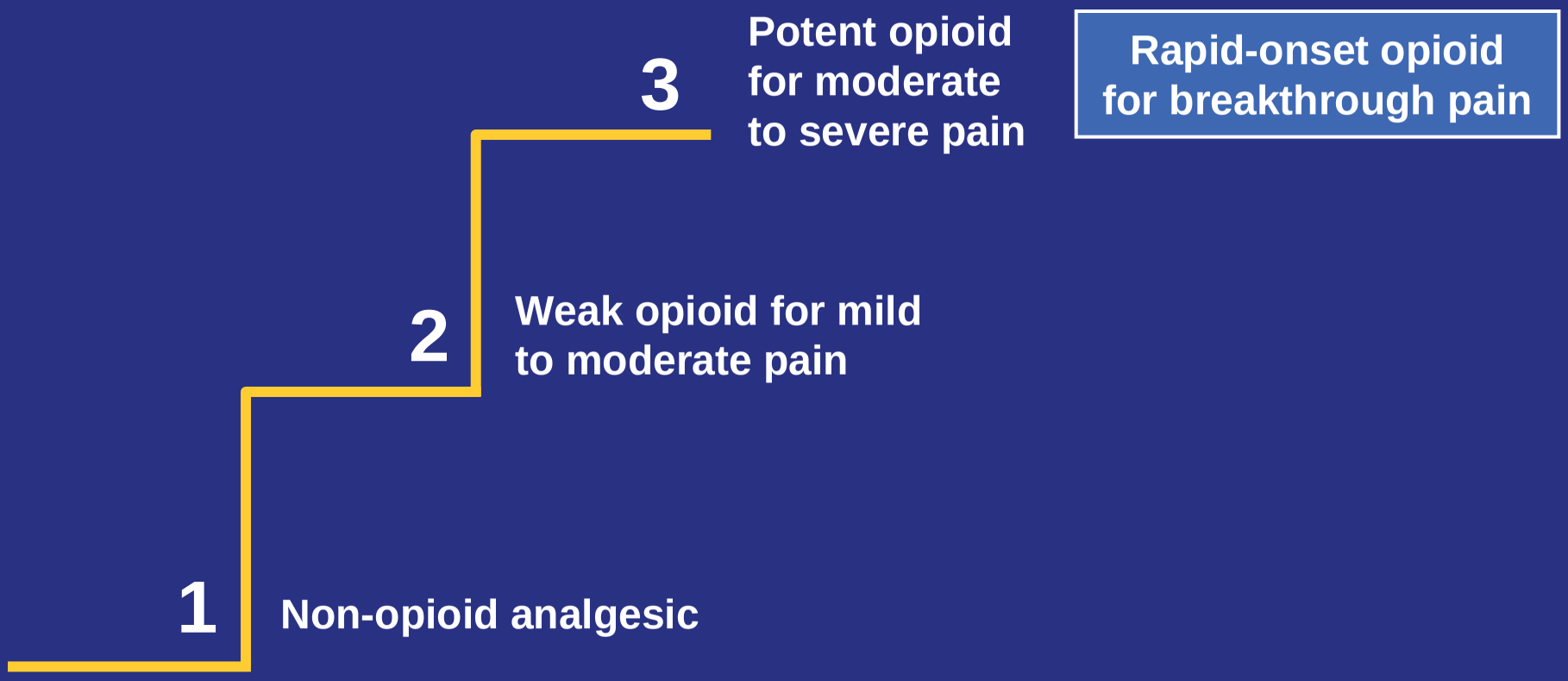
At study end

- Proven efficacy for FENTORA in noncancer BTP in randomized, controlled trials
- > 70% of patients expressed a preference for FENTORA over previous rescue medication

Portenoy RK, et al. *J Pain*. 2006;7:583-591.

Breakthrough Pain in Noncancer Chronic Pain Can Be Effectively Treated

Place of Supplemental Opioids in the Management of Chronic Pain



Based on the WHO Analgesic Ladder.

In Practice—Treating Breakthrough Pain With FENTORA®

Cancer diagnosis

Noncancer diagnosis

Pictures are not those of patients described.

The Central Principle of Balance

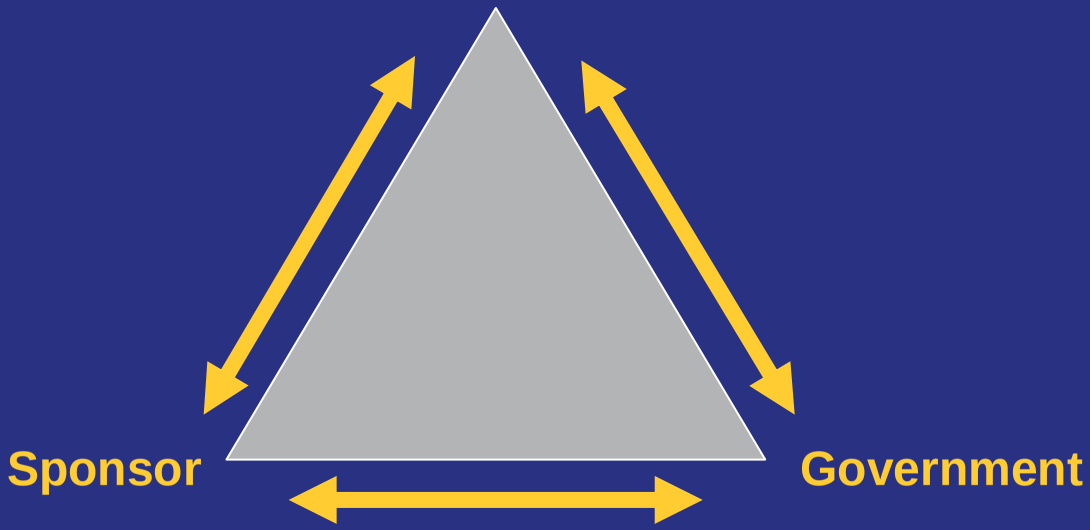
Medical availability

Opioid analgesics are essential and absolutely necessary for the relief of pain

Drug control

Controls are necessary to prevent abuse and diversion, but should not diminish medical usefulness or interfere with legitimate use

Healthcare professionals and patients



Pain and Policy Studies Group, University of Wisconsin School of Medicine and Public Health, July 2007.
Federal Register. Vol. 72, No. 222, Page 64929. Monday, November 19, 2007.

FENTORA® (fentanyl buccal tablet) CII Efficacy

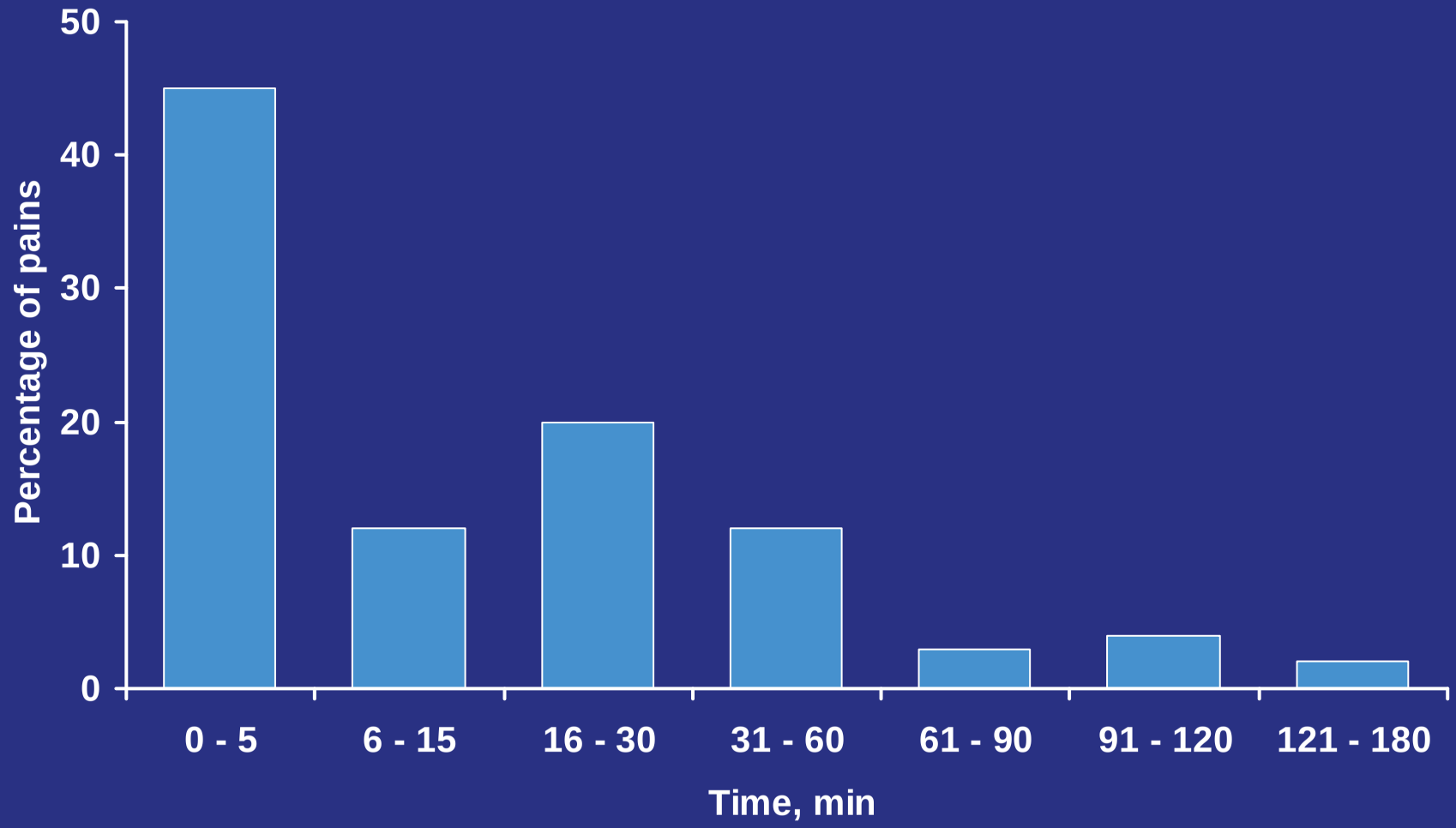
John Messina, PharmD

Senior Director, Clinical Research
Cephalon, Inc.

Rationale for FENTORA® Development Based on Experience With ACTIQ®

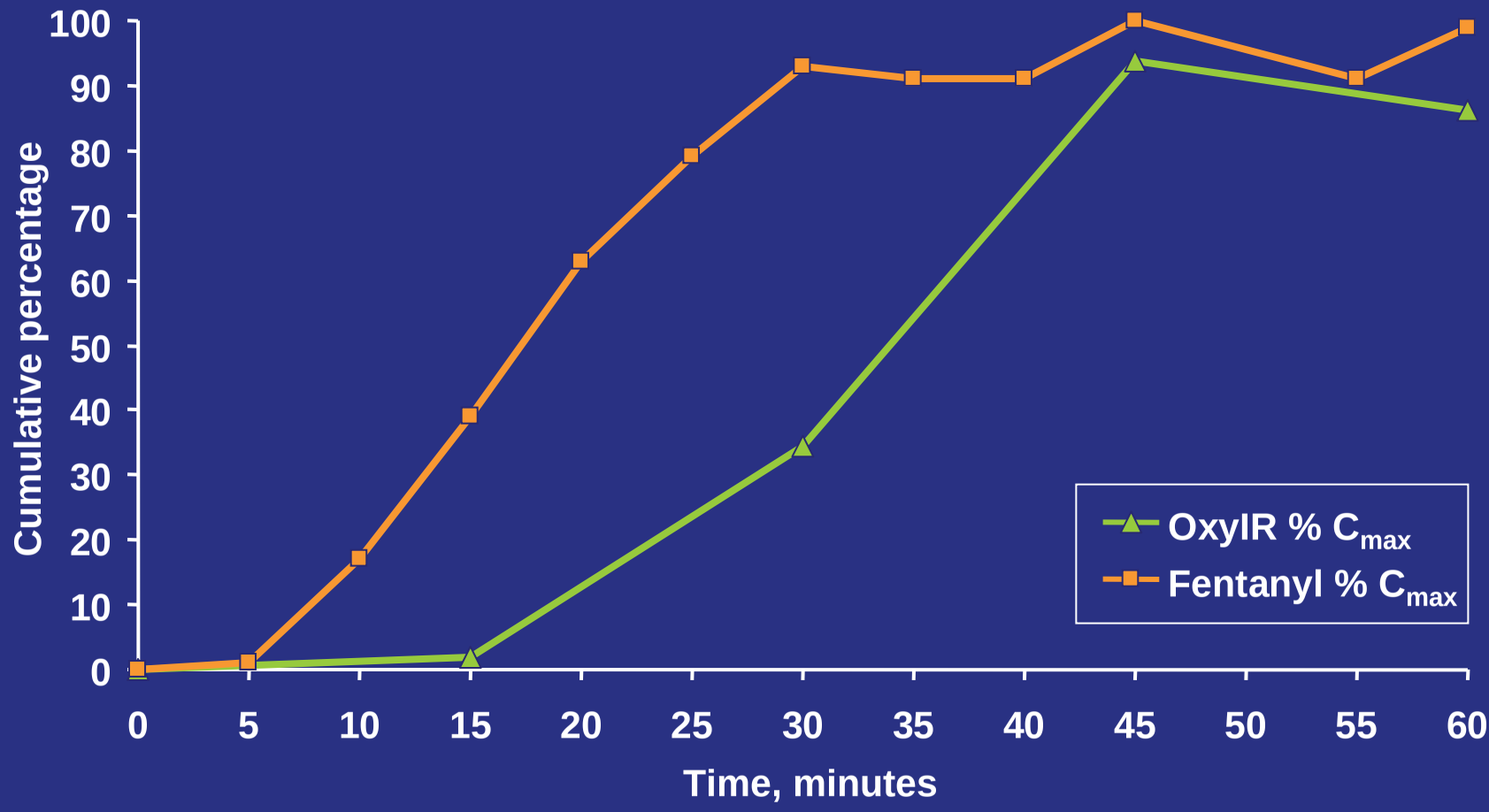
- ACTIQ used in treatment of noncancer-related BTP
- Clinical development program for cancer and noncancer BTP indications overlapped
- FENTORA—tablet designed to deliver fentanyl across oral mucosa more efficiently
- Pharmacokinetic profile more closely matches onset of BTP

Maximum Intensity of Breakthrough Pain Reached Rapidly



In total, 168 patients provided information about 189 episodes of BTP.
Portenoy RK, et al. *J Pain*. 2006;7:583-591.

Plasma Fentanyl Concentrations From FENTORA® More Closely Match Pattern of BTP



FENTORA pharmacokinetic data, N = 199.
Oxycodone data on file (N = 28): Cephalon, Inc. Report No. DP-2007-084.

First Clinical Program in Opioid-Tolerant Patients With Noncancer-Related BTP

- Data from four Phase 3 studies submitted with sNDA
  - 3 efficacy/safety (1 pivotal, 2 supportive)
  - Pivotal study assessed efficacy over 12 wk
  - One 18-mo, open-label, safety study
- Patients were using ATC opioids and treating BTP with opioid
- Patients began titration at lowest dose (100 mcg), and dose increased until successful dose found
- Efficacy assessed using within-patient design
  - Patients randomized to sequence of 9 treatments (6 FENTORA®, 3 placebo) for double-blind periods

ATC = Around-the-clock.

Study Population Reflective of Intended Population

Key patient characteristics	Total (N = 941)
Mean age (SD), yr	49 (10)
Women, %	57
Chronic pain condition, % (> 5%)	
Low back pain	55
Neuropathic pain	20
Traumatic injury	10
Complex regional pain syndrome	6
Osteoarthritis	6
Average pain of BTP episode	7/10

Studies 3040, 3041, 3042, 3052.

Population Characterized by Substantial Comorbidities

Category	Patients, n (%) N = 941
Musculoskeletal	928 (99)
Neurological	722 (77)
Gastrointestinal	704 (75)
Psychiatric	691 (73)
Genitourinary	554 (59)
Cardiovascular	550 (58)
Respiratory	373 (40)
Endocrine	329 (35)

Studies 3040, 3041, 3042, 3052.

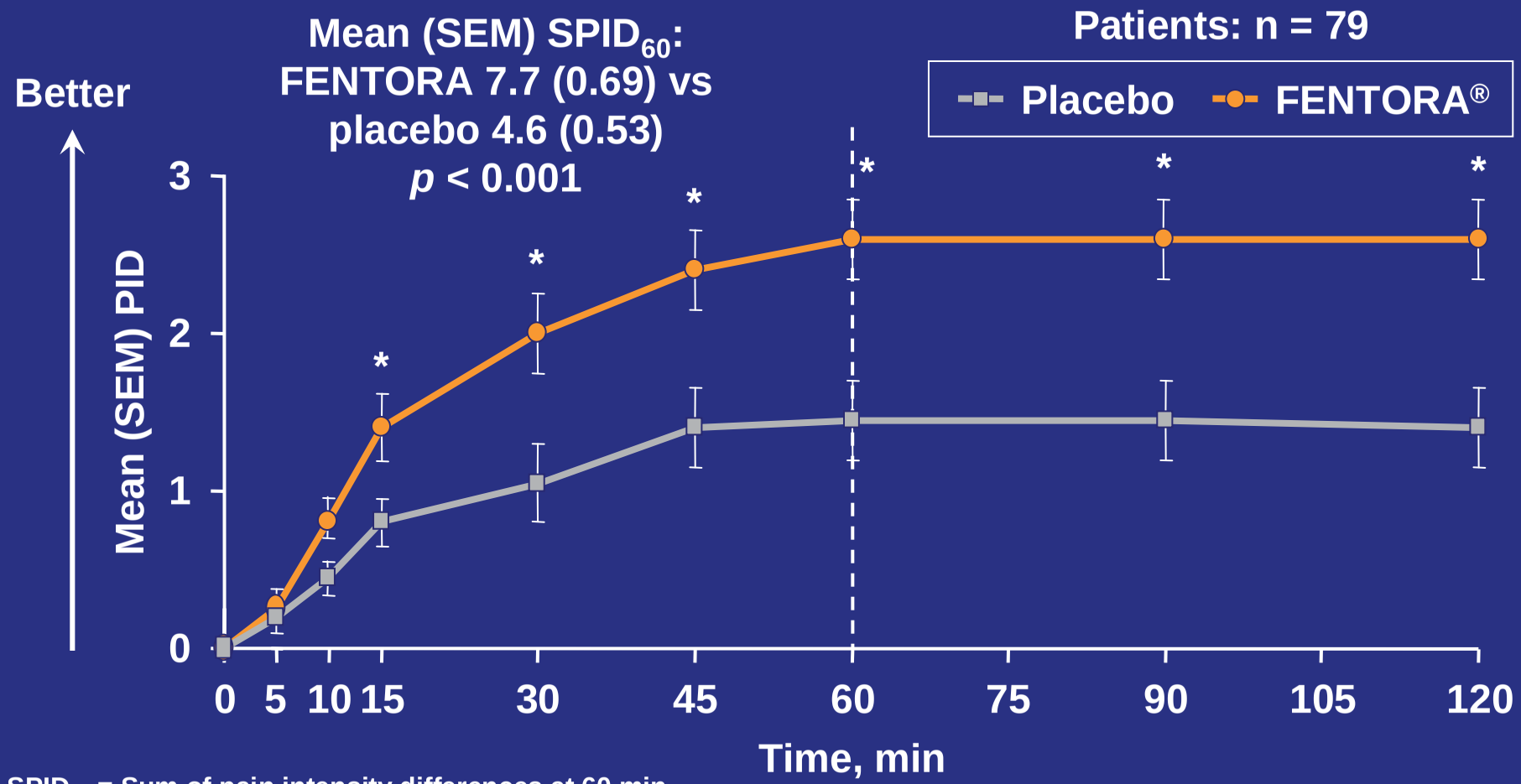
Significant Doses of Opioid Being Used at Study Entry

	ATC medication		
Dose, mg	Oral opioids	Transdermal fentanyl	Intrathecal medications
ATC	n = 688	n = 223	n = 30
Mean (SD)	211.1 (210)	209.3 (140)	—
Rescue	n = 683	n = 220	n = 29
Mean (SD)	27.0 (27.3)	31.8 (102)	35.2 (47.6)

Studies 3040, 3041, 3042, 3052.

Reductions in BTP Intensity for 2 Hours

Pain intensity differences (PID) over time after 12 wk of treatment

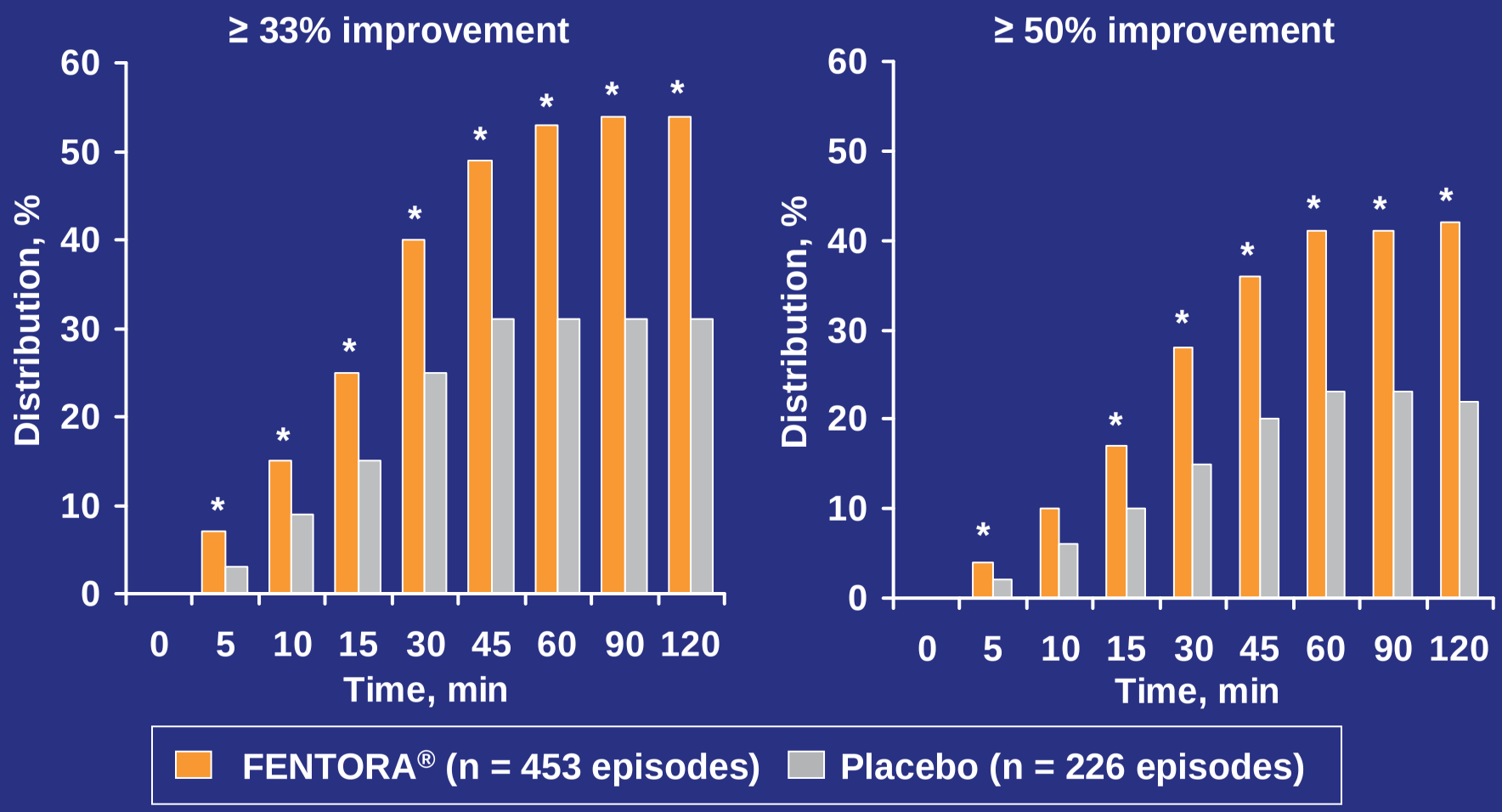


$SPID_{60}$ = Sum of pain intensity differences at 60 min.

* Nominal $p < 0.05$ vs placebo ANOVA. Study 3052.

Clinically Significant Improvements in Pain Intensity Observed for 2 Hr

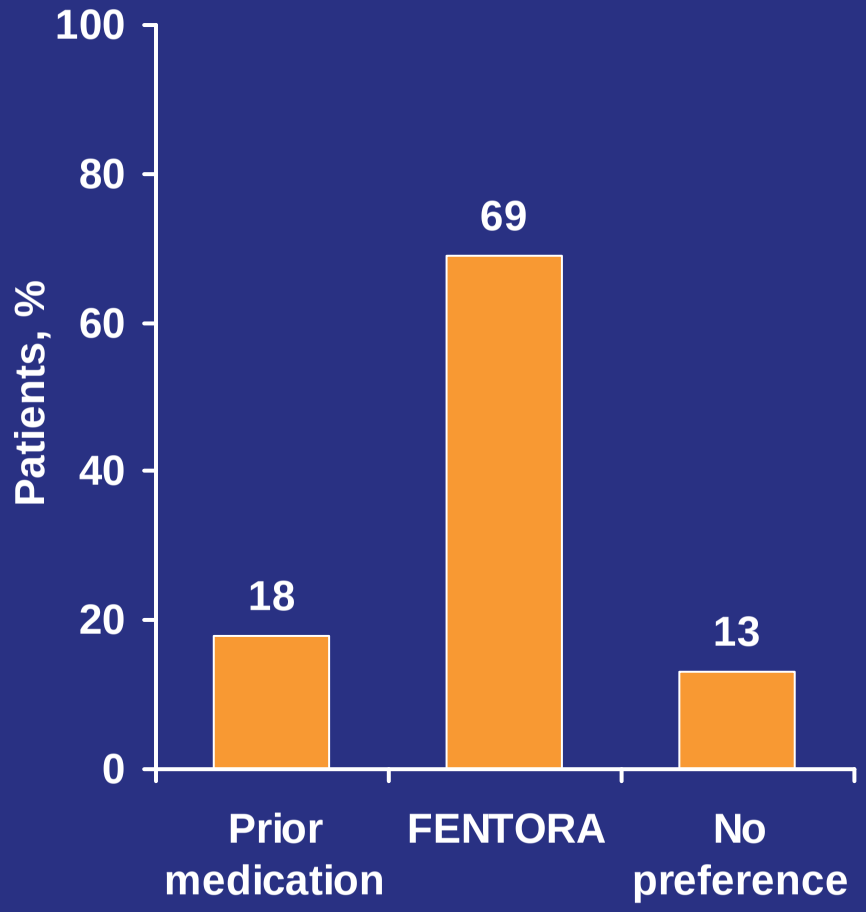
Percentage of episodes meeting response criteria after 12 wk of treatment



*Nominal $p < 0.05$ vs placebo GEE; Study 3052.

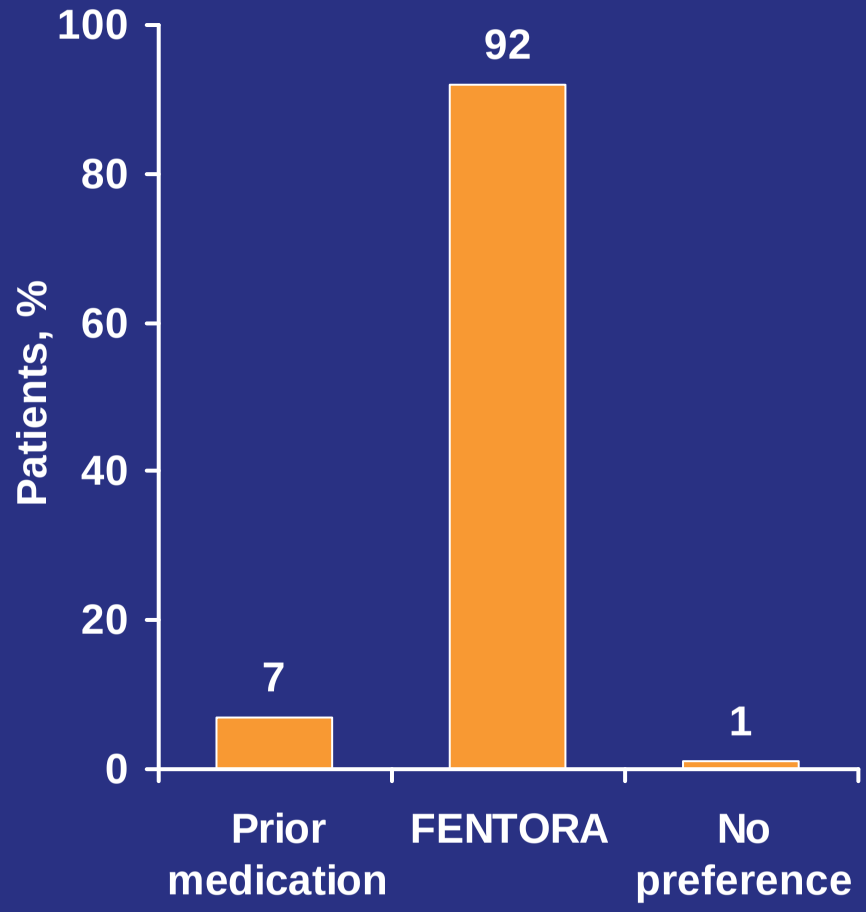
Patients Prefer FENTORA® to Previous Short-Acting Opioids

Which medication would you prefer to use when treating your pain flares?



N = 97

Which medication do you feel worked faster for pain flare control?



N = 98

Effect of FENTORA® Well-Matched to BTP Characteristics

- Efficacy of FENTORA demonstrated in noncancer-related BTP
- Clinically relevant improvements in BTP observed
- Efficacy seen throughout 12 wk
- Patients enrolled in clinical studies reflect intended population

FENTORA®
Clinical Trial and Postmarketing Safety

Juergen Schmider, MD, PhD

Corporate Safety Officer and Vice President,
Global Pharmacovigilance and Epidemiology
Cephalon, Inc.

Clinical Trial Safety
Noncancer BTP

Clinical Safety Noncancer BTP Trials

Patient Exposure

- 1299 patients treated in clinical trials with FENTORA®
- 941 patients in noncancer BTP trials
  - 227,047 patient treatment days

Clinical Safety Noncancer BTP Trials

Adverse Event Profile

Adverse event	n (%)
Nausea	222 (24)
Application site events	116 (12)
Vomiting	114 (12)
Back pain	105 (11)
Dizziness	107 (11)
Headaches	100 (11)
Somnolence	95 (10)
Constipation	67 (7)
Arthralgia	66 (7)

Clinical Safety Noncancer BTP Trials
Overdose

- 10 patients
  - Intentional exposure (2)
    - Suicide attempt
    - Polysubstance abuse
  - Unintentional exposure (8)
    - Multiple dose strengths available during titration

  Addressed in proposed Package Insert

  - Exact circumstances unknown
  - No overdose deaths
- 1 non-study subject with fatal overdose

Cancer vs Noncancer BTP Safety
Frequent AEs

Preferred term	Noncancer BTP N = 941	Cancer-related BTP N = 358
Nausea	222 (24)	110 (31)
Application site events	116 (12)	31 (9)
Vomiting	114 (12)	63 (18)
Dizziness	107 (11)	83 (23)
Back pain	105 (11)	20 (6)
Headaches	100 (11)	52 (15)
Somnolence	95 (10)	41 (11)
Constipation	67 (7)	48 (13)

Cancer vs Noncancer BTP Safety
Nonserious Adverse Events

		Noncancer N = 941, PYR = 673.6			Cancer N = 358, PYR = 128.0		
	FDA-defined pooled terms	Patients, n	Events, n	Rate/ 100 PYR	Patients, n	Events, n	Rate/ 100 PYR
Higher in noncancer	Withdrawal	16	17	2.5	1	1	0.8
Higher in cancer	Dizzy	55	71	10.5	71	131	102.3
	Lightheaded	59	80	11.9	22	68	53.1
	Syncope	6	6	0.9	3	3	2.3
	Sedation	127	163	24.2	53	84	65.6
	Confusion	30	39	5.8	27	37	28.9
	Likeability of opioid	12	14	2.1	9	9	7.0
	Fall	33	36	5.3	10	12	9.4
	Fracture	26	28	4.2	5	10	7.8
	Car accident	2	2	0.3	1	1	0.8

PYR = Patient-years.
All severities were included. Cluster of events subsequent to the same incident were counted only once for each pooled term (eg, 9 fractures caused by a motor vehicle accident).

Cancer vs Noncancer BTP Safety
Conclusion

- Cancer and noncancer safety profile largely comparable
- Adverse events of interest more frequent in cancer population (except withdrawal)

Assessment of Abuse and Diversion Risk Within Clinical Trials

Assessment of Abuse and Diversion

Drug Abuse

- 21 patients with drug abuse events
  - 8 (< 1%) patients had a reported event of drug abuse
  - 13 patients tested positive on random urine drug screen for illicit substance or non-prescribed medication
- Similar rates observed with trials for other opioids

Assessment of Abuse and Diversion
Aberrant Drug-Related Behavior

- Aberrant drug-related behaviors are signals for potential substance abuse disorders
  - **Neither indicators nor surrogates for a diagnosis of abuse or addiction**
- Post-hoc analysis of clinical trial database for occurrence of potential aberrant drug-related behaviors
  - Patient characteristics associated with aberrant behaviors were evaluated

Assessment of Abuse and Diversion
Aberrant Behavior Analysis

Events indicative of substance abuse or overdose		Aberrant behaviors			
		Behaviors involving use of study medication		Behaviors not involving use of study medication	
• Abuse/ dependence (described by investigator)	8 (<1%)	• Fear of addiction	6 (<1%)	• Motor vehicle accident	4 (<1%)
• Positive UDS	13 (1%)	• Report of medication theft	35 (4%)	• Discharged from pain-management practice	2 (<1%)
• Overdose	10 (1%)	• Report of lost study medication	5 (<1%)	• Using non-prescribed medication	4 (<1%)
		• Overuse of study medication	44 (5%)	• Lost to follow-up	33 (4%)
		• Unapproved use of drug to treat another symptom	2 (<1%)	• Seeking prescriptions from other sources	1 (<1%)
		• Unreliability	2 (<1%)	• Acquiring opioids from other medical sources	1 (<1%)

UDS = Urine drug screen.

Postmarketing Safety

Postmarketing Safety

Postmarketing Patient Exposure

- Cumulative from launch (October 2006) through December 31, 2007
- 2,175,287 patient treatment days
- 20,000 unique patients

Postmarketing Safety
Adverse Event Profile

Adverse event	n
Application site events	125
Nausea	34
Drug ineffective	20
Drug ineffective for unapproved indication	19
Vomiting	17
Somnolence	13
Drug prescribing error	11
Dry mouth	10
Hyperhydrosis	10
Withdrawal/drug withdrawal syndrome	10

Postmarketing Safety
Diversion and Nonmedical Use

- 2 cases of diversion (fatal)
  - Partner of patient
- 2 cases of nonmedical use
  - Drug dependence
  - Drug abuse

Postmarketing Safety
Accidental Exposure

- 1 report in adults
- No reports in children

Postmarketing Safety
Use in Opioid Non-Tolerant Patients

Data source and methodology	< 60 mg/day morphine eq.	≥ 60 mg/day morphine eq.
Spontaneous postmarketing reports[a]	14% (208/1497)	86% (1289/1497)
IMS prescription claims database[b]	23%	77%
Verispan with IMS methodology[b]	25%	75%
	No pain product	Any pain product
Verispan VOCON concurrency analysis[b]	41%	59%

Addressed in RiskMAP

[a] Cumulative through Dec 31, 2007 (n = 1989).
[b] 2007.

Postmarketing Safety
Reports of Medication Error

	Prescribing	Dispensing	Patient use	Total
Dose conversion	5	3		8
Administration route	3 SL		3 SL, 2 PO, 5 Unk	13
Frequency of use	2	0	1	3
Other	1		1	2
Total	11	3	12	26

Addressed in RiskMAP

SL = Sub lingual; PO = Per os (by mouth); Unk = Unknown.

Postmarketing Safety
Fatalities/Life-Threatening Events in Patients

Case ID	Age/sex	Indication	Events (PT)
US020247	34/F	Headache	Accidental OD; drug dispensing error
US021000 (LTE)	34/F	Migraine, trigeminal neuralgia	OD; loss of consciousness; respiratory arrest
US021127	44/F	Migraine	Arrhythmia, multiorgan failure; anoxic encephalopathy
US021157	40/F	Chronic back pain and radiculopathy	Drug toxicity

Specific RiskMAP Interventions
Root Cause Analysis

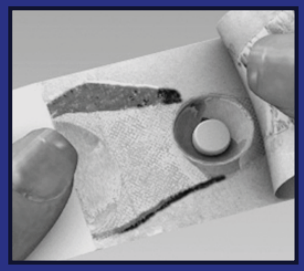
- **Root causes**
  - Prescribing errors
  - Lack of awareness about appropriate patient selection
  - Lack of understanding of dosage and administration associated with use of FENTORA®

- **Points of intervention**

Prescribing

Dispensing

Patient use

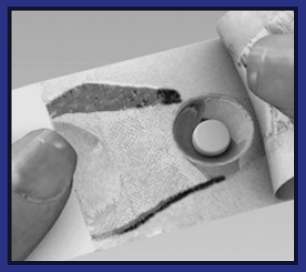


Specific RiskMAP Interventions
Targeted Interventions

- Dear Healthcare Professional letter addressing all subsequent points

- Point of prescribing
  - Changes to Package Insert and Medication Guide

- Point of dispensing
  - Changes to Medication Guide and carton
    - More instructions on dosing with FENTORA®
  - NotifyRx™: Computer-Facilitated Messaging System (screen pop-ups)



- Patient use
  - Changes to Medication Guide and carton
    - Do not use FENTORA more often than instructed
  - Patient Kit - addition of a safety activation card

Specific RiskMAP Interventions
Package Insert Changes

Reports of serious adverse events, including deaths in patients treated with FENTORA have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of FENTORA for any other fentanyl product may result in fatal overdose.

…

FENTORA is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure.

FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

When prescribing, do not convert patients on a mcg per mcg basis from Actiq® to FENTORA. Carefully consult the Initial Dosing Recommendations table.

When dispensing, do not substitute a FENTORA prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of FENTORA compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of FENTORA for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing FENTORA. If the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY one additional dose using the same strength and must wait at least 4 hours before taking another dose.

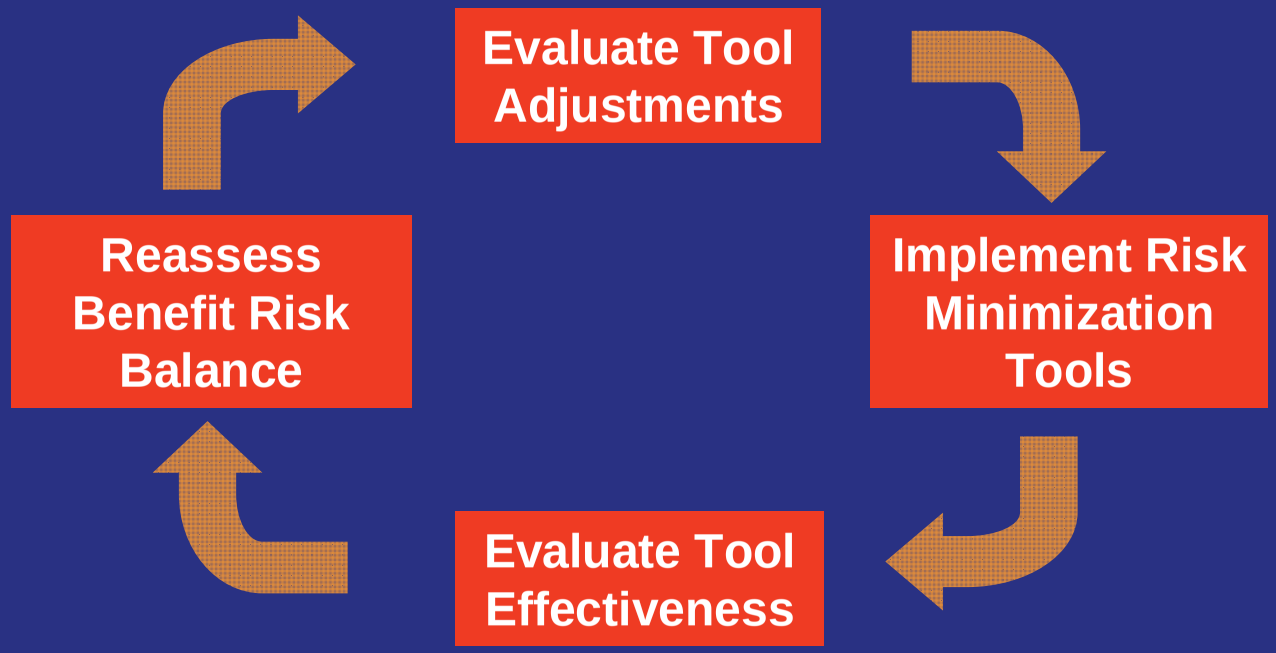
- Boxed Warning
- Indication and Usage
- Contraindications
- Warnings
- Precautions
- Information for Patients and Caregivers
- Dosage and Administration

Postmarketing Safety
Conclusions

- Consistent with clinical trial safety and tolerability
- Consistent with fentanyl
- Risk of overdose specifically addressed in RiskMAP

FENTORA® Risk Management

FENTORA® RiskMAP
Overview of Risk Management



FENTORA® RiskMAP
Risk Identification

Risks	Goals
Abuse and diversion	Abuse should not occur
	Diversion should not occur
Overdose	Should be used only by opioid-tolerant individuals
	Unintended (accidental) exposure should not occur
	Dosage and administration instructions should be provided to and understood by anyone who may prescribe, dispense, or use FENTORA

FENTORA® RiskMAP
Tools and Interventions

1. F1 Blister
2. Carton label
3. Medication Guide (originally patient leaflet)
4. Package insert
5. Educational introductory letters to HCPs
6. Risk management training to field reps
7. Product returns and disposal
8. Physician and pharmacist education
9. Reports of diversion and abuse
10. Web site
11. Blister label
12. Pharm Alert
13. Physician education to Pain Centers of Excellence
14. Pharmaceutical compendia
15. Counseling messages
16. Counseling aids
17. Emerging Solutions in Pain (ESP)
18. Prescriber education targeted to members of professional societies
19. Patient Kit with Safety Activation Card (pilot)
20. NotifyRx messaging (pilot)
21. Healthcare education (PROTECT) for prescribers, pharmacists, patients
22. RFID (pilot)
23. PEDIGREE
24. Tamper-resistant prescription pads
25. Catalina newsletter
26. Auxiliary Rx labels
27. Pharmacy checklist/stamp
28. Book on appropriate opioid prescribing
29. Secure Resource Folder
30. RiskMAP Core Visual Aids
31. Speaker programs
32. Speaker training
33. Safety letters responding to reports of inappropriate patient selection and/or dosing
34. Controlled Voice Enrollment Registration System (COVERS)

FENTORA® RiskMAP
Points of Intervention

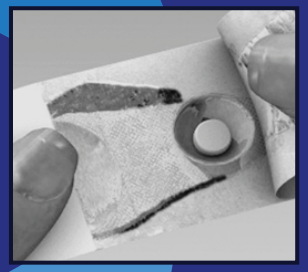
Dispensing

Consumer storage

Prescribing

Prescriber
Pharmacist
Patient

Patient use



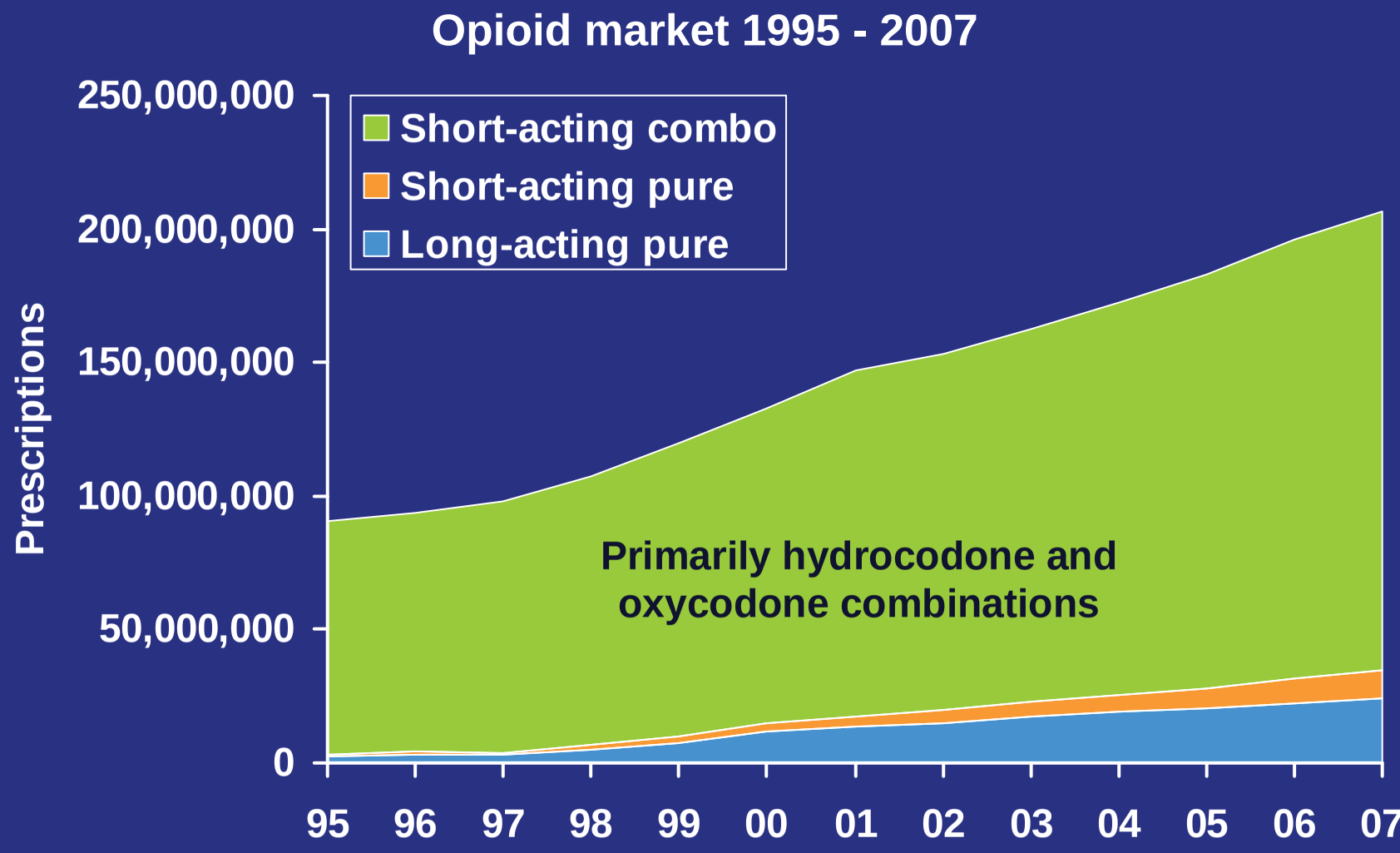
Manufacture and distribution

Disposal

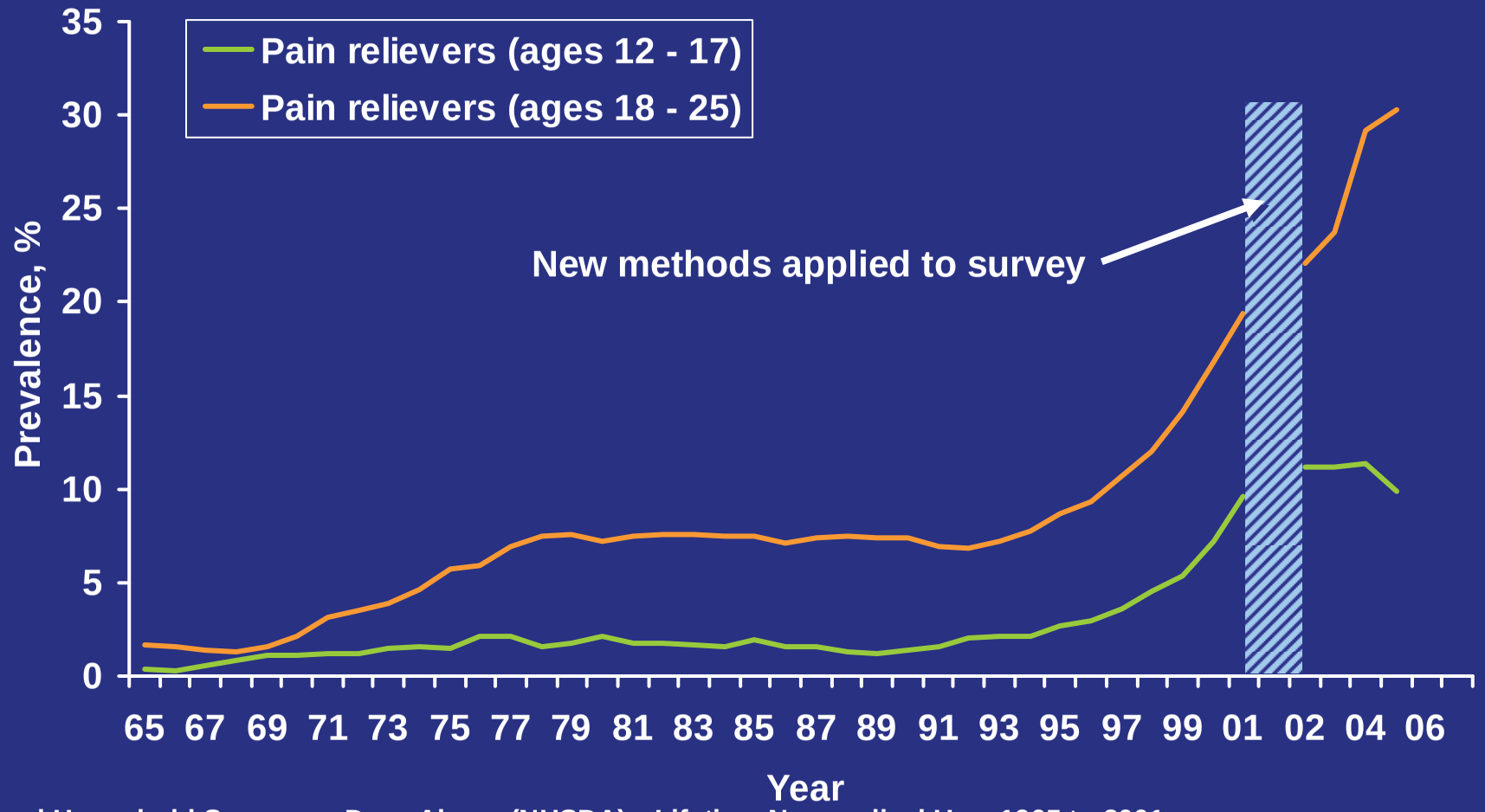
FENTORA® RiskMAP
Mitigating Risk of Abuse and Diversion

John Messina, PharmD

Prescriptions for Opioids Have Been Steadily Rising

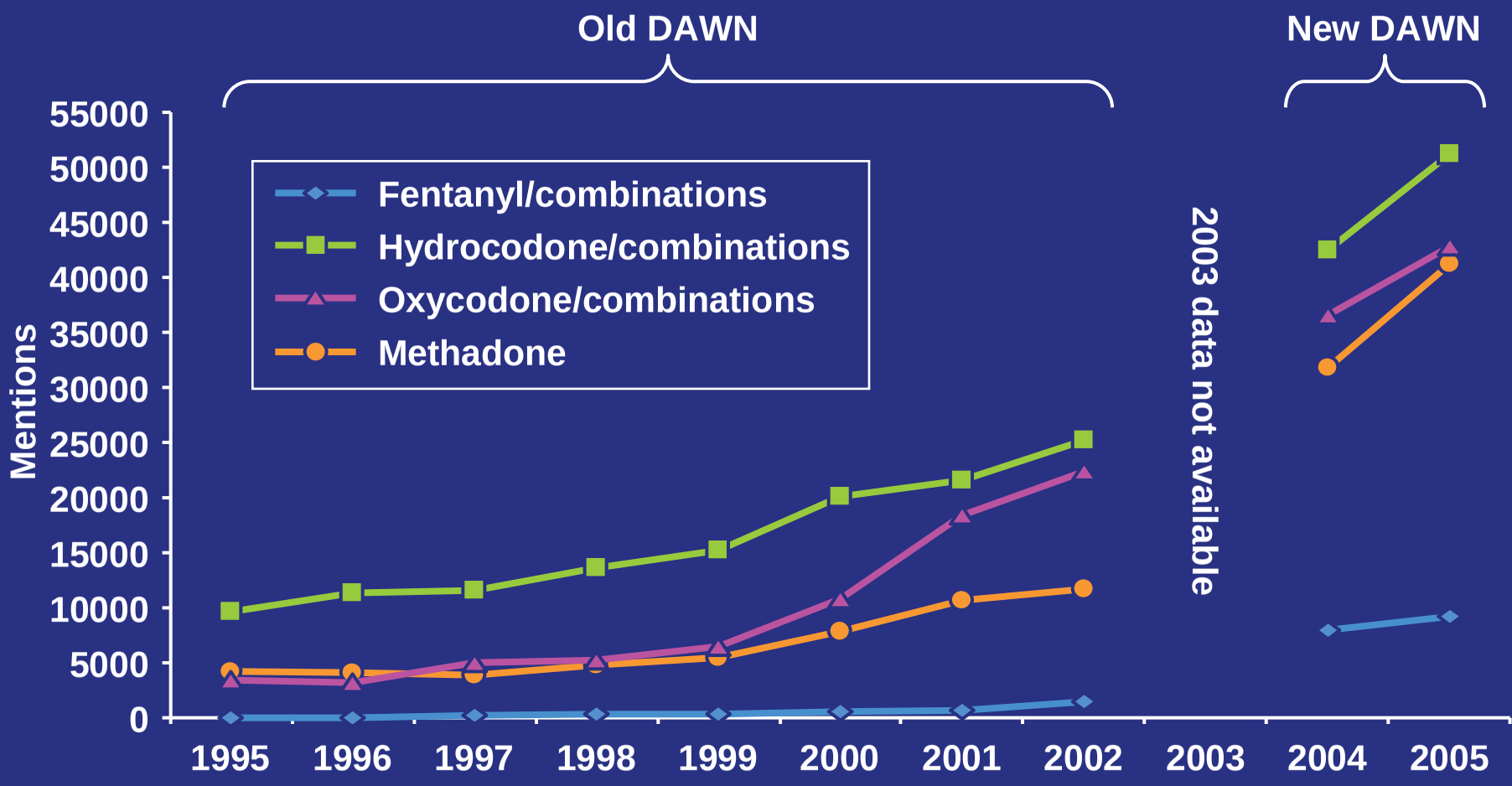


Nonmedical Use of Pain Relievers Has Also Been Increasing



National Household Survey on Drug Abuse (NHSDA)—Lifetime Nonmedical Use, 1965 to 2001
National Survey on Drug Use and Health- Lifetime Non-Medical Use 2002-2006
Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse.

Comparative Rates of Emergency Room Mentions in Drug Abuse Warning Network

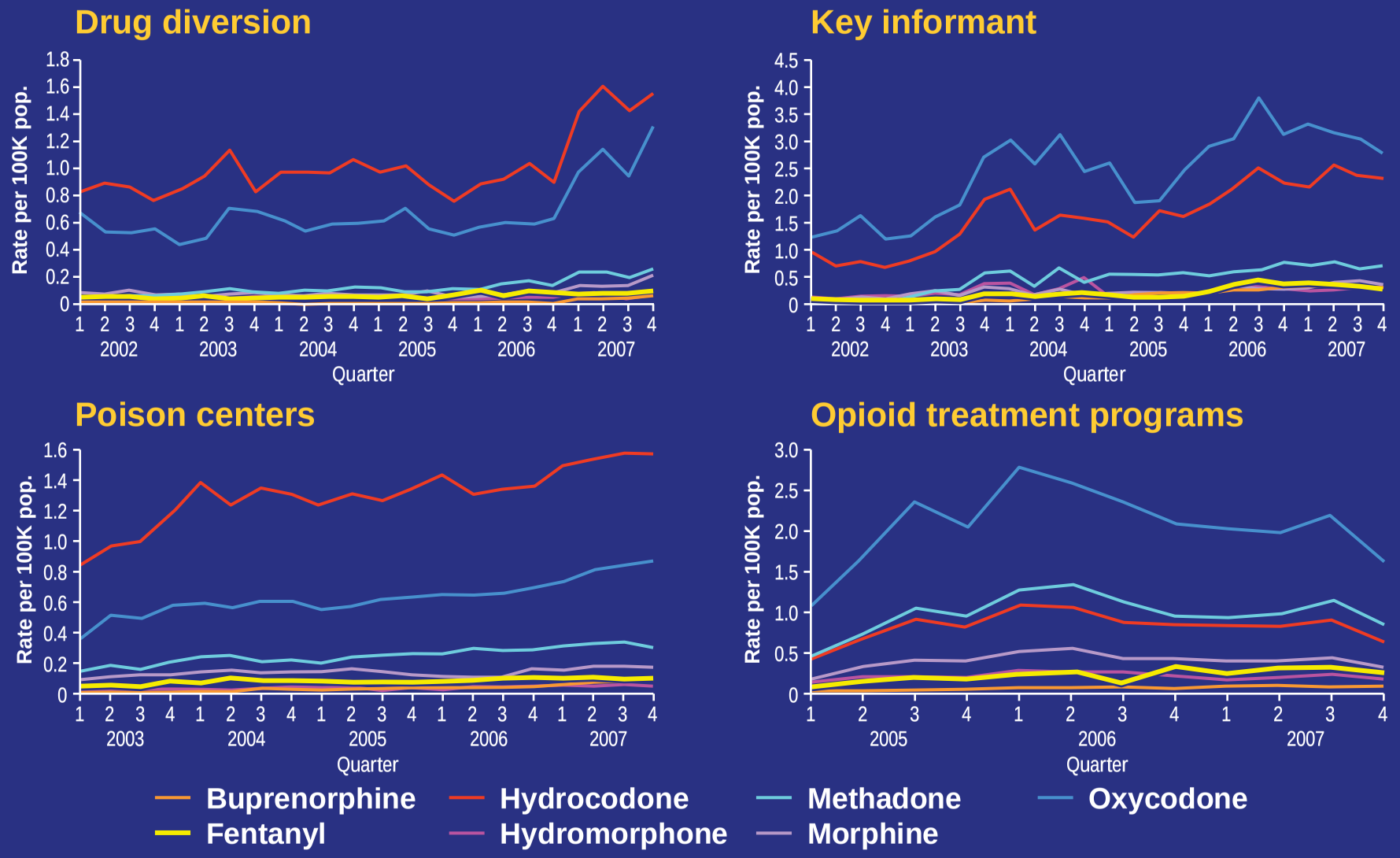


Source: Drug Abuse Warning Network – Emergency Department.

Real-Time Surveillance Systems

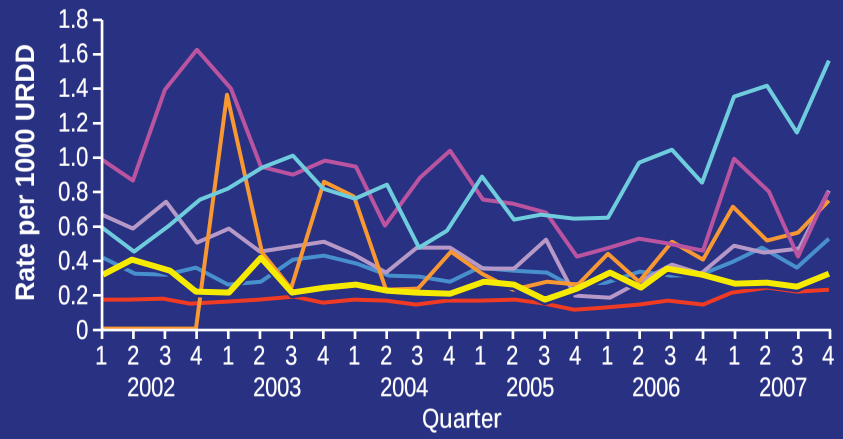
- Captures events and calculate rates of misuse, abuse, and diversion of prescription opioids and stimulants
- Covers 90% of US population with information from every state
- Information gathered from 4 sources
  - Poison centers
  - Law enforcement
  - Key informants
  - Opioid treatment programs

RADARS Results for Rates of Prescription Opioid Abuse per 100,000 Population

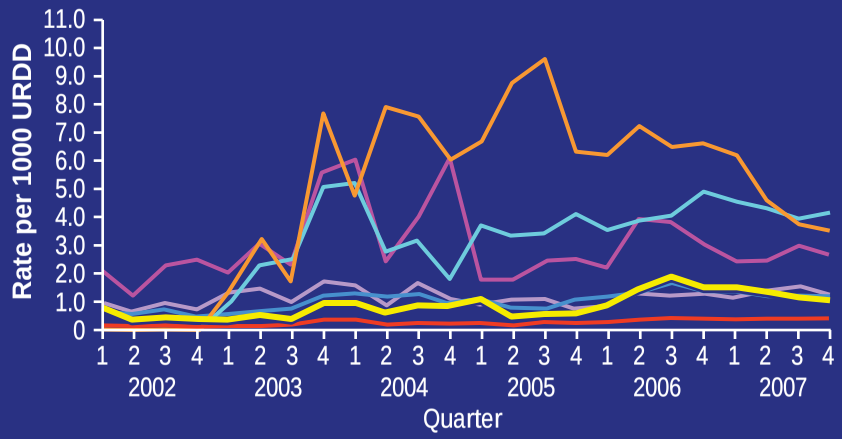


RADARS Results for Rates of Prescription Opioid Abuse—URDD

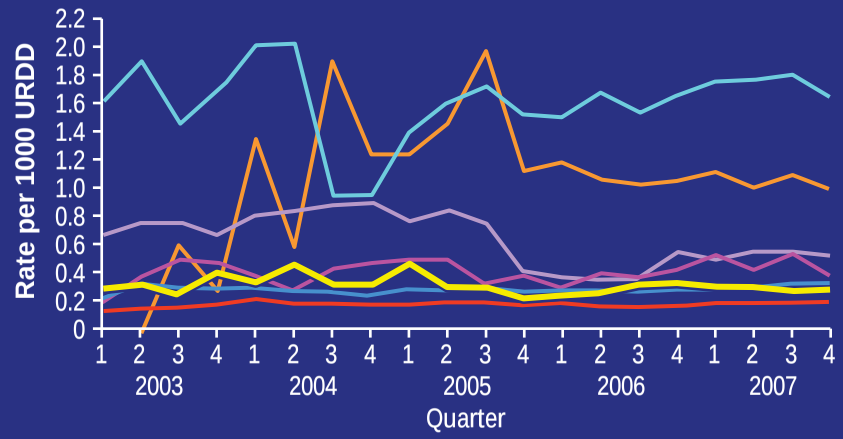
Drug diversion



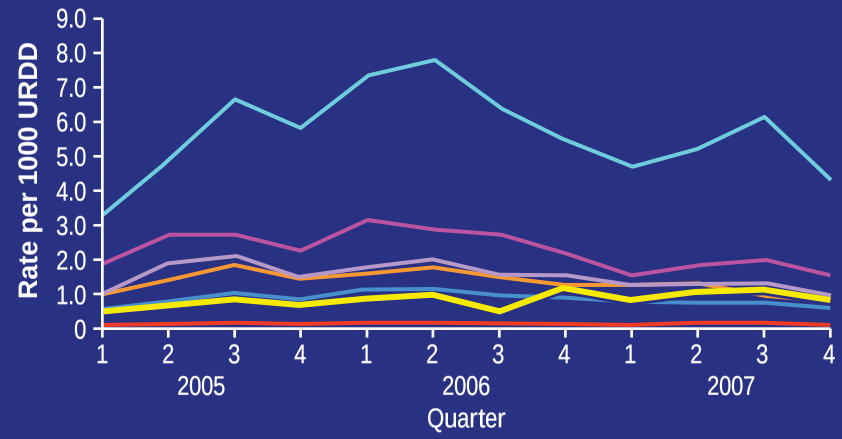
Key informant



Poison centers



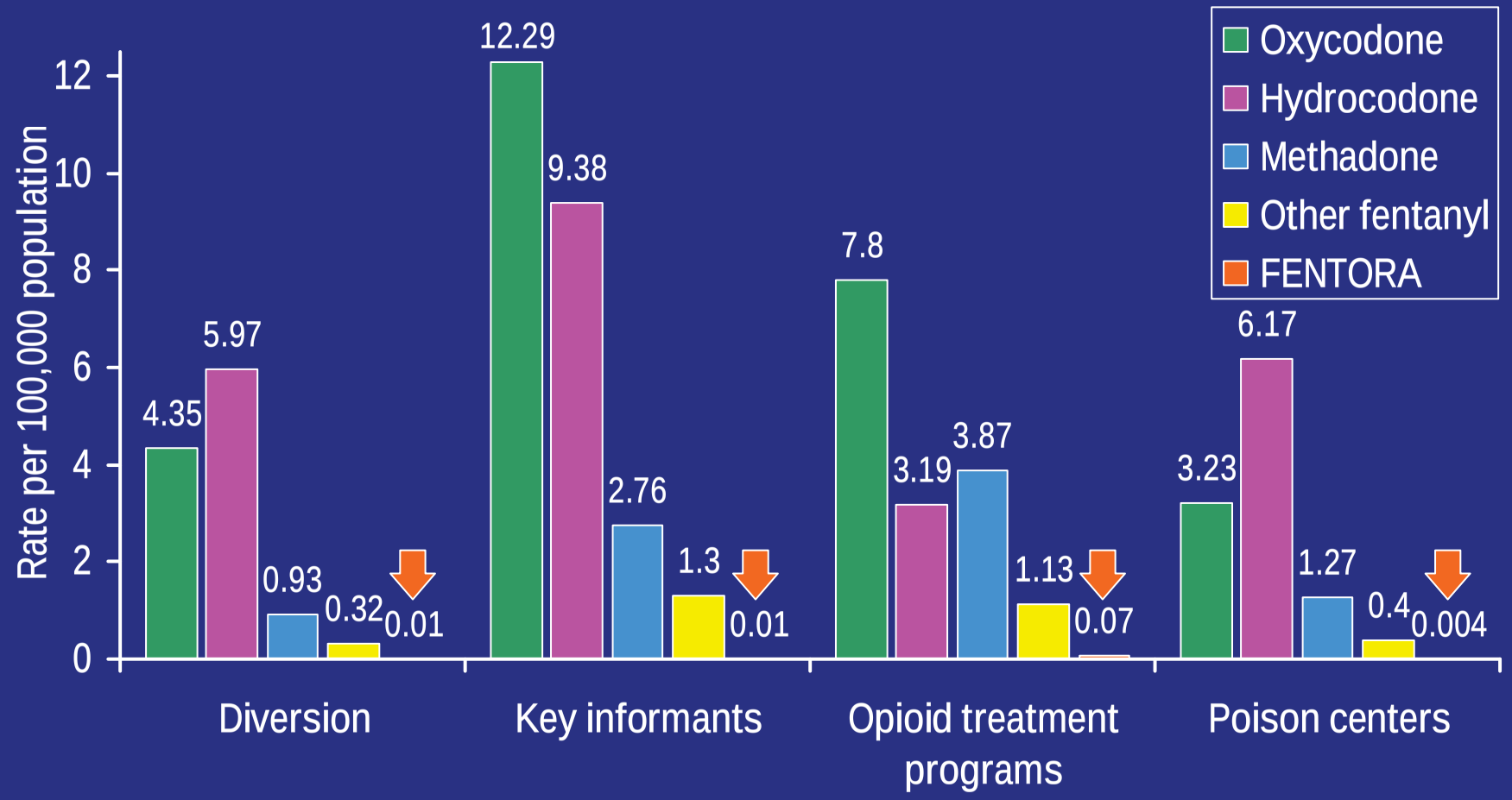
Opioid treatment programs



Buprenorphine
Fentanyl
Hydrocodone
Hydromorphone
Methadone
Morphine
Oxycodone

URDD = Unique recipients of dispensed drug.

RADARS Results for Rates of Abuse in 2007 by Component



Goal of FENTORA® RiskMAP—Abuse and Diversion Should Not Occur

- Mitigation strategies
  - Control availability and growth of FENTORA
  - Provide information and education to healthcare professionals and patients
  - Employ multiple surveillance systems
  - Actively intervene

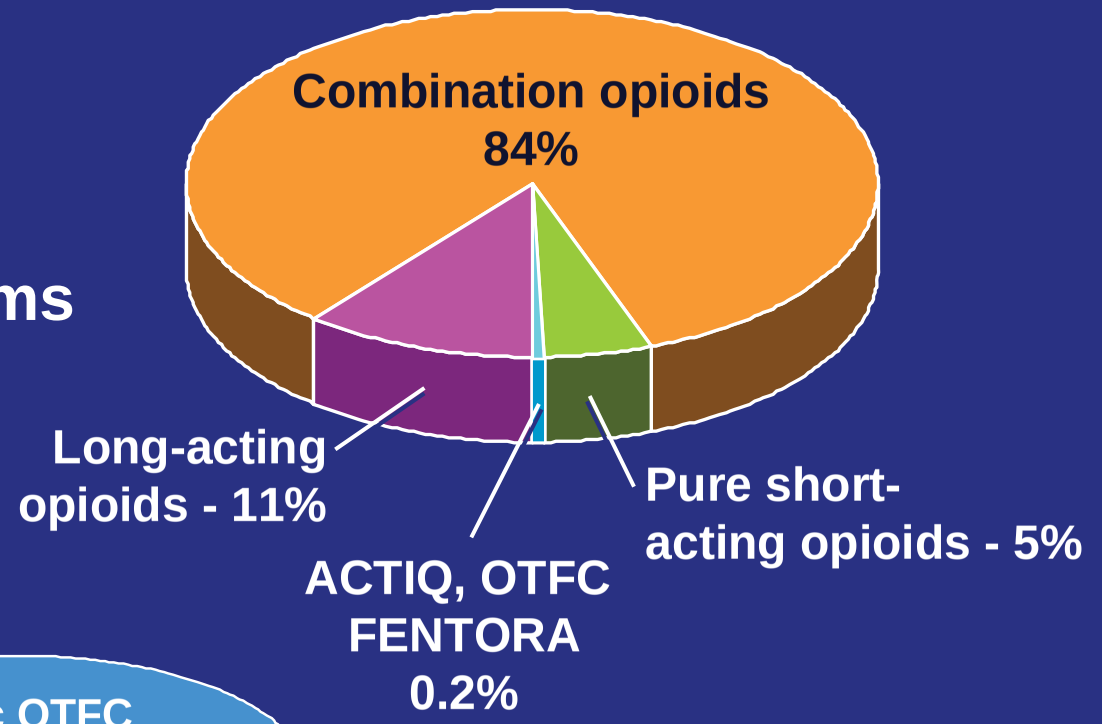
FENTORA® Indicated for a Subset of Chronic Pain Patients

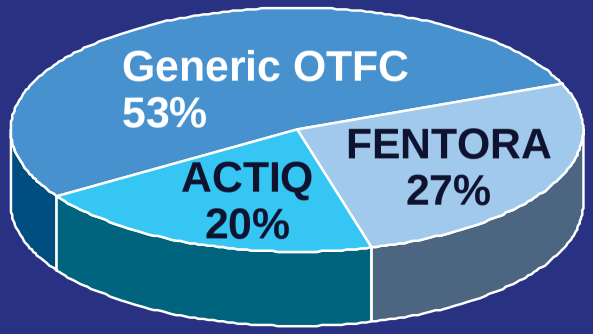
	Prevalence	Diagnosed	Treated for pain	Treated w/ opioids
Cancer	813,750	651,000	488,250	341,775
Back pain	9,026,240	5,867,056	4,693,645	891,793
Arthritic pain	11,486,400	7,007,248	5,758,976	593,724
Neuropathic pain	9,648,679	6,965,190	6,147,833	860,697
Totals	30,975,069	20,490,494	17,088,704	2,687,989

Adjusted for comorbidity.
Source: Analysis of secondary data reports by Cephalon Market Research Department.

FENTORA® Represents a Small Fraction of Opioid Prescriptions

- 204 million prescriptions for opioids in the US
- ACTIQ®, Generic Forms of ACTIQ, and FENTORA represent 0.2% of those prescriptions





FENTORA has been prescribed by 5900 physicians

OTFC = Oral transmucosal fentanyl citrate.

Controlled Launch Plan Associated With Expanded Indication

- At launch, commit within RiskMAP to limit face-to-face detailing to current FENTORA® prescribers (~ 6,000)
- After 12 mo, assess safety and surveillance information and review with FDA
  - If safety data allow, expand to additional ~ 6,000 prescribers
- Additional stepwise expansions up to a maximum of ~ 30,000 provided safety data allows

FENTORA® RiskMAP Tools to Minimize Abuse and Diversion

Labeling and policy

- Schedule II
- Package Insert
- Carton label
- Medication Guide
- RFID
- e-Pedigree

Print communications

- Introductory letters to Drug Diversion Authorities
- Core Visual Aid (CVA) with pt tear sheet
- Patient selection CVA
- Tamper-resistant Rx pads
- Patient use kit with safety card
- Pharm Alert
- SECURE reprint folder
- ESP tool kit
- PROTECT initiative
- Book: “Responsible Opioid Prescribing” by Fishman & FSMB

In-person communications and Distance-learning initiatives

- Sales force interactions
- Cephalon speaker programs
- Emerging Solutions in Pain (ESP)
- PROTECT initiative
- Independent CME

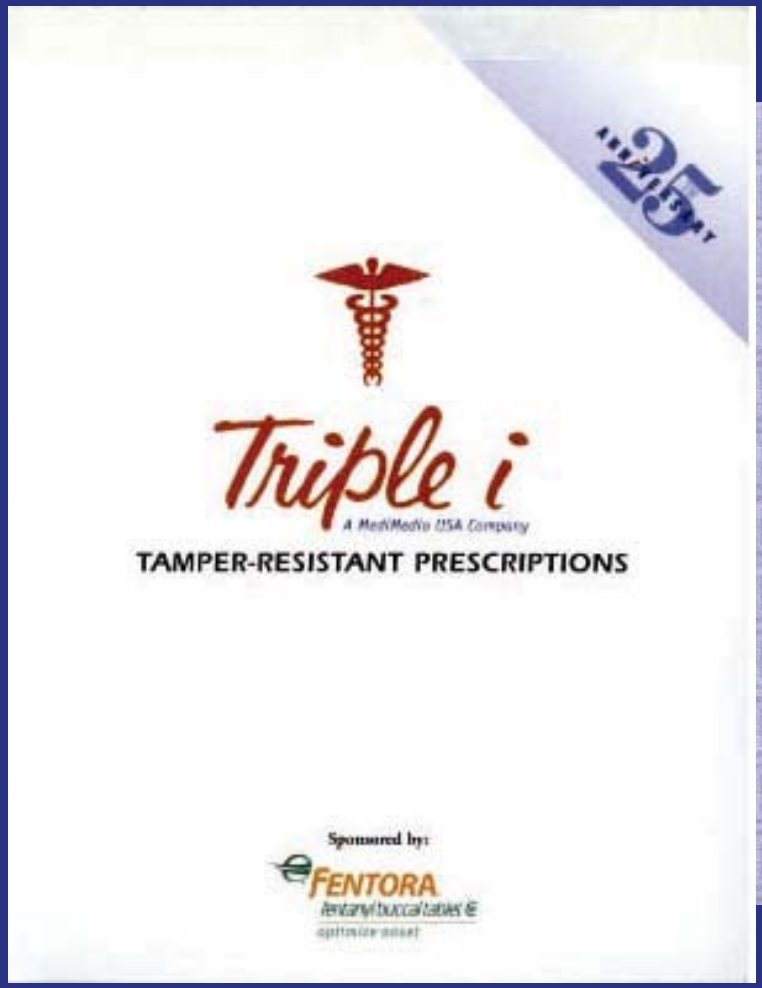
Computer-based initiatives

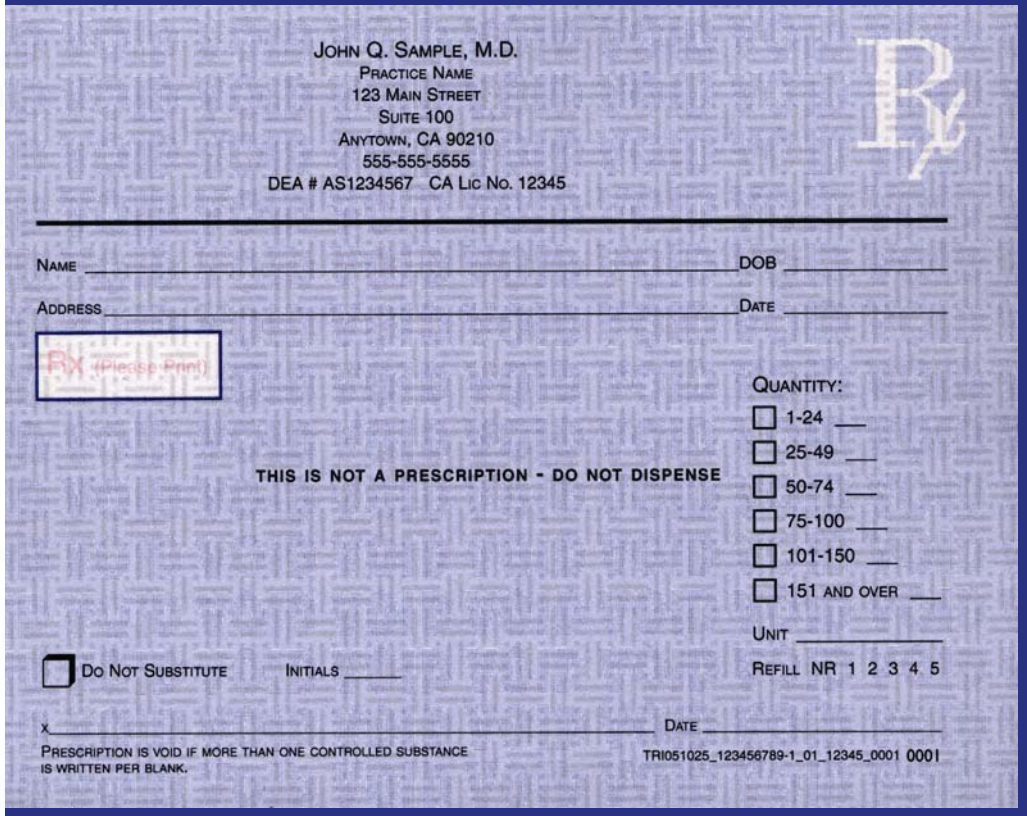
- SECURE Web site
- ESP Web site and tool kit
- Principles in Rational Opioid Therapy: Education, Collaboration & Translation (PROTECT)

FENTORA® RiskMAP
Radio Frequency Identification (RFID)

- Designed to track shipments of medication
  - Tagging cases and pallets of FENTORA
- Automatic identification method relying on storing and remotely retrieving data using RFID tags
- Increases speed and accuracy with which inventory can be tracked and traced
- Carton level tagging Q1 2009

FENTORA® RiskMAP
Triple-I Tamper-Resistant Prescription Pads





FENTORA® RiskMAP
Emerging Solutions in Pain (ESP) Continuing Medical Education Program

- Initiative developed to address critical issues in pain management
- Provides guidance on implementing best practice techniques
  - Understanding federal and state regulations
  - Evidence-based scientific data
  - Validated tools
  - Content driven by leading pain and addiction medicine experts

FENTORA® RiskMAP
Emerging Solutions in Pain Elements

- Active Web site continually updated with new information and guidance
- Presence at national meetings to provide in-person educational opportunities
- Tool kit
  - Appropriate patient selection
  - Identification of aberrant or drug-seeking behaviors
  - Screening tests to employ when considering starting a patient on opioids
  - Techniques to monitor patients once opioid is prescribed

FENTORA® RiskMAP
Unbranded Cephalon Speaker Programs

Abuse, addiction, and diversion

- Educational slide kit developed by experts in pain and addiction medicine
- Slide kit focuses on
  - Minimizing risks through appropriate patient assessment, comprehensive treatment plans, and proper documentation
  - Optimizing treatment while complying with laws and regulations

Educational Initiatives for the Public and the Medical Community

- Partnership for a Drug-Free America
  - Teen abuse of prescription pain medications
- National Pain Foundation
  - Safeguarding medications
  - Effect of pain medication abuse
- American Pain Foundation
  - Safe and appropriate use of opioids
- Federation of State Medical Boards
  - Co-sponsored “Responsible Opioid Prescribing”

FENTORA® RiskMAP
Comprehensive Surveillance and Assessment

- Surveillance systems
  - RADARS, DAWN, DAWN Live!, AAPCC
- Review of prescribing data
- Media monitoring
- Internal reviews
  - FENTORA® Safety Group
  - Corporate Safety Board
- External reviews
  - RiskMAP Advisory Committee
  - FDA

FENTORA® RiskMAP
Interventions

- Inform appropriate authorities about any illegal activity
- Abuse
  - Community-based education
  - Local physician and pharmacist education

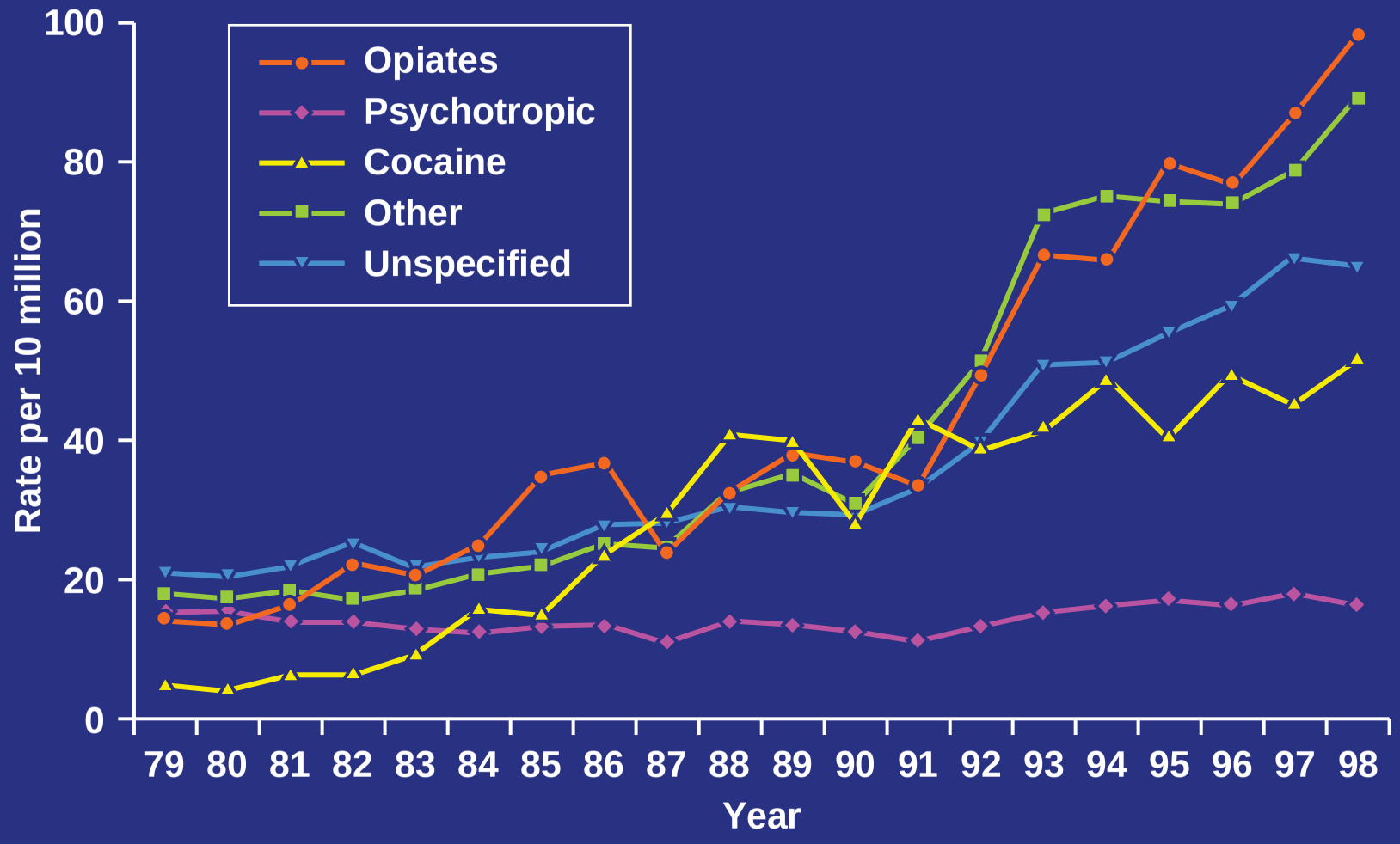
Summary

- Cephalon recognizes issue of prescription opioid abuse in the United States
- Risk of abuse and diversion can be effectively mitigated with
  - Controlled growth
  - Prescriber education
  - Supply chain control
  - Surveillance and intervention

FENTORA® RiskMAP
Mitigating Risk of Overdose

Juergen Schmider, MD, PhD

Unintentional Drug Poisoning Mortality Rates by Drug Category



Paulozzi LJ, et al. *Pharmacoepidemiol Drug Saf.* 2006;15:618-627.

FENTORA® RiskMAP
Mitigating Risk of Overdose

Risks	Goals
Overdose	Should be used only by opioid-tolerant individuals
	Unintended (accidental) exposure should not occur
	Dosage and administration instructions should be provided to and understood by anyone who may prescribe, dispense, or use FENTORA

FENTORA® RiskMAP
Key Messages

- Safety messages
  - Use only in opioid-tolerant patients
  - Do not use for acute pain, postoperative pain, or headache/migraine
  - Should only be prescribed by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids
  - Do not convert on a mcg per mcg basis from ACTIQ® to FENTORA®
  - Do not substitute a FENTORA prescription for other fentanyl products
  - Keep FENTORA in a safe and secure place
- Dosing instructions
  - Use only 1 more dose of FENTORA after 30 min if necessary
  - Wait at least 4 hours before treating another BTP episode
  - Do not treat more than 6 BTP episodes per day
  - Continue taking your around-the-clock opioid medicine

FENTORA® RiskMAP
Mitigation Strategy

- Targeted education and outreach
- Reminder systems
- Performance-linked access system

FENTORA® RiskMAP
Targeted Education and Outreach

Print Communications

- Package Insert
- Medication Guide (originally patient leaflet)
- Blister label
- Carton label
- Patient Kit
- RiskMAP Core Visual Aids
- Educational introductory letters to HCPs
- Catalina newsletter
- Auxiliary Rx labels
- Pharmacy checklist/stamp
- Pharm Alert
- Independent CME (ESP)
- Prescriber education targeted to members of professional societies
- Physician education to Pain Centers of Excellence
- Pharmaceutical compendia
- Counseling aids
- Secure Resource Folder
- Healthcare education (PROTECT)
- Book on appropriate opioid prescribing

In-Person Communications

- Risk management training to field reps (Sales Force interactions)
- Speaker Programs
- Speaker training
- Independent CME (ESP)
- Healthcare education (PROTECT)

Computer-Based Initiatives

- SECURE Web site
- Independent CME (ESP)
- Healthcare education (PROTECT)
- Counseling messages

Continuing Education & Distance-Learning Initiatives

- Independent CME (ESP)
- Healthcare education (PROTECT)

FENTORA® RiskMAP
Reminder Systems

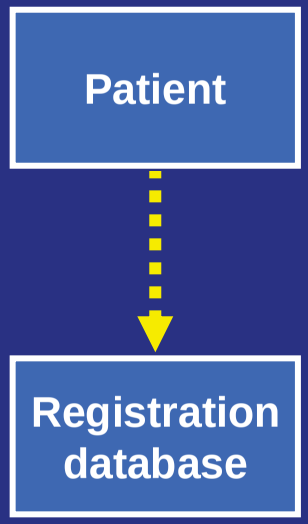
- Pharmacy checklist/stamp
- Safety letters responding to reports of inappropriate patient selection and/or dosing
- NotifyRx™ messaging (pilot)
- Safety activation card (pilot)

Reminder Systems
NotifyRx™

Before dispensing FENTORA:
- ☑ ensure that patient is opioid-tolerant
- ☑ print the reminder auxiliary label and provide to the patient
- ☑ counsel the patient about the proper use and storage of FENTORA
- ☑ instruct the patient to read the FENTORA Medication Guide

- **Hard stop to the transaction to deliver and reinforce the message**
- **Random override code to acknowledge reading of message**
- **Transaction can be completed**

Reminder Systems
Safety Activation Card

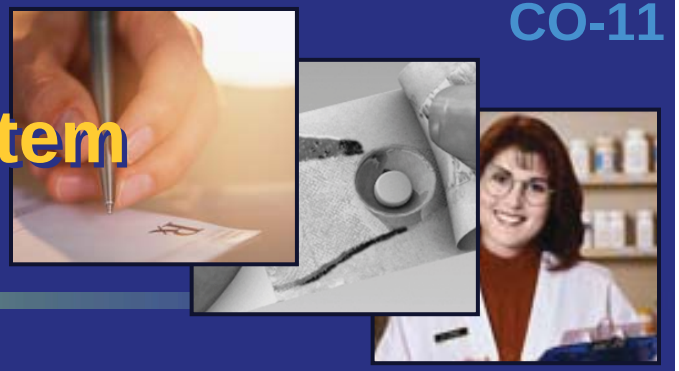


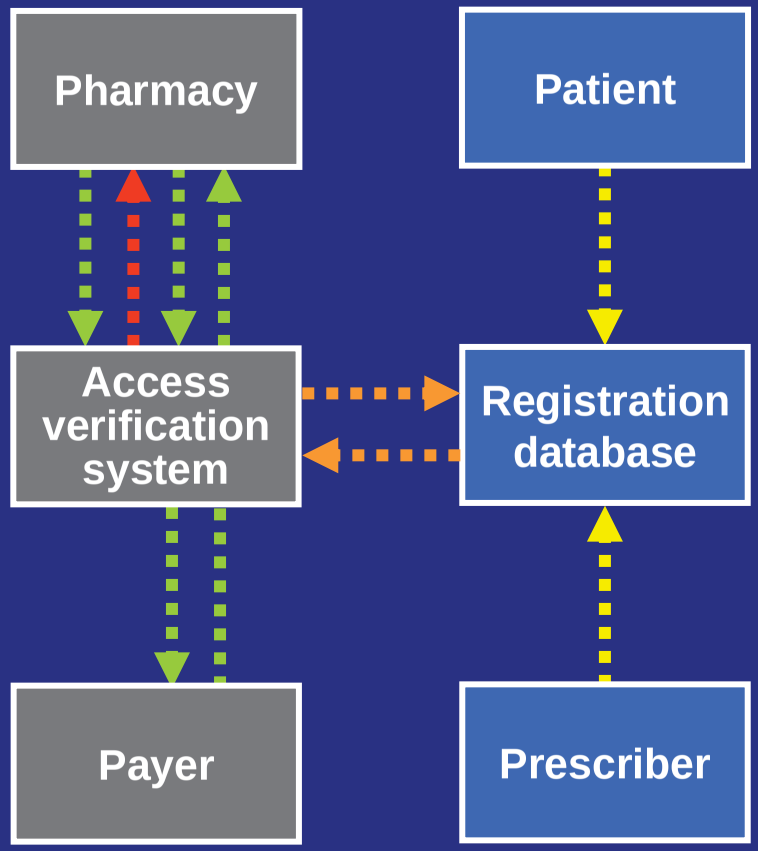
- Pilot program
- Vehicle to deliver key safety messages to the patient
- Patient to call a 1-800 number and listen to key safety information for FENTORA®

FENTORA® RiskMAP
Performance-Linked Access System

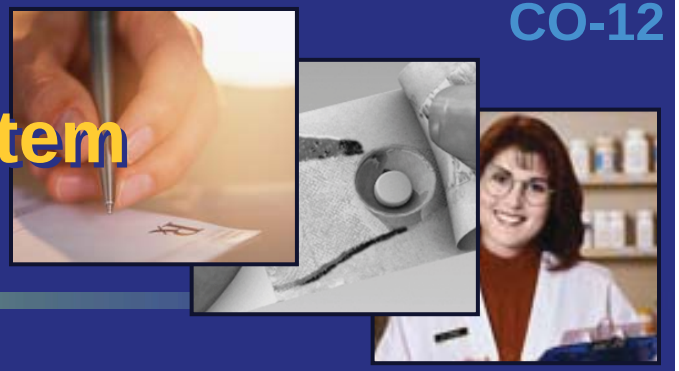
- COntrolled Voice Enrollment Registration System (COVERS™)
  - Minimizing risk
  - Maintaining patient access

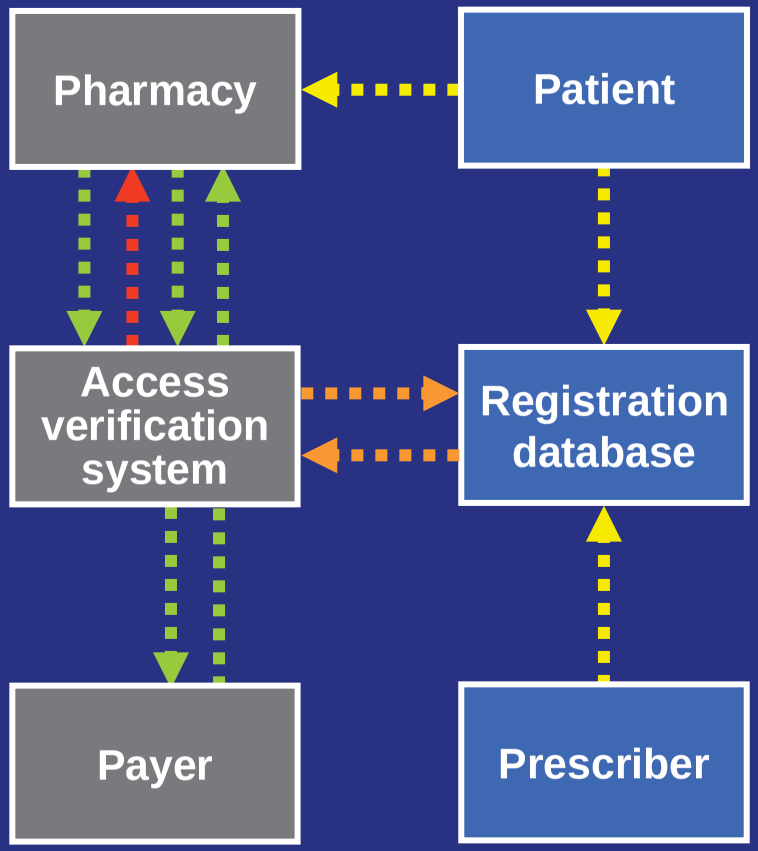
Performance-linked Access System
COVERS™





Performance-linked Access System
COVERS™

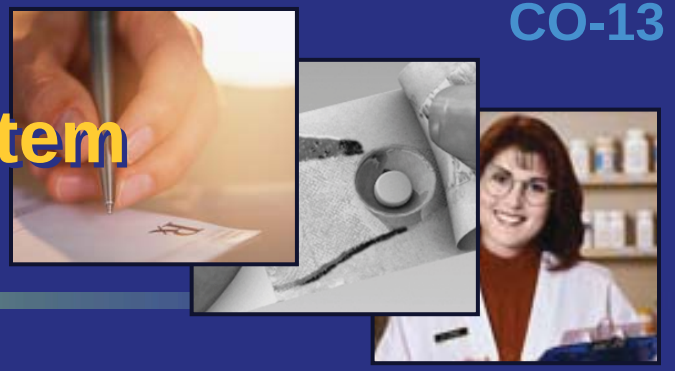


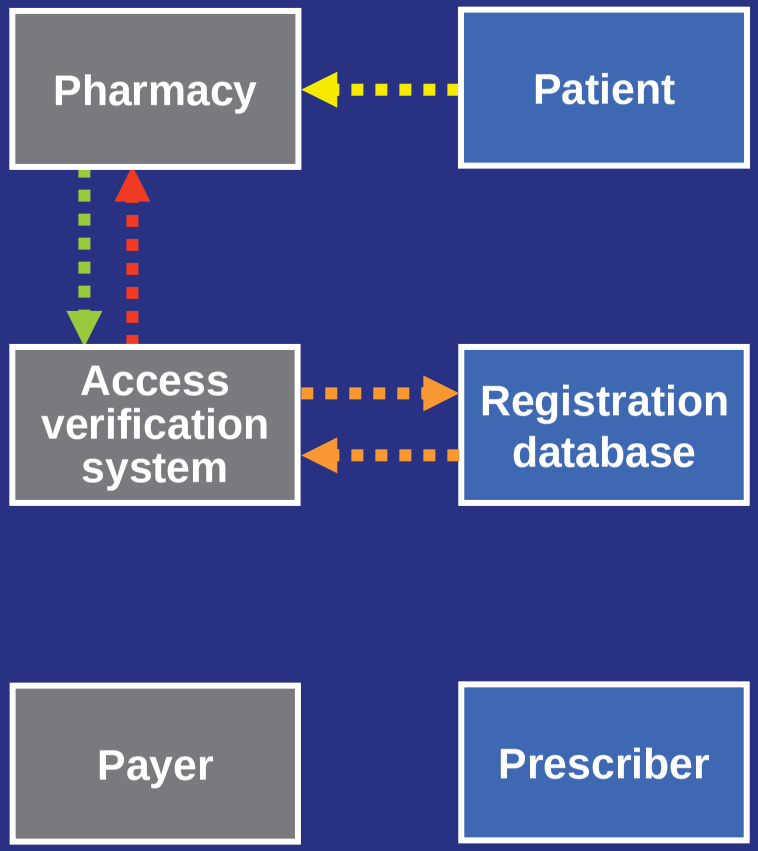


Before dispensing FENTORA:

- ☑ ensure that patient is opioid-tolerant
- ☑ print the reminder auxiliary label and provide to the patient
- ☑ counsel the patient about the proper use and storage of FENTORA
- ☑ instruct the patient to read the FENTORA Medication Guide

Performance-linked Access System
COVERS™





FENTORA cannot be dispensed:

- ☑ notify patient to register using Safety Activation Card
- ☑ notify prescriber to register

FENTORA® RiskMAP
Evaluate Effectiveness

- Pharmacovigilance (adverse event reporting)
- Surveys
  - Patient, physician, pharmacist
- Review of prescribing data (IMS)

FENTORA® RiskMAP Interventions

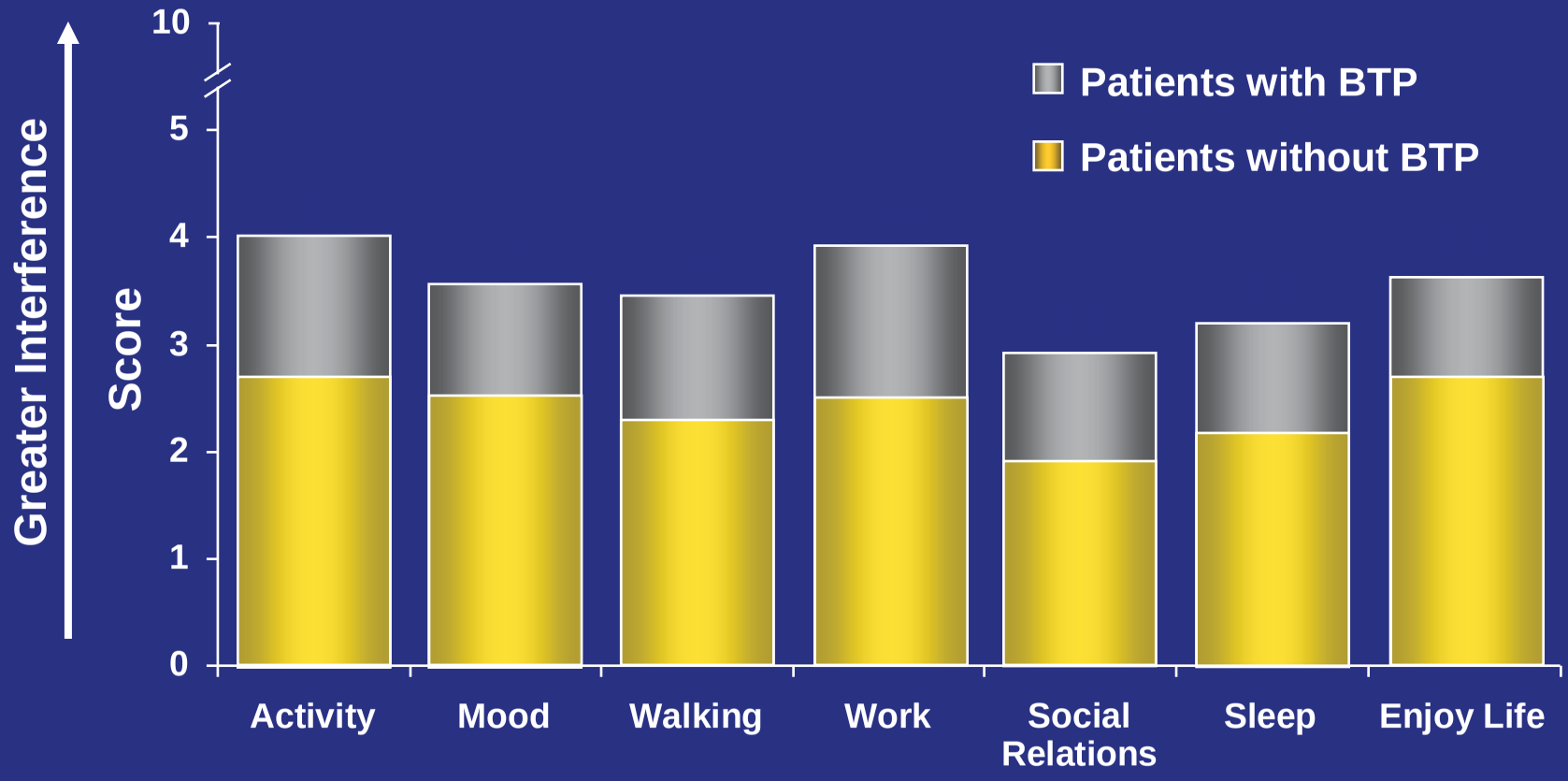
- Dear Healthcare Professional letter
- Label change
- Core safety message adjustment
- Message dissemination tool adjustment
- Targeted education of individual prescribers with apparent inappropriate prescribing patterns
- Removing prescriber from registry

FENTORA® RiskMAP
Summary

- Comprehensive tools to preempt abuse and diversion as well as to monitor for emerging signals and intervene
- An innovative registration system that provides the advantages of a registry while maintaining appropriate access to patients
- Favorable benefit-risk balance: keeping risks at a minimum while preserving patient benefits

BTP Adversely Affects Function and Quality of Life

Brief Pain Inventory Functional Component Scores



BPI = Brief Pain Inventory.
Portenoy RK, et al. *Pain*. 1999;81:129-134.

Application Site Adverse Events
Safety Analysis Set

Preferred term	Patients, % N = 941
Patients with application site AEs	116 (12)
Irritation	37 (4)
Pain	31 (3)
Ulcer	22 (2)
Erythema	16 (2)
Reaction	7 (< 1)
Vesicles	7 (< 1)
Anesthesia	4 (< 1)
Discoloration	3 (< 1)
Bleeding	2 (< 1)
Discomfort	2 (< 1)
Swelling	2 (< 1)
Nodule	1 (< 1)
Paresthesia	1 (< 1)

Medical History and Age by Aberrant Drug-related Behavior

Safety Analysis Set

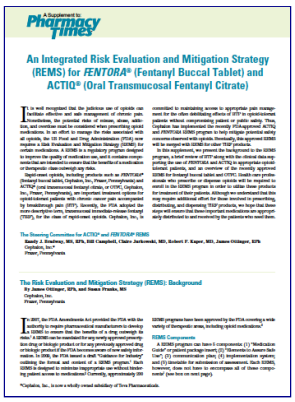
Medical history	Patients with aberrant drug-related behavior, n (%) Yes n = 156	No n = 785	Odds ratio (all/none)	95% CI (all/none)	*p* value
Anxiety					
Yes	58 (37)	272 (35)	1.1162	0.8, 1.6	0.5454
No	98 (63)	513 (65)	1.0000	1.0, 1.0	—
Depression					
Yes	78 (50)	438 (56)	0.7922	0.6, 1.1	0.1845
No	78 (50)	347 (44)	1.0000	1.0, 1.0	—
Psychotic sx's / mania					
Yes	9 (6)	21 (3)	2.2274	1.0, 4.8	0.0499
No	147 (94)	764 (97)	1.0000	1.0, 1.0	—
Age group					
≤ 42 years	55 (35)	189 (24)	2.5178	1.5, 4.3	0.0006
> 42 to ≤ 49 years	50 (32)	209 (27)	2.0699	1.2, 3.6	0.0072

EXHIBIT 85

Back to issue

An Integrated Risk Evaluation and Mitigation Strategy (REMS) for FENTORA ® (Fentanyl Buccal Tablet) and ACTIQ® (Oral Transmucosal Fentanyl Citrate)

JANUARY 13, 2012


A Supplement to Pharmacy Times

An Integrated Risk Evaluation and Mitigation Strategy (REMS) for *FENTORA*® (Fentanyl Buccal Tablet) and ACTIQ® (Oral Transmucosal Fentanyl Citrate)

The Steering Committee for ACTIQ® and FENTORA® REMS

The Risk Evaluation and Mitigation Strategy (REMS): Background

It is well recognized that the judicious use of opioids can facilitate effective and safe management of chronic pain. Nonetheless, the potential risks of misuse, abuse, addiction, and overdose must be considered when prescribing opioid medications. In an effort to manage the risks associated with all opioids, the US Food and Drug Administration (FDA) now requires a Risk Evaluation and Mitigation Strategy (REMS) for certain medications. A REMS is a regulatory program designed to improve the quality of medication use, and it contains components that are intended to ensure that the benefits of a medication or therapeutic class outweigh any risks.

Rapid-onset opioids, including products such as *FENTORA*® (fentanyl buccal tablet, Cephalon, Inc., Frazer, Pennsylvania) and ACTIQ® (oral transmucosal fentanyl citrate, or OTFC, Cephalon, Inc., Frazer, Pennsylvania), are important treatment options for opioid-tolerant patients with chronic cancer pain accompanied by breakthrough pain (BTP). Recently, the FDA adopted the more descriptive term, transmucosal immediate-release fentanyl (TIRF), for the class of rapid-onset opioids. Cephalon, Inc., is committed to maintaining access to appropriate pain management for the often debilitating effects of BTP in opioid-tolerant patients without compromising patient or public safety. Thus, Cephalon has implemented the recently FDA-approved ACTIQ and FENTORA REMS program to help mitigate potential safety concerns observed with opioids. Eventually, this approved REMS will be merged with REMS for other TIRF products.

In this supplement, we present the background to the REMS program, a brief review of BTP along with the clinical data supporting the use of *FENTORA* and ACTIQ in appropriate opioid-tolerant patients, and an overview of the recently approved REMS for fentanyl buccal tablet and OTFC. Health care professionals who prescribe or dispense opioids will be required to enroll in the REMS program in order to utilize these products for treatment of their patients. Although we understand that this may require additional effort for those involved in prescribing, distributing, and dispensing TIRF products, we hope that these steps will ensure that these important medications are appropriately distributed to and received by the patients who need them.

To view the full supplement, please click here or the image to the right.

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EXHIBIT 86

Medscape

CME

Pharmacologic Management of Breakthrough or Incident Pain

Authors: Authors: Michael J. Brennan, MD; Steven D. Passik, PhD; Kenneth L. Kirsh, PhD Writer: Brigid Kane
Faculty and Disclosures

THIS ACTIVITY HAS EXPIRED

Introduction

Chronic pain can be defined as unrelenting, intractable pain commonly caused by injury or disease, and often occurs after healing is complete; chronic pain can also exist in the absence of disease. According to pain researchers John Loeser and Ronald Melzack, chronic pain is distinguished from acute pain in that therapies for the former only provide transient relief and do not resolve the underlying pathologic and healing processes: "Chronic pain will continue when treatment stops."[1] The American Pain Society has adopted the definition of chronic pain offered in the *Textbook of Pain* (4th edition, 1999):[2]

> "Generally considered to be pain that lasts more than 6 months, is ongoing, is due to non-life-threatening causes, has not responded to current available treatment methods, and may continue for the remainder of the person's life."

The intensity and persistence of chronic pain may be influenced by physical, emotional, and social and other environmental stresses. Of note, the intensity of chronic pain may not be related to the extent of tissue injury or other quantifiable pathology, and the persistence of pain may be due to factors

other than the initial tissue damage or insult that triggered the onset of pain.[1]

Chronic pain of moderate to severe intensity is typically associated with advanced stages of cancer and may be due to tumor invasiveness or metastasis, or to current or prior chemotherapy or radiotherapy.[3] Moderate to severe chronic pain is also encountered outside of the cancer setting, and may be associated with noncancer disorders such as arthritis, sickle cell anemia, low back pain, headaches, neuralgia, and fibromyalgia.[1,4,5] Frequently, patients with chronic cancer or noncancer pain experience relatively short episodes of worsening pain, which are referred to as breakthrough or episodic pain.[6,7] Thus, chronic pain can be thought of as consisting of two components: a relatively constant component (baseline pain) and an intermittent component superimposed on the baseline pain (breakthrough pain).

Regardless of its cause, chronic pain negatively impacts quality of life, often profoundly affecting mobility, mood, personality, and social relationships. Patients typically experience concomitant decreased overall physical and mental functioning, depression, sleep disturbance, and fatigue.[4,8,9] Because of the multidimensional impact of chronic pain (ie, severely reduced physical, psychological, and social well-being), pain is only one of many issues that must be addressed in the management of patients with chronic pain. Optimal pain

management of patients with chronic pain frequently requires both pharmacologic and nonpharmacologic interventions. Nevertheless, pharmacologic therapy remains the foundation of cancer pain management. Effective pain management is best achieved by a team approach involving patients, their families, and healthcare providers.[10] It is important to note that this activity is not a comprehensive review of all chronic pain management strategies; rather, this article considers only the pharmacologic management of moderate to severe chronic pain, including breakthrough pain, in cancer and other patient populations.

The use of opioid analgesics for the treatment of chronic pain represents a key component of a comprehensive care program. Indeed, long-acting opioids have been shown to improve the quality of life in patients with chronic pain of both cancer and noncancer etiology.[11] Opioid analgesics are considered the cornerstone of cancer pain management, especially for the relief of moderate to severe chronic pain.[12,13] Opioids act by blocking the repeated transmission of pain signals and the resulting neural remodeling underlying the pathophysiology of chronic pain (discussed in detail below). Although the appropriate use of opioids can lead to effective control of chronic pain, including breakthrough pain, these drugs do not wholly eliminate the pain. The goal of therapy is the control of pain and rehabilitation so that the patient can regain some degree of their former

functional status. Opioids are administered with the aim of easing or reducing pain and suffering while improving physical and mental functioning.[4]

For a variety of reasons, chronic pain is often undertreated, particularly in the noncancer patient population. Opioids are the strongest pain relievers available, but because of their potential for abuse, they are classified as scheduled drugs by the US Drug Enforcement Agency (DEA), under the Controlled Substances Act of 1970. The continued stigmatization of opioids and their prescription, coupled with often unfounded and self-imposed physician fear of dealing with the highly regulated distribution system for opioid analgesics, remains a barrier to effective pain management and must be addressed. Clinicians intimately involved with the treatment of patients with chronic pain recognize that the majority of suffering patients lack interest in substance abuse. In fact, patient fears of developing substance abuse behaviors such as addiction often lead to undertreatment of pain. The concern about patients with chronic pain becoming addicted to opioids during long-term opioid therapy may stem from confusion between physical dependence (tolerance) and psychological dependence (addiction) that manifests as drug abuse. This misunderstanding can lead to ineffective prescribing, administering, or dispensing of opioids for chronic pain, resulting in undertreatment.

Nevertheless, the barriers to effective pain management are slowly breaking down, especially in the noncancer patient setting. Jointly, the DEA and 21 health organizations, including the American Medical Association, have written a consensus statement that supports the use of opioid analgesics for the treatment of pain while recognizing their potential for abuse.[14] In addition, many professional organizations, including the World Health Organization (WHO), the American Pain Society, and the American Medical Directors Association, have independently issued consensus statements supporting the use of opioids in select patients with chronic noncancer pain based on accumulated evidence indicating that patients treated with opioids for chronic noncancer pain show improvement in analgesia and/or level of function.

Thus, although state and local laws restrict the medical use of opioids to relieve pain, awareness of and adherence to these guidelines enables the physician to use these effective agents in the management of chronic pain. Indeed, the Joint Committee on Accreditation of Healthcare Organizations (JCAHO), which accredits nearly 80% of the hospitals in the United States, has developed standards for assessment and management of pain for patients and has begun monitoring compliance with these standards.[15]

EXHIBIT 87

CME

Breakthrough Pain: Treatment Rationale With Opioids

Authors: Daniel S. Bennett, MD, DABPM Faculty and Disclosures

THIS ACTIVITY HAS EXPIRED

Breakthrough Pain: Treatment Rationale With

Supported by an unre
educational grant f

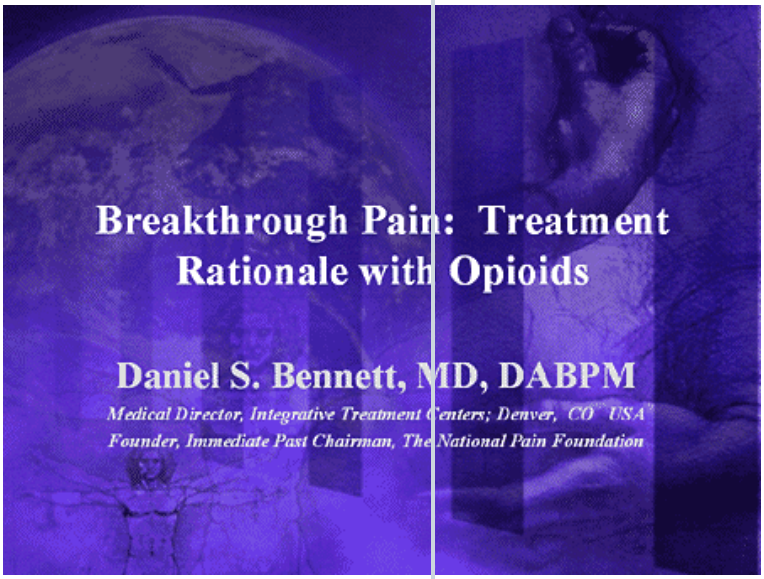
Opioids, Presented by Daniel S. Bennett, MD, DABPM

Breakthrough Pain: Treatment Principles

[CLOSE WINDOW]

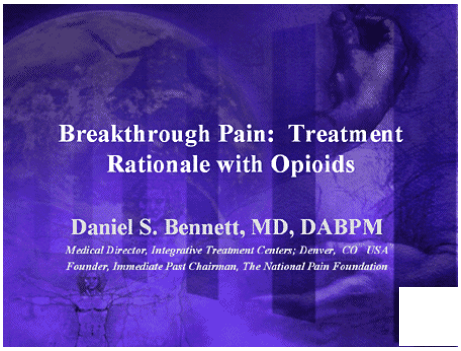
I'm an interventional spine and pain medicine physician who specializes in both pharmacotherapeutic management, as well as invasive management of pain syndromes. My interests include previously operated back, complex regional pain syndromes, the neuropathies, and interstitial cystitis.

Today's discussion is about breakthrough pain and the rational place of opioids for treatment. We'll begin with the concept of pain, the presentation of the person living with pain, and the dynamic state of acute to chronic pain. We will then discuss the concept of breakthrough pain, as well as episodic pain, and conclude with an overview of opioids and their place in the treatment of pain, in general, and specifically breakthrough and episodic pain.



Slide 1.

Breakthrough Pain: Treatment Rationale With Opioids



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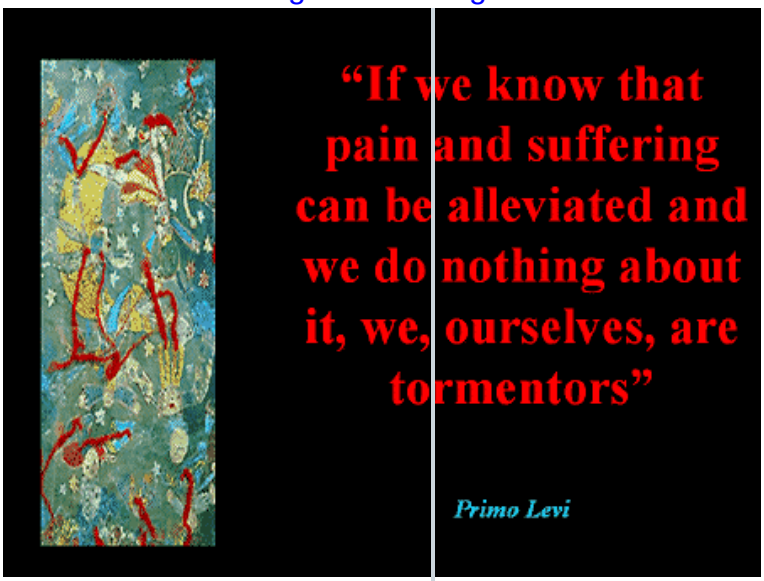
I'd like to begin with a quote by Primo Levi, a concentration camp survivor, physician, and philosopher, which I believe should be the banner for all who treat people living with pain. "If we know that pain and suffering can be alleviated and we do nothing about it, we, ourselves, are tormentors."



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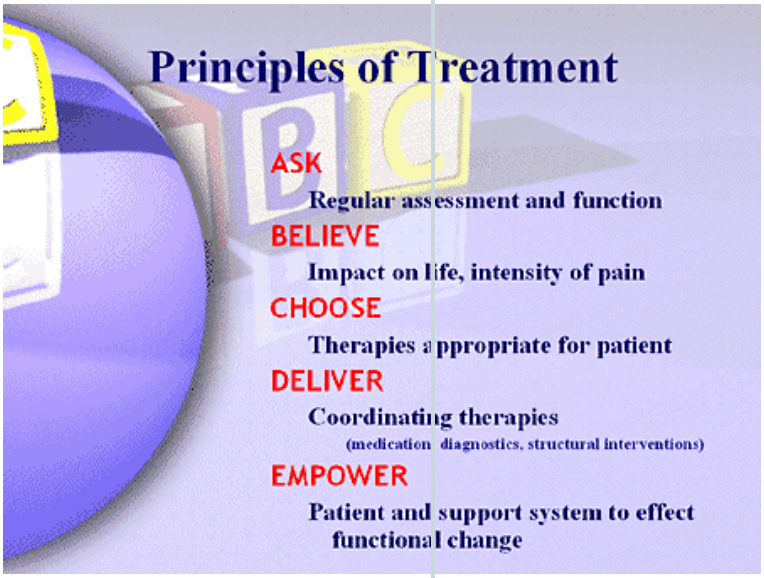
Our discussion of pain should begin with a few basic principles that apply to pain treatment in general. First, we must ask the patient if he or she is in pain and, if so, to quantify the pain with a special emphasis on the individual's function. This is then regularly assessed at each interaction with the patient.

Next, we must understand what the impact of pain is on his or her life. We then must choose the appropriate diagnostic and therapeutic steps that meet that particular patient's needs. Then we must deliver what we promised, coordinating therapies amongst varied specialists, as appropriate. We cannot all be expert in every area such as neurosurgery, physiatry, or psychology. It

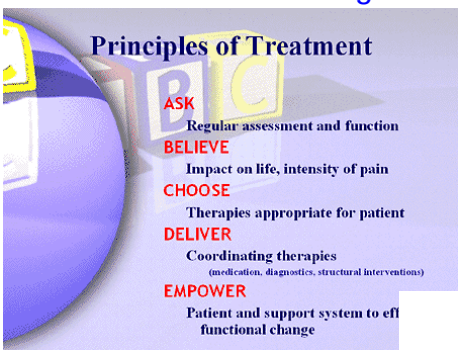


Slide 3.

Principles of Treatment

is in the delivery of the diagnostic and therapeutic plan that we pull together a virtual team of professionals to meet the needs of the individual patient.

All of this is necessary so that we can, most importantly, empower the person to take control of his or her pain. Failure to empower the person will undermine the most sincere therapeutic plan.



Pain: Manifestations and Types

We hear much about the pain signal. Thousands of references can be found describing the various parts and pathways involved in the pain signal and the eventual transmission to the brain. Unfortunately, we do not have a way of directly measuring the pain signal. It is important to understand some of the layers that occur between the pain signal and the presentation of the individual living with pain.

Cultural influences certainly play a role. I trained in Miami, Florida, where there was huge ethnic diversity. On the obstetrical deck, where at the time 22,000 to 25,000 deliveries occurred per year, one could see a bay with a woman of Haitian descent crying loudly and becoming more animated with each centimeter of dilation.

In the very next bay you could see a woman of Korean descent, in the same stage of labor, but without so much as a sound. Guess who quickly received the epidural or IV medication? Same pain signal, different representation, based on cultural influences.

Then there are gender differences. My nurses often tell me that men simply

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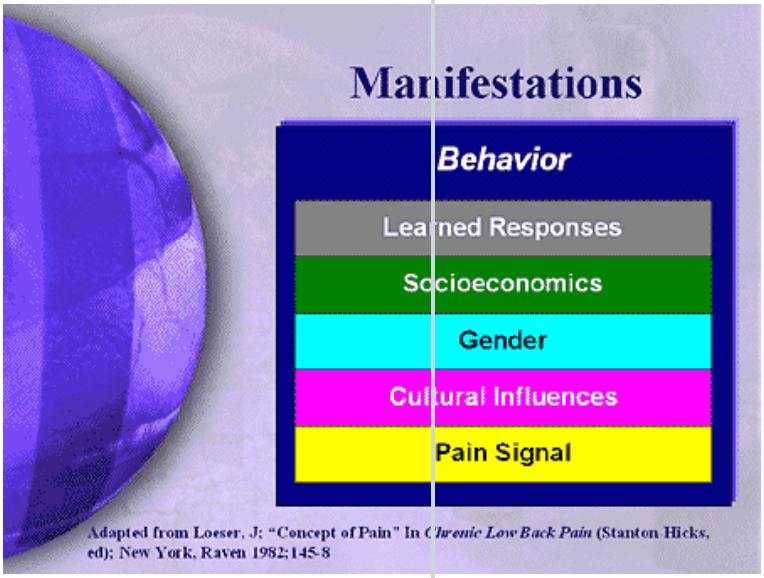

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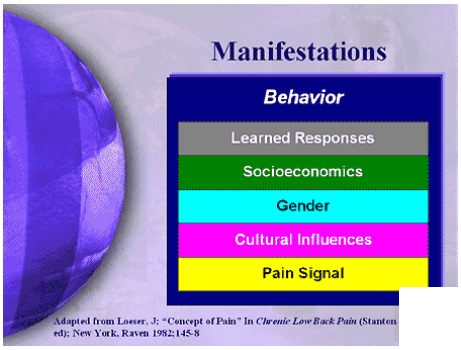
Manifestations



complain more and are more difficult to treat. It is more difficult to get them to do what you want them to do. As a general rule, women are more organized in their presentation of the problem. They often have a working idea as to what is wrong and can categorize their complaints, whereas men tend to be stoic and to generalize complaints rather than exact out a list of symptoms that can then be assessed.

We have all encountered different socioeconomic statuses. A patient whose name adorns the building has a far different reaction to an L5/S1 disk herniation with verticular pain than does the patient who labored to lay the blocks that built the building.

It is important to recognize the degree to which pain adversely affects the patient's ability to function given their means.

Then, there are learned responses. It is a far different experience for a woman to go through the various stages of labor to deliver a healthy child. Although painful, the majority of women would go through the very same experience again and many choose to do so. It is a far different matter to undergo a hysterectomy. Same nerve supply, similar pain pathways, but a far different experience.

To summarize, it is the pain behavior that we see when we meet and examine a person living with pain. It is, therefore, important to recognize what lies above the tentorium. That is what makes similar pathologies quite different among individuals.

Not too long ago pain was thought to be

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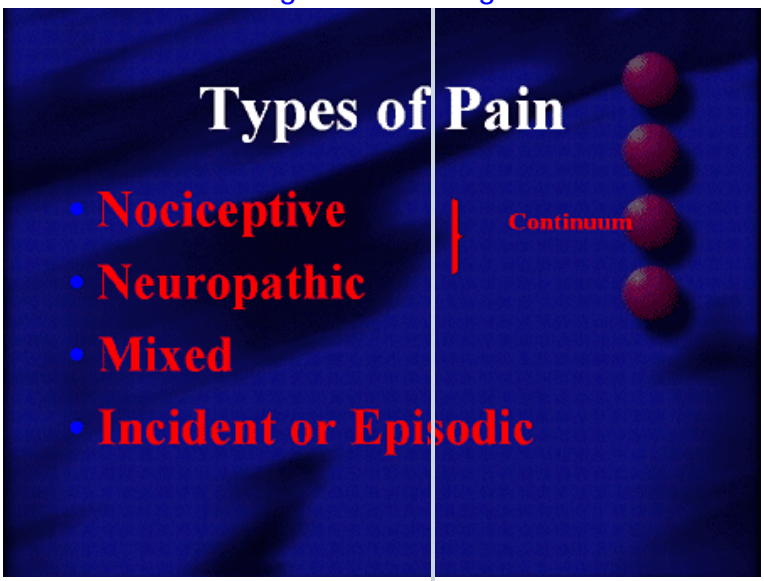
distinct as either nociceptive or neuropathic. What is important to understand, at least conceptually, is the dynamic continuum between the two.

What most often occurs is a combination of nociceptive and neuropathic pain; we refer to this as "mixed pain." We also see incident or episodic pain. In this situation, usually mechanical in nature, nociceptive pain pathways are activated, which occurs quickly and can dissipate as quickly.

An example of this is a bone fracture. If the person stays very still, with good support for the bone involved, little pain may be present. Upon movement, however, a barrage of nociceptive circuits leads to rapid onset of sharp and intense pain.

Incident or episodic pain is unique and should be distinguished from breakthrough pain, which is a pain signal that exceeds baseline or the persistent pain and, as a characteristic, is variable in both onset and intensity.

Now I'd like you to focus on the dynamic continuum between acute and chronic pain. Arbitrarily, chronic pain was defined as pain persisting in duration of 6 months or greater. It is important to understand that acute to chronic is not a matter of time but rather a complex series of physiologic processes that occur.



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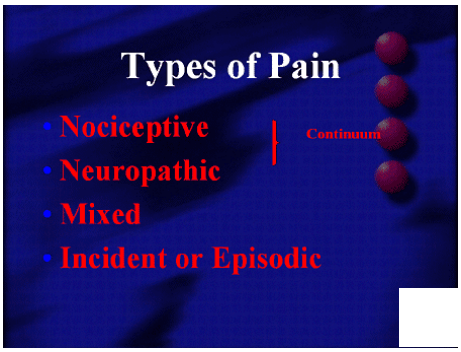
Types of Pain



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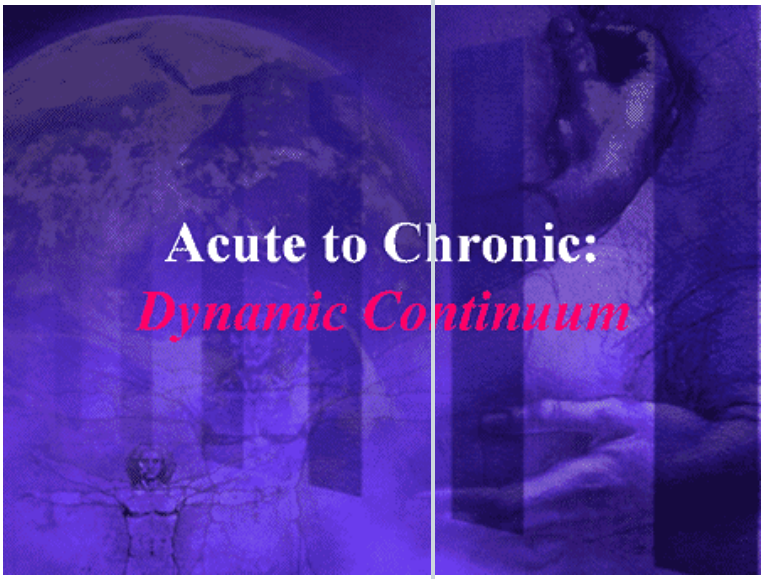

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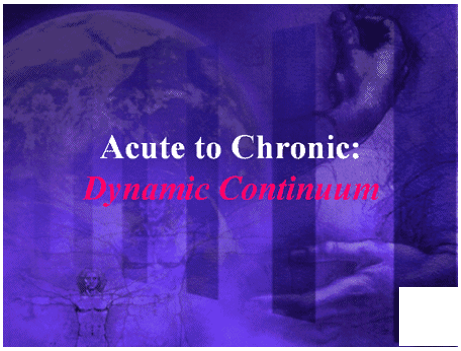
Acute to Chronic: Dynamic Continuum



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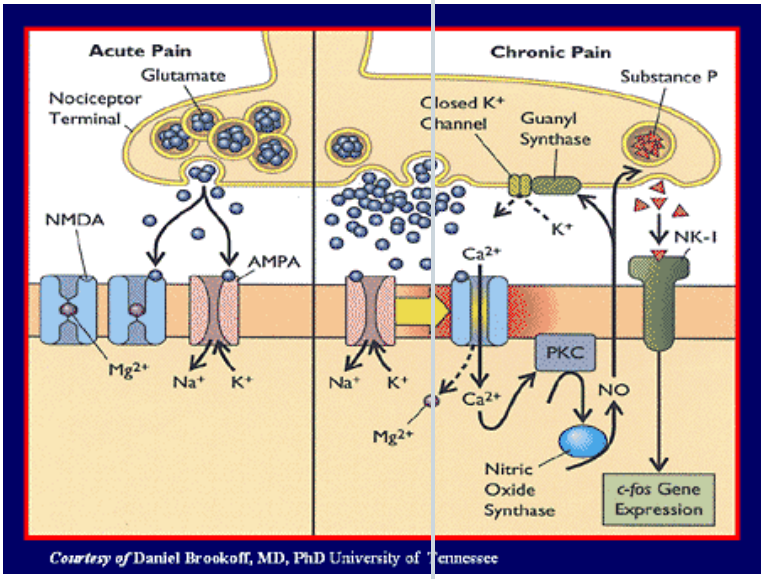
As an introduction, this graphical illustration portrays the general mechanisms that occur between the acute or nociceptive signal and the chronic or neuropathic signal.



In the acute state, the nociceptor is activated through A delta fibers after transduction of a sensory stimulus.

The primary neurotransmitter is glutamate, which is released and activates channels on the dorsal root ganglion (DRG) interface. Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-mediated sodium-potassium channels are activated allowing sodium entry with potassium efflux.

Potassium then negatively feeds back to stabilize the nociceptor membrane, thereby decreasing glutamate discharge. This negative feedback loop is also facilitated by sympathetic discharge, which in the normal state causes vasoconstriction, in part decreasing secondary inflammatory mediators.

Although receptive to glutamate, the N-methyl-D-aspartate acid (NMDA)-

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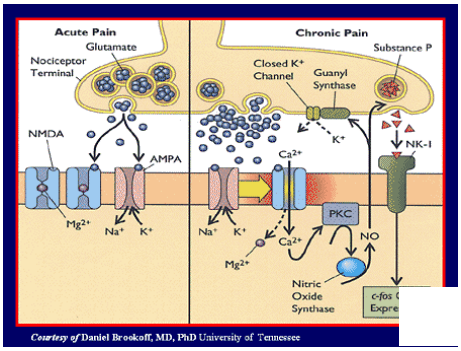

mediated channels remain relatively inactive, plugged by magnesium.

In the chronic state, with pronounced input glutamate bombardment can occur. A transformation can occur in which the magnesium plug is lost, and NMDA channels are then activated. This leads to a transformation of the signal from a predominantly sodium-potassium flux to a calcium flux. This then leads to increased intracellular calcium, which via protein kinase C activation, leads to increased nitric oxide synthase with a resultant production of nitric oxide.

Nitric oxide then diffuses out of the dorsal root to the nociceptor terminal where it shuts off the potassium channels via activation of guanyl synthase, leading to an interruption of the normal negative feedback loop. This mechanism is often referred to as "sensitization."

In addition, nitric oxide stimulates the release of substance P, which in turn acts via neurokinin-1 receptors to stimulate formation of early oncogenes such as *c-fos*. Once this occurs, a permanent change affects the cell.

Now while this is occurring at the nociceptor DRG terminal, other changes, both segmentally (such as Y-dynamic neuron recruitment) and supersegmentally, occur to begin the sensitization process of the neuraxial structures. Eventually, higher centers in the thalamus and beyond are activated, with evidence accumulating that in any of these structures dynamic changes occur, analogous to the ones mapped at the nociceptor DRG complex. Thus, acute to chronic pain is not a time issue but an issue of process.

With the centralization of pain, one can see changes in the periphery. The usual direction of the signal is one of afferent discharge. This occurs from the periphery to the cord, then up to higher brain centers for processing.

In the sensitized state, normal dromic input -- that is, signals that are afferent -- also is met with abnormal antidromic input -- that is, signals that originate in the DRG and are sent to the periphery. This leads to discharge of substance P, which stimulates the degranulation of mast cells, which leads to discharge of the mediators of inflammation. The accumulation of these mediators leads to vasodilation and consequential edema. This is further perpetuated by the release of calcitonin gene-related peptide (CGRP), which also produces vasodilation.

This cascade of events is the model for neurogenic edema, often seen in such diverse states as diabetic neuropathy, dorsal nerve root injury, complex regional pain syndromes, and postherpetic neuralgia.

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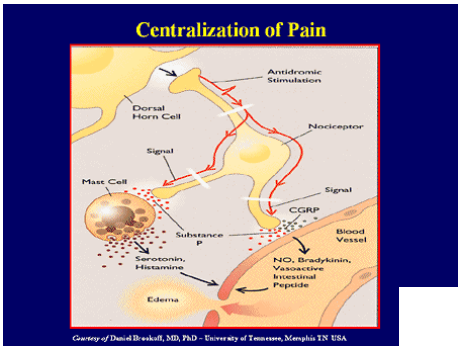
Centralization of Pain



Balanced Analgesia

It is important when treating pain states to remember the dynamic continuum of acute to chronic pain transmission. Just as the physiologic processes governing acute to chronic pain are not time dependent but process dependent, the paradigm of treatment should not be based on a time continuum.

Cognitive behavioral therapy, along with other aspects involving spiritual through complementary modalities, forms a basis

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upon which treatment of the individual is accomplished.

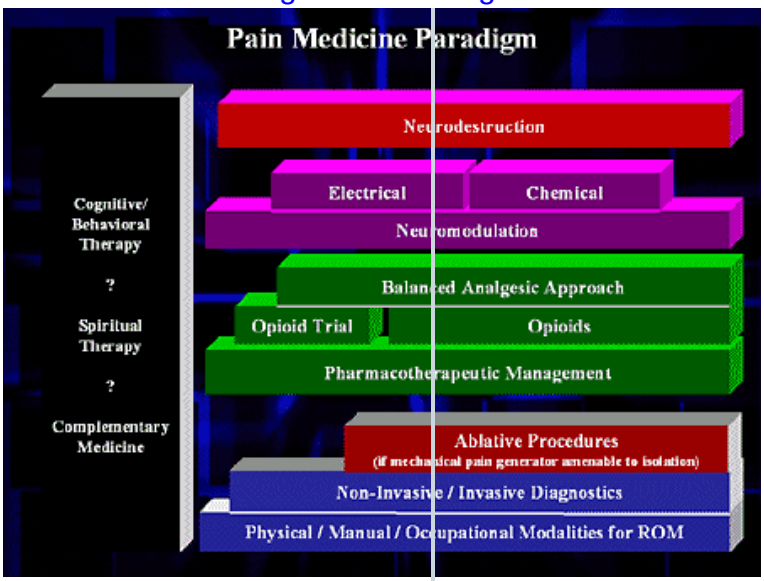
If we forget that what lies above the tentorium is just as important as the physiologic processes generating the pain signal, we miss the treatment of the individual, often at the expense of a suboptimal functional outcome.

Certainly, mobilization is crucial to prevent the often serious sequelae of myofascial pain. This should be facilitated as much as possible while a definitive diagnosis or diagnoses are sought. Combinations of invasive and noninvasive diagnostics, such as radiographic studies and diagnostic injections, can be used to narrow the diagnoses. It is crucial to realize that a definitive diagnosis is always optimal, as targeted therapeutics are more effective in producing a functional outcome.

Certainly, if mechanical diagnoses are found -- as an example a segmental facet arthropathy producing painful dysesthesias and consequential muscular spasm and dysfunction -- then ablative procedures are often indicated. In this example, radiofrequency neurolysis or rhizotomy.

It is important to remember that pharmacotherapeutic interventions also may be necessary -- either to allow mobilization, or to palliate the pain signaling while a definitive diagnosis is sought.

In this process one must decide when, or even if, an opioid is indicated. This process should rest on a well-orchestrated opioid trial to prove or disprove the effectiveness of opioids on



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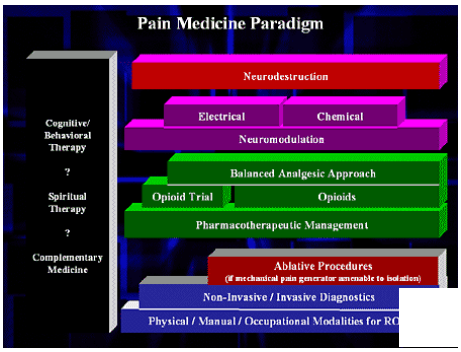
Pain Medicine Paradigm



the individual pain presentation. To reduce side effects and to reduce the formation of chronic circuits, one should think of pharmacotherapeutics in a balanced analgesia approach.

Of course, one also should consider when advanced therapeutics are indicated. Electrical neuromodulation -- such as spinal-cord stimulation, nerve-root stimulation, peripheral-nerve stimulation -- or chemical neuromodulation -- such as intrathecal or intraventricular medication delivery systems -- can be quite effective. Their use should not be based on repetitive failures of the less invasive therapies.

Last, one should not forget neurodestructive procedures. Dorsal root entry zone (DREZ) lesions and cordotomy, as an example, can be very effective in spinal-cord injury or intractable and recalcitrant pain associated with malignancy.

Balanced analgesia is the concept of targeted pharmacotherapeutics to affect multiple points in the pain-signaling pathway.

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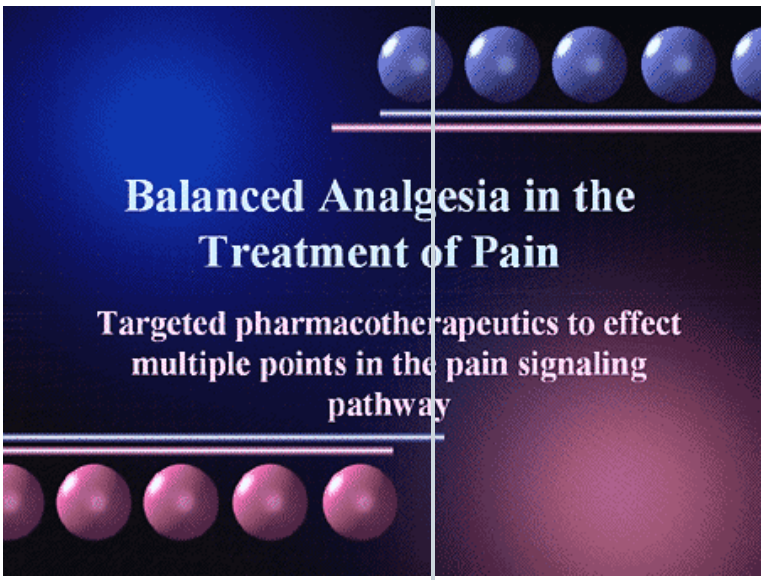

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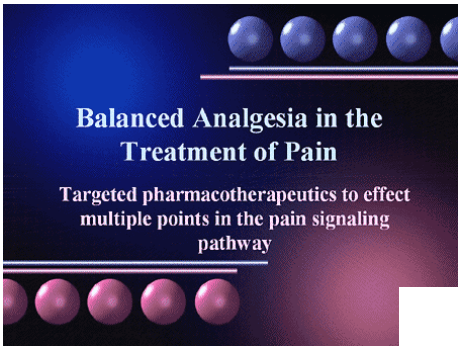
Balanced Analgesia in the Treatment of Pain



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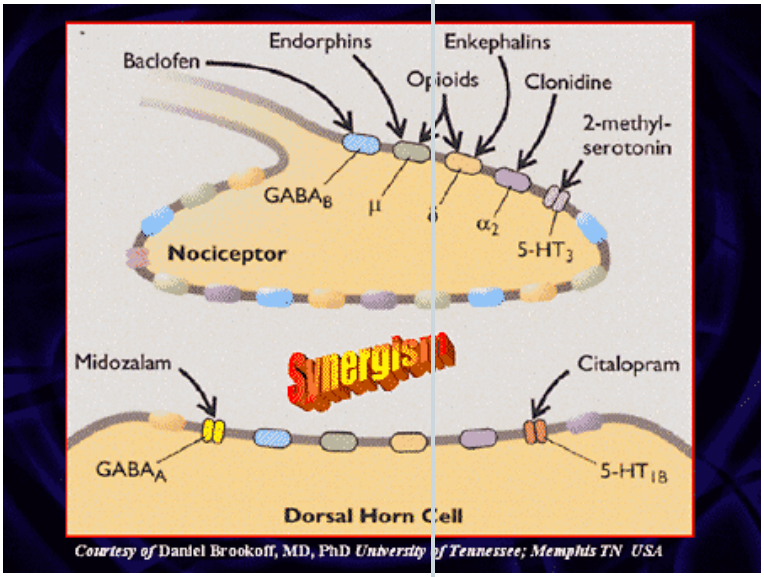
If we go back to the nociceptor DRG complex as an example, one sees multiple and diverse receptor types. The principle is that occupancy of one receptor type, say an opioid binding to a mu receptor, will give you a certain dampening of the signal as the opioid facilitates reduction in the neurotransmitter discharge.

Now, if you occupy another receptor, say an alpha$_2$ receptor such as with clonidine, the effect on dampening the signal may be many-fold greater than with either medication alone. So in this case, 1 plus 1 may equal 5. This effect is referred to as synergism.



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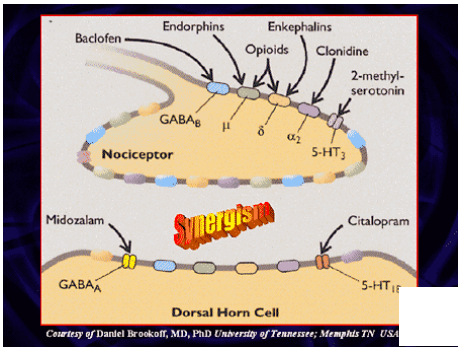

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The rationale for balanced analgesia could be illustrated by looking at the parts of the whole. In the periphery, receptors exist which could be utilized to

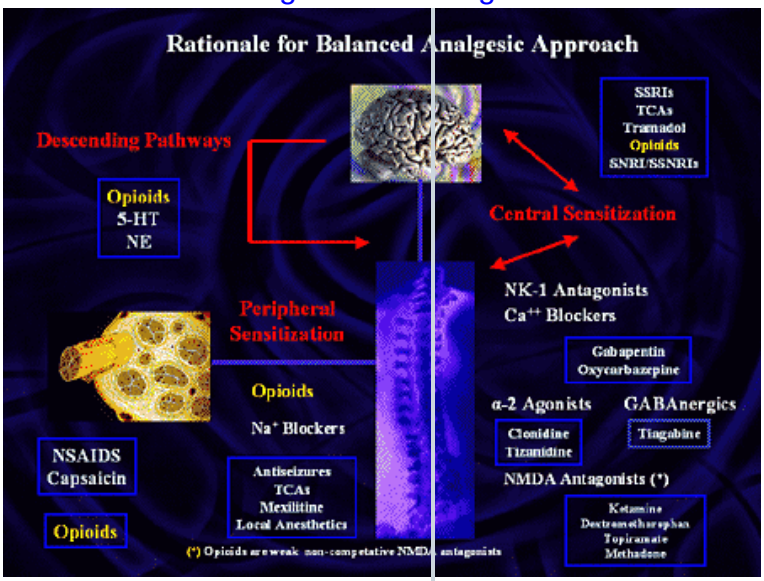
dampen the signal to the dorsal root and the result in segmental and supersegmental structures. Thus, dampening the signal can be accomplished to prevent peripheral sensitization. Opioids, of course, have receptor representation in such diverse peripheral structures as joint spaces and throughout the enteric tract, as well as in the nociceptor DRG complex.

Other agents such as cyclooxygenase (COX) inhibitors have representation both for signal dampening, as well as for reduction in secondary mediators of inflammation. Other agents can be effective in depleting substance P.

Sodium-channel blockers, such as antiseizure medications, tricyclic antidepressants, and local anesthetics, also could be utilized. On the neuraxial end, calcium-channel blockers, alpha$_2$ presynaptic agonists and GABAnergics can be utilized to further dampen the various aspects within the pain signaling pathway. NMDA antagonists are another promising class of medications, which could be quite effective.

The purpose of aggressive interruption at multiple points in the pathway is to prevent central sensitization. Medications such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, as well as the newer selective norepinephrine reuptake inhibitors (SNRIs) all can affect higher brain centers to lessen the central sensitization that can occur.

This is analogous to the sensitization that was illustrated at the nociceptor dorsal nerve root earlier. Opioids have representation at the brain level as well --



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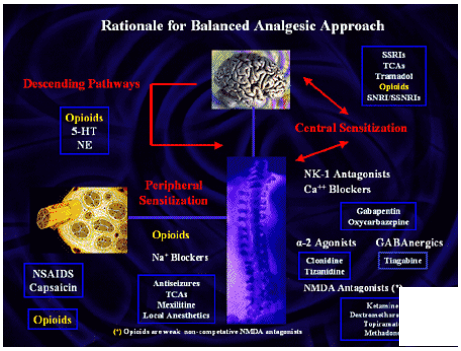
Rationale for Balanced Analgesic Approach



both in the modulation centers for pain and in the descending pathways mediating or dampening the pain signal. Opioids, therefore, are broad-spectrum agents having effects at all levels of the pain-processing network.

So to review, balanced analgesia is the concept of multiple receptor occupancy leading to synergism, which lowers the amount of each medication and, therefore, the overall side effect profile. The goal is to arrest or retard formation of neuropathic circuits, to affect multiple components of the pain signaling, to reduce inflammation, to decrease nociceptor input, and hopefully, to retard the formation of neuropathic signaling.

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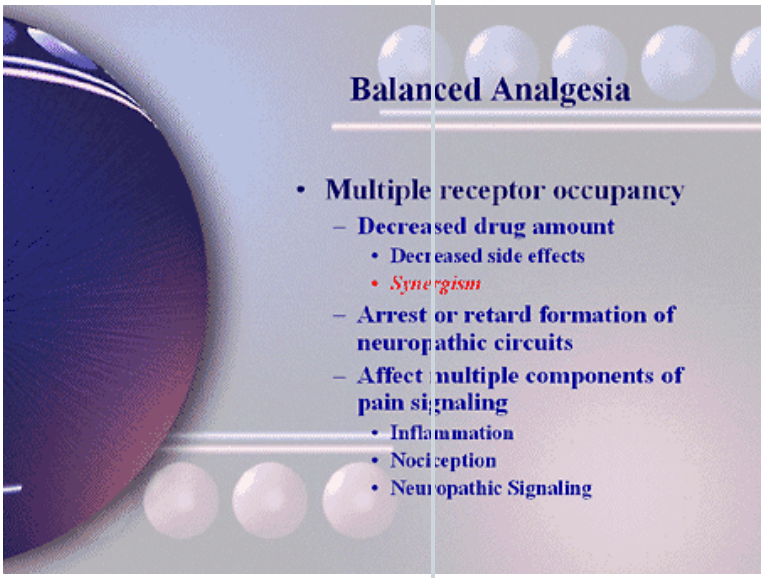

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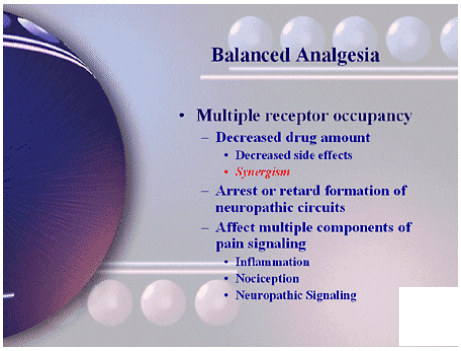
Balanced Analgesia



Principles of Opioid Dosing

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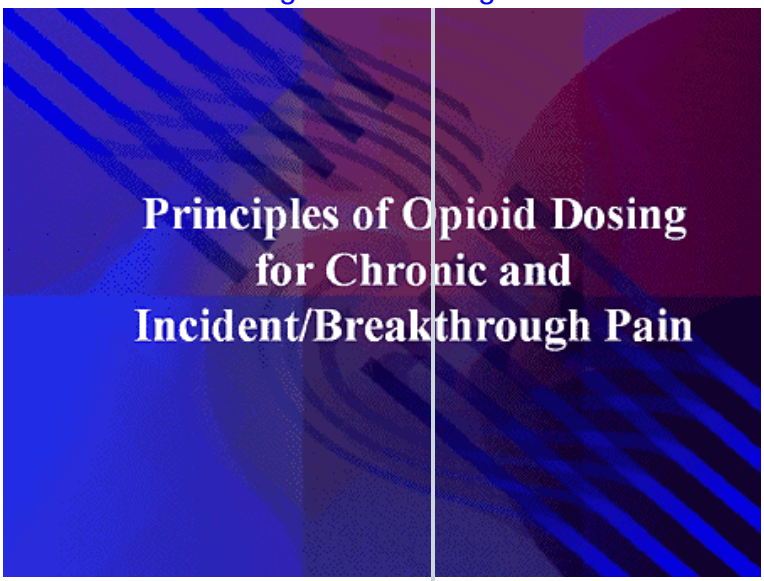
In the persistent pain state, a certain degree of pain is experienced all the time. This is an important distinction, as unless pain exists 24 hours a day, 7 days a week, maintenance of a sustained serum level of an analgesic is not

necessary and may predispose the patient to deleterious effects, such as respiratory depression.



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Principles of Opioid Dosing for Chronic and Incident/Breakthrough Pain

In treating pain, there is a defined therapeutic window for each analgesic agent which, when breached, leads to overmedication. Within this window, one ideally desires to maintain a serum level of an analgesic, which is often accomplished with slow-release or sustained-release preparations

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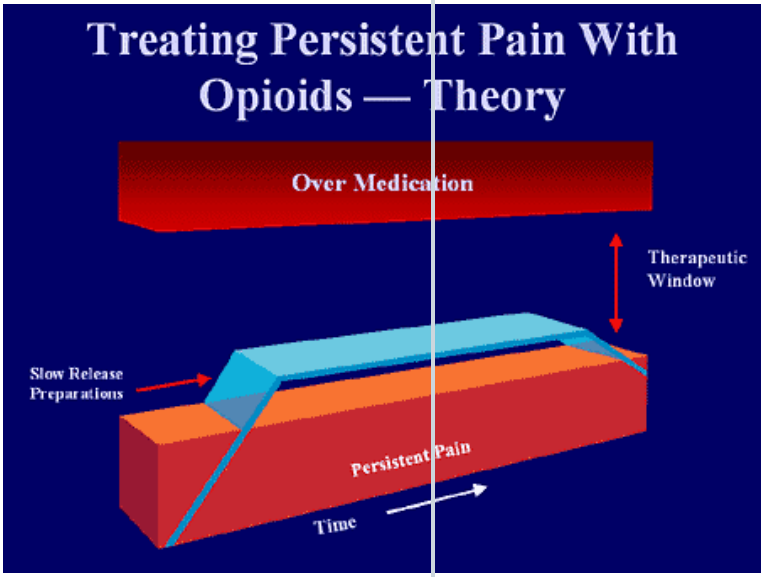

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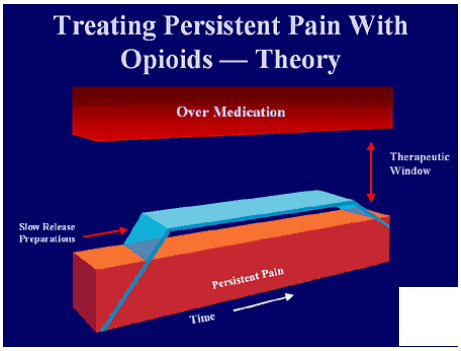
Treating Persistent Pain With Opioids -- Theory



Although persistent pain is present, it is not uncommon for episodes of increased pain to occur. These episodes can occur suddenly and as a rule, have variable intensity. Even more bothersome, these breakthrough episodes occur at inconsistent intervals during the day.

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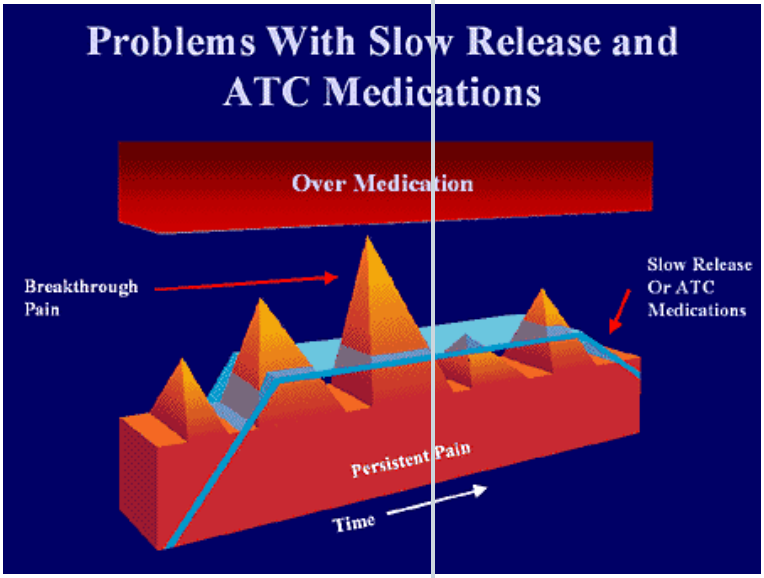

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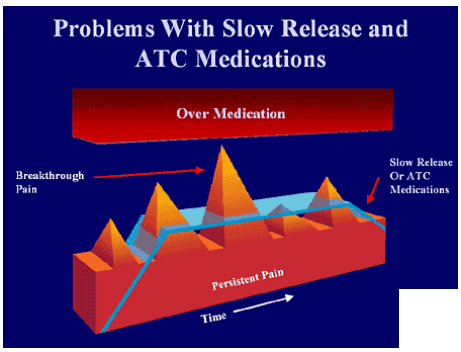
Problems With Slow Release and ATC Medications



If you increase the dose of sustained-release medication to meet the increased pain of breakthrough episodes, you can easily exceed the therapeutic window, leading to overmedication and drug toxicity.

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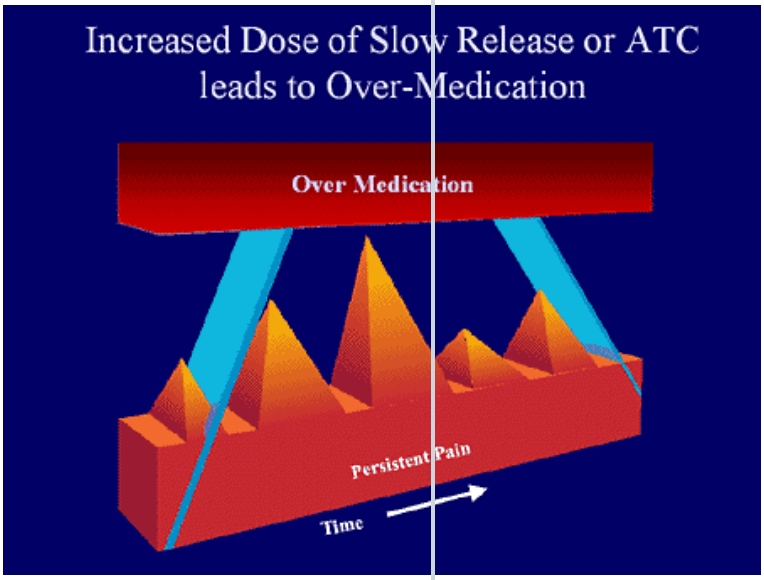
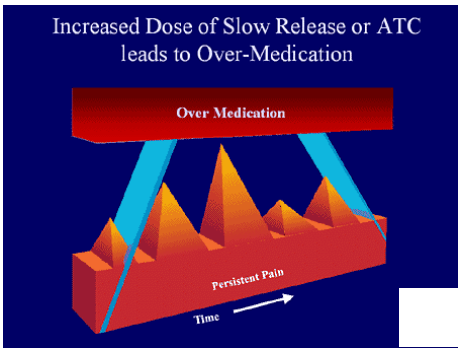


Slide 17.

Increased Dose of Slow Release or ATC Leads to Over-Medication



An additional problem exists when normal-released preparations, which some refer to as immediate-release preparations, are mixed with sustained-release preparations. If the normal-release preparation has a delay in onset, of say 40 or 45 minutes, the breakthrough pain episode may now be on the down slope. If another breakthrough episode occurs, taking additional normal-release medication can lead to an overshoot secondary to summation. Now, too much medication

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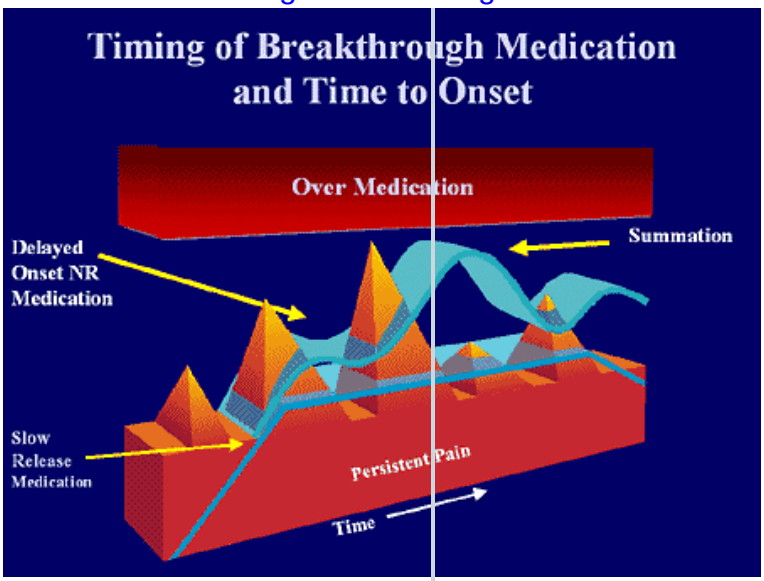
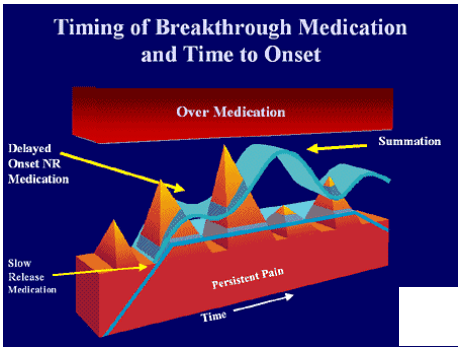
is present and side effects are seen. This is typified by the commonly used opioid morphine. Because normal-release morphine must first be absorbed, which is delayed in part secondary to ionization in the acidic contents of the stomach, it takes as long as 45 to 60 minutes to reach peak serum concentrations. If additional morphine is taken prior to the peak serum concentration, you have an initial dose on an upward curve plus the newer dose on an upward curve. This is the process of summation.



The typical patient will say, "Doc, I took my dose, but I still hurt so I took another. And then my pain started decreasing. But I was so sleepy, I had to lay down for a few hours."

Slide 18.

Timing of Breakthrough Medication and Time to Onset



The Ideal Opioid

The ideal in treatment of pain with underlying persistent features of breakthrough pain episodes is a normal-release medication that has rapid onset and then rapid offset, so that pain is controlled without overmedication. This is analogous to patient-controlled analgesia (PCA), which is routinely employed in postsurgical units.

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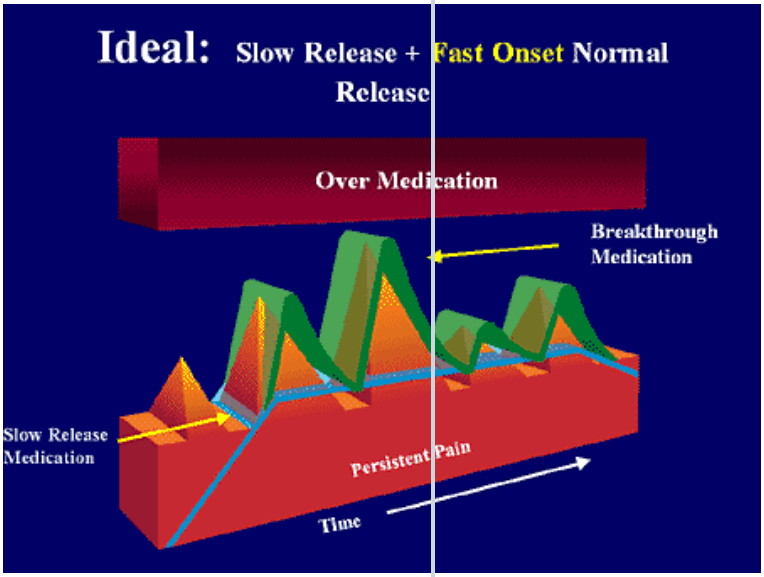
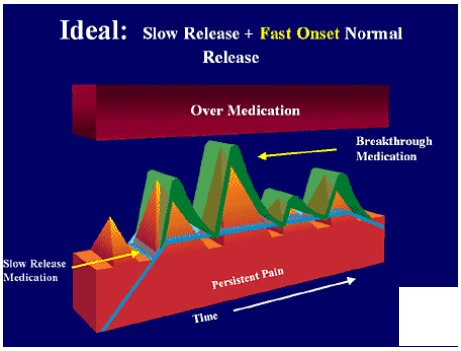


Slide 19.

Ideal: Slow Release + Fast Onset Normal Release



In discussing narcotic treatment, we should understand our existing tools. The best way of compartmentalizing these tools is to classify the drugs according to their hydrophilic (water-loving) properties or lipophilic (fat-loving) properties. As the nervous system is made up of lipids, a lipophilic drug will enter the nervous system much more rapidly than a hydrophilic drug. In addition, the more lipophilic the drug, the more potent the drug. Potency refers to the degree to which the drug binds to a particular receptor. So, the more potent the drug, the less you need.

An opiate is a naturally occurring compound that mimics the initial amino acid sequence of the body's naturally occurring enkephalins and endorphins. An opioid is a synthetic compound that acts in the same fashion. For the sake of discussion, I will refer to any of these compounds as an opioid.

Within the hydrophilic class, the prototypical opioid is morphine. In general, this class binds to the mu receptor approximately 60% of the time. Within this class there are compounds

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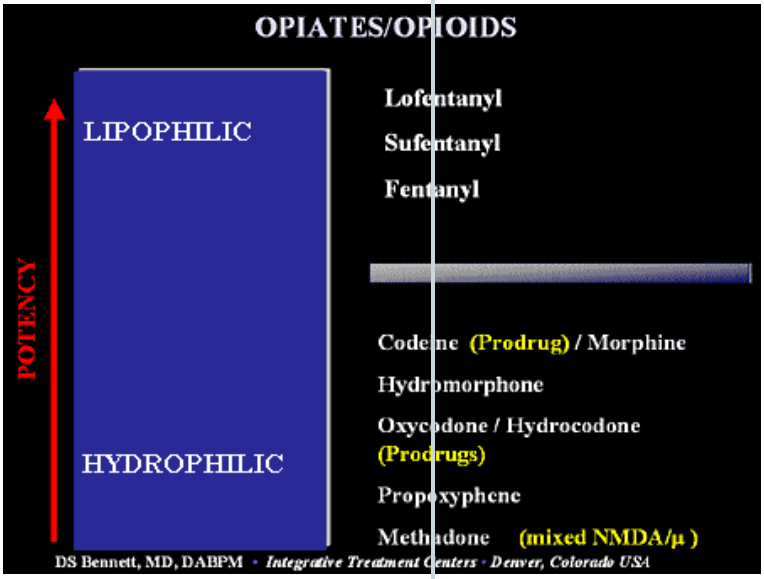
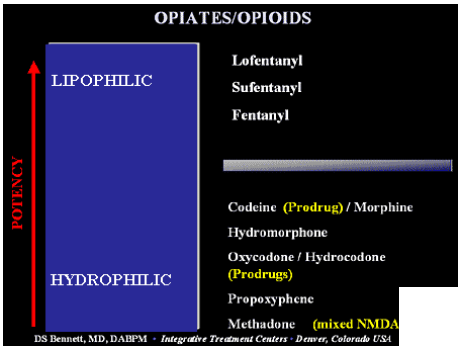


Slide 20.

Opiates/Opioids



that in their ingested state are prodrugs. That is, the compound itself is not an analgesic. A prodrug must first be acted upon, usually by an enzyme system, to produce byproducts that are active analgesics.

A good example is codeine, which is in part converted to morphine and then exerts analgesic action. It is important to remember that if an individual does not have enough representation of the enzymes necessary to convert a prodrug, the individual will have no analgesic action from that agent.

If you now look at the lipophilic compounds, all are derivatives of meperidine; but unlike meperidine, they do not have toxic byproducts. Fentanyl, which is the only one currently available in nonparenteral form, binds approximately 82% to 85% of its life to the mu receptor. Sufentanyl is 92% and lofentanyl is 100%. Therefore, the lipophilic compounds are a bigger bang for the buck.

When discussing opioids, there are several features that one ideally would like. The ideal opioid is easy to take, has no active metabolic byproducts, is absorbed easily, does not induce its own metabolism, facilitates steady state rapidly, and has minimal side effects. While we strive for that perfect opioid, at the present time none exist.

What should drive the clinician's choice is (1) the most conforming opioid to the ideal and (2) what is tolerated and effective for the individual patient. This second point is one that is realized during the patient's opioid trial.

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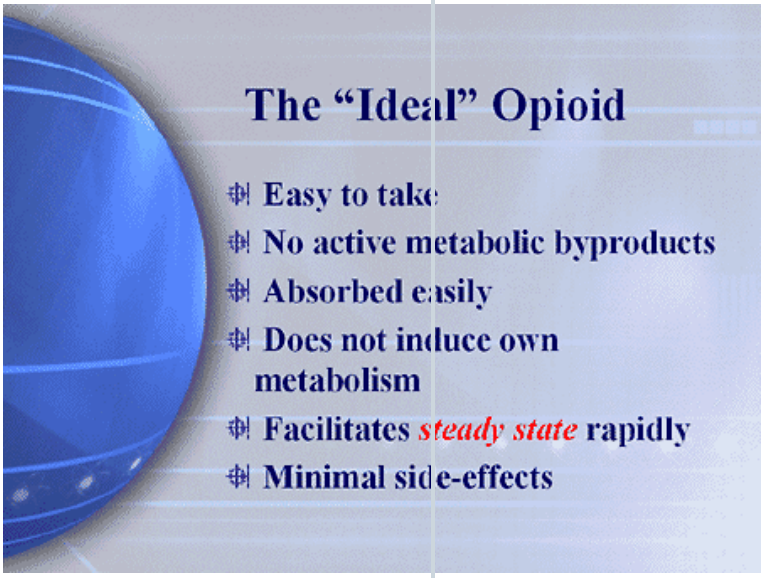

Slide 21.

The "Ideal" Opioid

Opioids: Metabolism and Classification

In deciding on an opioid, it is important to remember the enzyme systems involved in processing the various medications. The most common enzyme system is cytochrome P450. Of this, the 2D6 subsystem processes over 90% of the medications commonly prescribed. It is important to remember the inducers and inhibitors, as few pain patients are on monotherapy. Many come to us on antidepressants, antiseizure medications, and benzodiazepines, to name a few. The other important subsystems are the 3A4, 3A5, and 3A7 subsystems.

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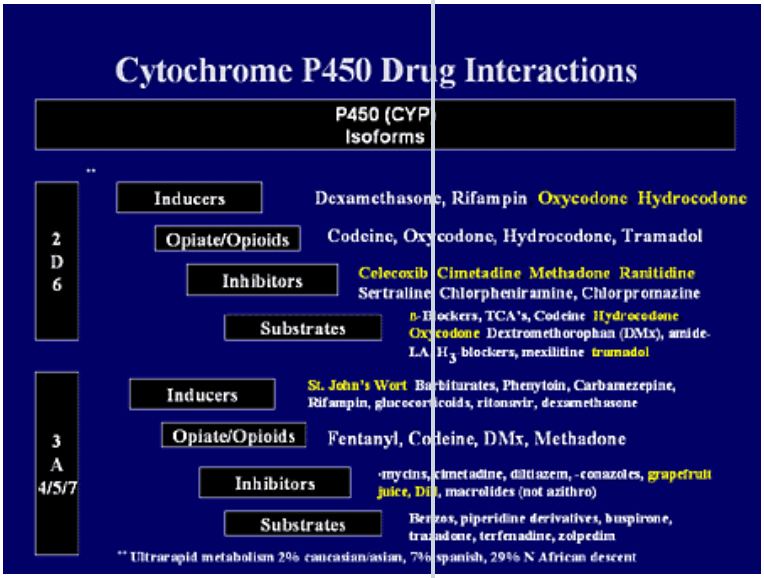

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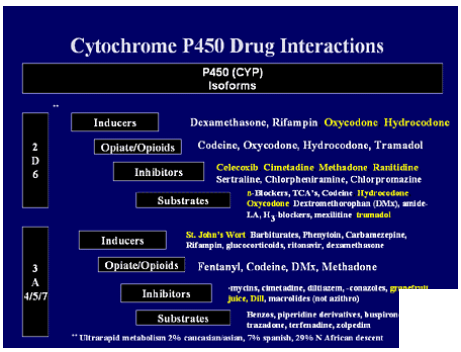
Cytochrome P450 Drug Interactions



As mentioned, the hydrophilic opioids are typified by morphine. While morphine is certainly not the gold standard to many, it is the one most studied. Typical of hydrophilic opioids, it has a slower entry into the central nervous system (CNS). In addition, it has an unattractive side, secondary to byproducts that are metabolically active and are unable to be controlled. These include morphine-3-glucuronide, which binds to delta and sigma receptors leading to the dysphoric side effects, as well as others.

Morphine induces the 2D6 subsystem in the liver and induces serum enzymes, which leads to further breakdown. Therefore, stable serum levels are harder to achieve.

As is typical of hydrophilics, the drug passes easily into the gastrointestinal (GI) tract.

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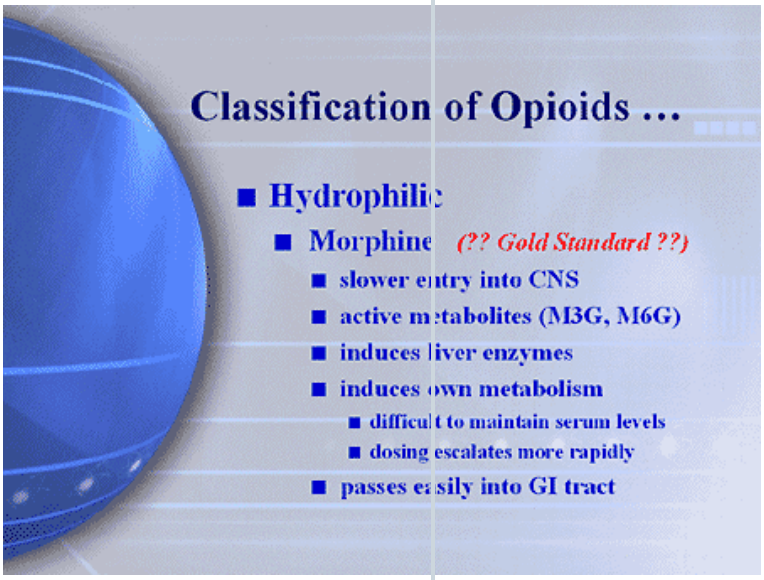

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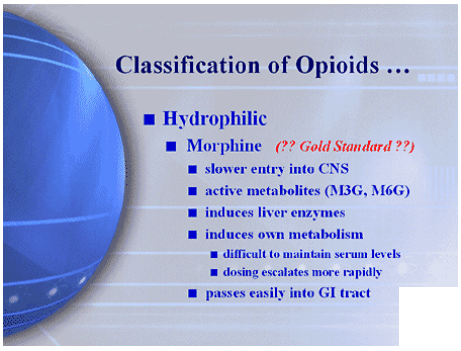
Classification of Opioids...



The most commonly prescribed opioids within the United States are hydrocodone and oxycodone. It's important to remember that hydrocodone is a prodrug and must be metabolized to the 6 alpha and 6 beta hydroxyl derivatives. In addition, as with most hydrophilics, if other medications are being given that inhibit 2D6, toxicity can occur at lower than expected levels. As with other hydrophilic opioids, the medications pass easily into the GI tract.

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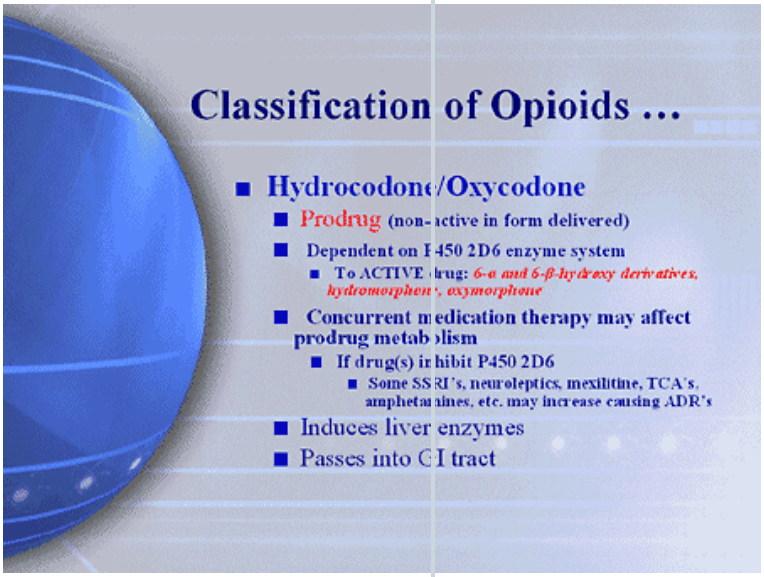

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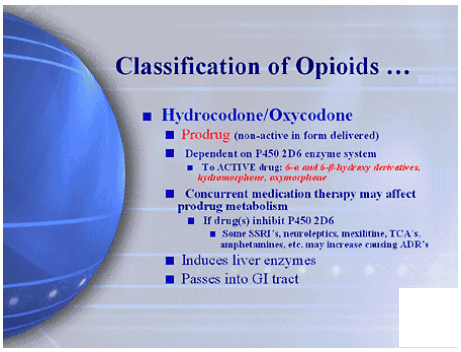
Classification of Opioids...



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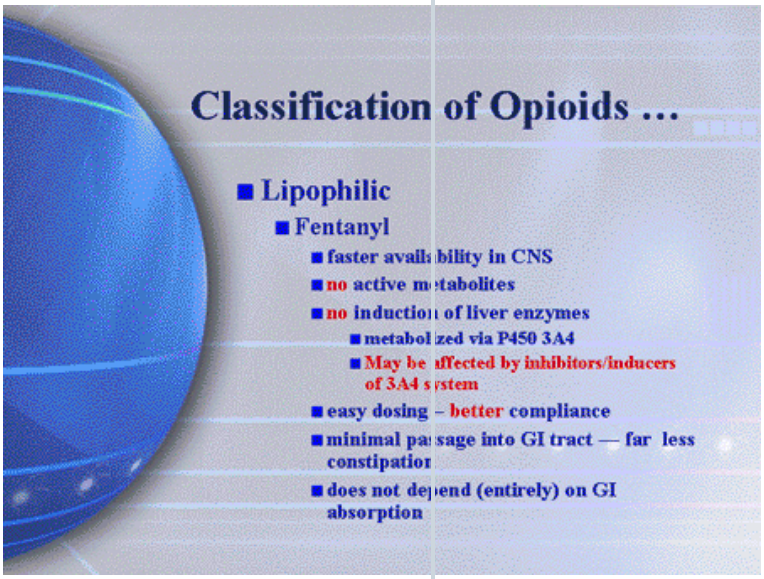
Lipophilic opioids, such as fentanyl, have far more rapid availability in the CNS. In addition, fentanyl has no active metabolites at clinical dosing and does not induce the 3A4 subsystem, which is responsible for its metabolism. It is easier to dose for rapid effect and is also available in a more convenient, sustained-release form than hydrophilics, which are available in tablets. Easier dosing leads to increased compliance. With minimal passage through the GI tract, less constipation occurs.



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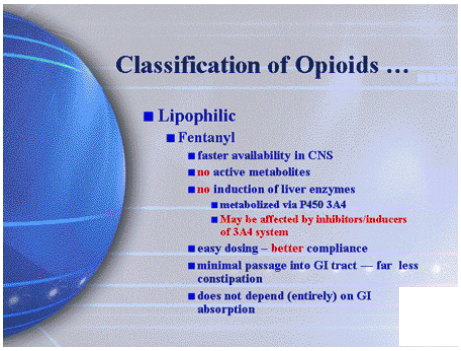
Classification of Opioids...



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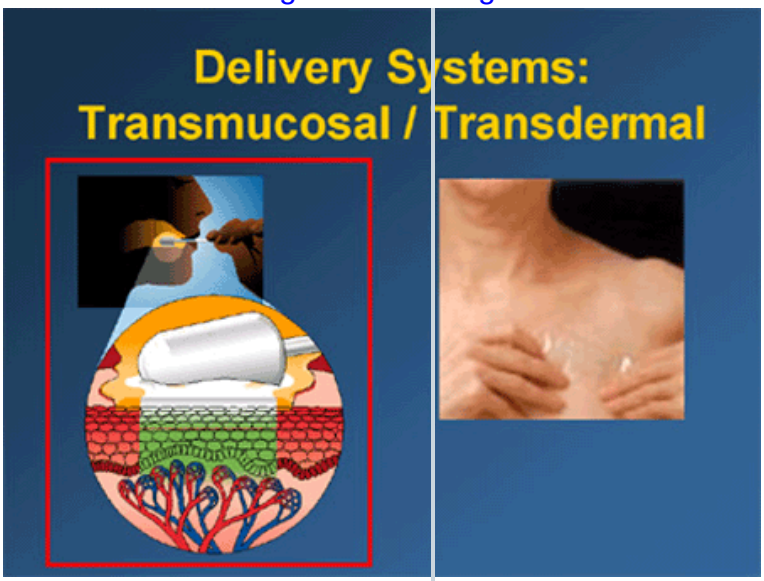
There are two forms of deliver of fentanyl citrate. The first available to the

clinician is transmucosal delivery. Transmucosal delivery has the advantage of rapid onset and a very forgiving serum concentration to allow complete patient control.



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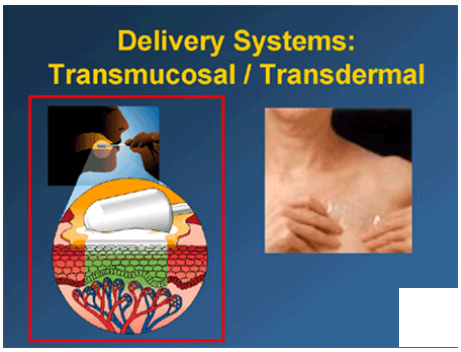
Delivery Systems:



The second is a sustained delivery system known as the transdermal fentanyl citrate delivery system. This gives the clinician additional advantages of the sustained release preparation to maintain constant serum levels in persistent pain states.

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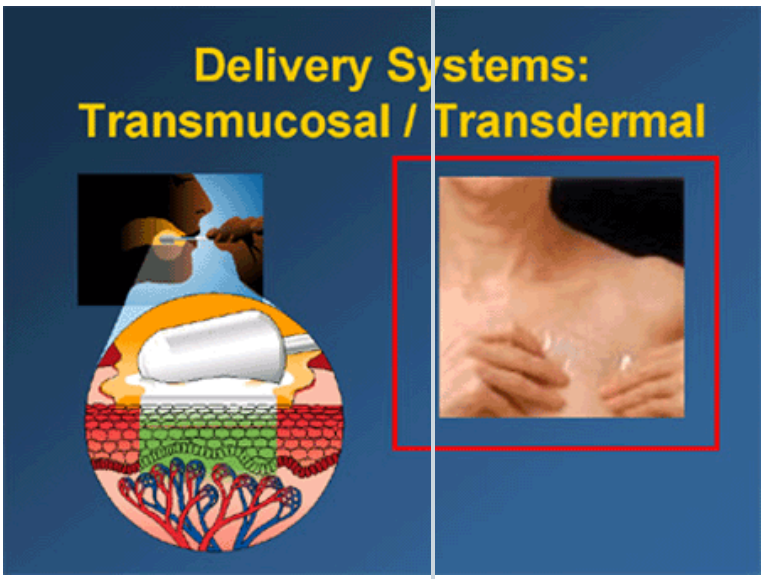

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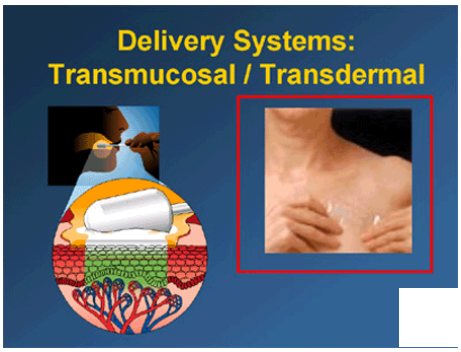
Delivery Systems:



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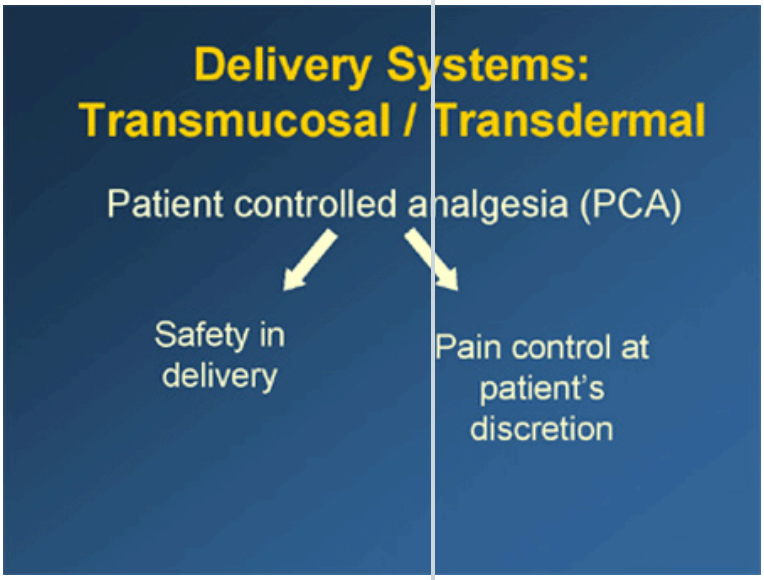
The best analogy for use of these two systems is the patient-control analgesia system. In a hospital environment a patient is placed on patient-control analgesia and given a demand, or incremental dosing, which is completely at the discretion of the patient. This allows safety in delivery of fentanyl and provides the patient with a means of controlling their pain on demand. In a persistent pain state a basal, or continuous infusion, analogous to the transdermal delivery system could be applied, and this could be supplemented by an immediate delivery, or demand dosing, which is analogous to the transmucolsal fentanyl delivery system.



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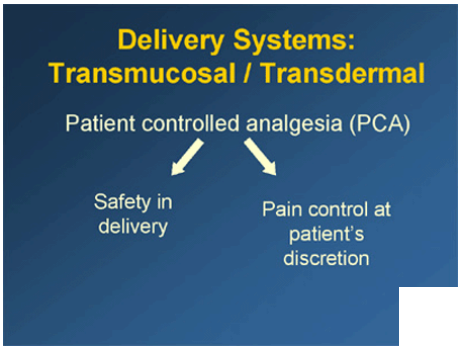
Delivery Systems:



A Place for Opioids?

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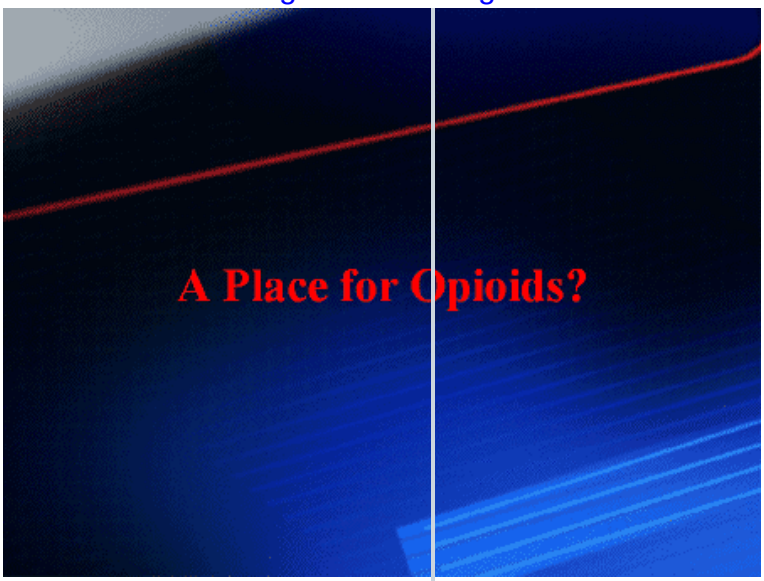
It is crucial to contemplate the place for opioids within the pharmacotherapeutic

treatment of the individual patient.



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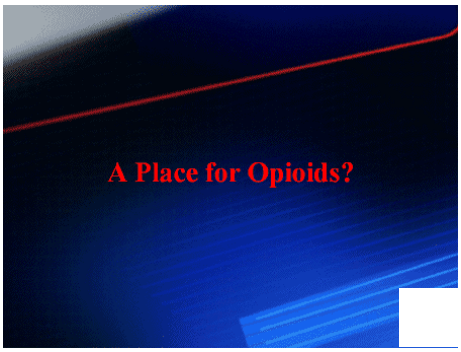
A Place for Opioids?



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We already saw that opioids are broad-spectrum analgesics. Opioids have proven safety and efficacy without the end-organ damaging effects that are often seen with other analgesics.

There are no prospective data showing abuse patterns in clinical use different from those of the general population. As broad-spectrum analgesics, opioids act to decrease glutamate discharge at the nociceptor DRG level and reduce excitatory neurotransmitter discharge in other parts of the system as well as potentiating the descending modulation of the pain-signaling pathway.

Slide 30.

A Place for Opioids???

The actual efficacy in the individual patient should be determined by a well-orchestrated opioid trial. Certainly the timing of the opioid trial is important, as is a reasonable certainty that the patient has no untreated cognitive behavioral or personality disorder that may adversely affect the patient and their compliance with an opioid regimen.

The opioid trial should begin with identifying several functional goals for the patient that can be used as benchmarks for success. The success should be based on a combination of diminution of pain intensity and increase in functioning as benchmarked by the percentage of attainment of the patient's goals.

Adverse effects should be documented and controlled. If adverse effects of an opioid significantly and negatively impact functional goals, another opioid may be necessary. Initial pain and functional impact should be documented. A thorough physical examination and working diagnoses should be documented. Discussion should occur regarding the goals, expectations, and duration of the trial and length of proposed therapy.

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Slide 31.

A Place for Opioids??

For instance, if you are adding an opioid to allow pain control to facilitate physical therapy, this may only be an interim therapy with a definite and defined end. This is different than establishing an opioid regimen that would be maintained indefinitely.

Every interaction with a patient also should include a review of the opioid regimen with several key features. These have been proposed by Passik as the 4 A's. The first A is for analgesia. This is usually measured either by a visual analog score or by a numeric score using 0 to 10 as a scale. In addition, it's important to realize that none of the currently used scales have been standardized. They are simply used standardly.

The second A is for activities of daily living. This is, in particular, referencing the desired goals of the patient and the percentage of attainment that patient has had.

The third A is for adverse effects. All adverse effects of the opioid should be documented. This could be as simple as constipation or more complex as daytime somnolence, or in some cases, confusion.

The fourth A is for abuse issues. This is where one can look at a patient and think out loud. Is this patient's seeking a drug secondary to pseudoaddictive properties? This often happens when pain is undertreated. Or, is this more ominous and a sign of potential diversion or opioid abuse?

It is important to remember that every interaction with a patient should

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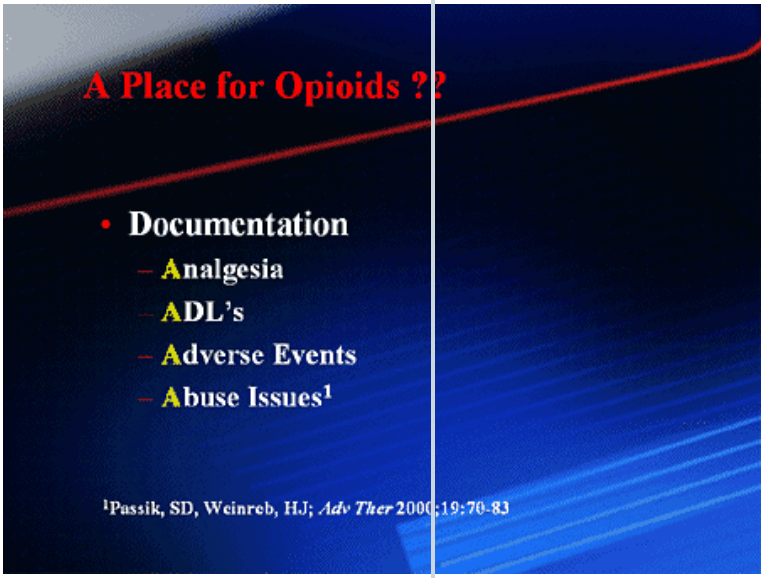

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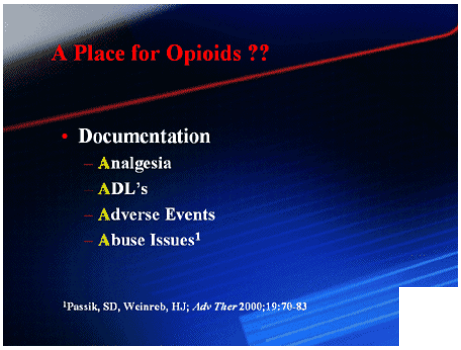
A Place for Opioids??



document these 4 critical areas. By doing this we actually show that we are affecting a positive change for the patient. That is, we are assisting them to attain functional outcome that is positive.

The number of opioids trialed is certainly practitioner dependent. I will often try with at least a lipophilic and a hydrophilic. Often I will trial 3 different opioids, each for 2 weeks, prior to abandoning opioid therapy. With emerging animal evidence for genetic variation in mu receptor subtypes, certainly more than 1 type of opioid should be trialed prior to abandoning opioids as part of the analgesic regimen.

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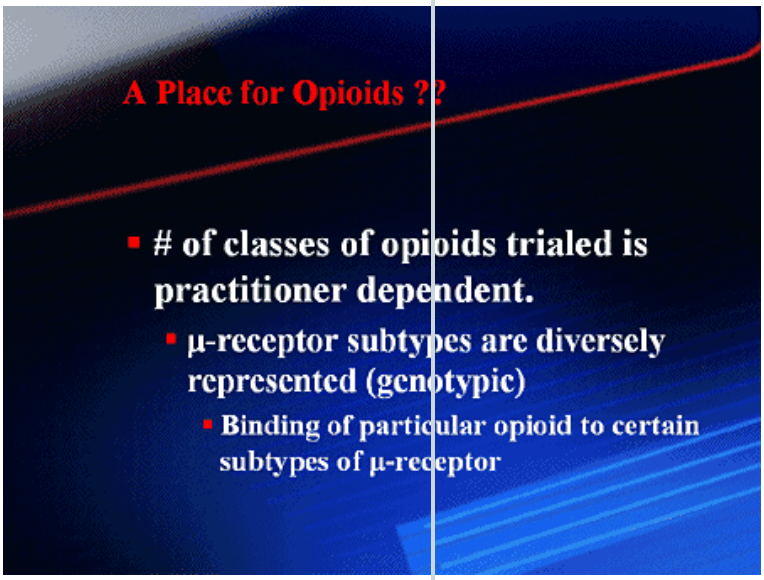
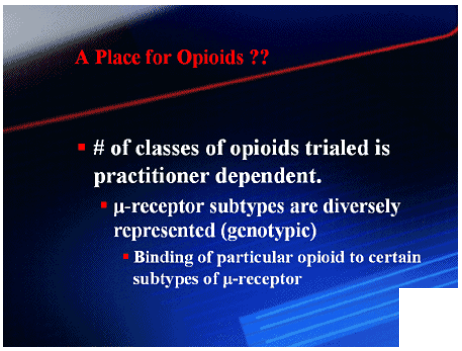


Slide 33.

A Place for Opioids??



In closing, it is important to remember that many patients do not vocalize their pain complaints. It is crucial to ask, believe, choose, and deliver to empower the individual patient.

There is a quote by Dobrisa Cesaric that I would like to leave with you. "Some walk with their pain like an open wound

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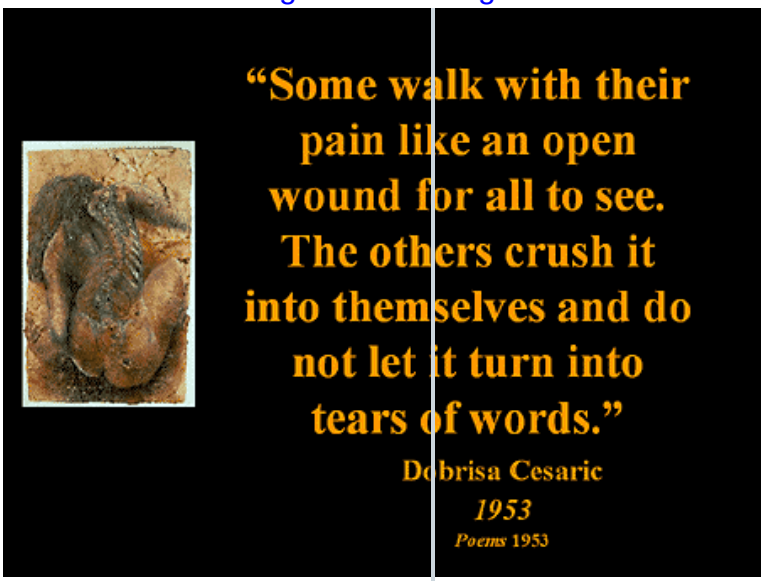
for all to see. The others crush it into themselves and do not let it turn into tears of words." Remember to ask, believe, choose, and deliver to empower your patient for a better life and functional outcome.



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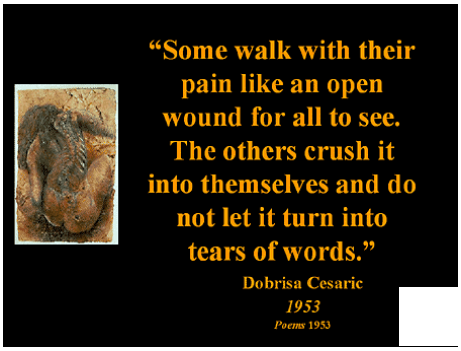

EXHIBIT 88

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Stephen H. Landy, MD

DISCLOSURES | Headache. 2004;44(8)

IN THIS ARTICLE

Patients and Methods

This case series evaluated 20 patients with acute, refractory migraine headaches who had been referred to this headache clinic. All patients had a history of migraine as defined by the International Headache Society[16] and reported unsatisfactory or inconsistent pain relief with their usual outpatient medications, including opioids, 5-HT_1 receptor agonists, ergots, antiemetics, and prescription and over-the-counter (OTC) analgesic and anti-inflammatory medications. All patients had been followed in our clinic and had been previously fully evaluated with history, vital signs, and physical and neurological examinations, and testing as indicated. These patients had a history of tolerating parenteral opioids in the ED when experiencing refractory migraine pain, and all patients had been treated with outpatient opioid therapies in attempts to manage their migraine pain.

Patients were prescribed OTFC (400 µg) as rescue treatment for moderate or severe migraine headache pain as outpatients, after their usual antimigraine medications were ineffective. Patients were instructed to self-administer OTFC at home to treat a refractory attack of moderate or severe migraine pain and to complete a treatment diary. A refractory attack that was to be treated with OTFC was, therefore, patient-defined by failure to respond to usual treatment and residual migraine pain of at least moderate severity. In the diary, patients rated pain intensity on an 11-point scale (10 = worst pain imaginable to 0 = no pain) before and 15, 30, 60, and 120 minutes after OTFC. Patients were also to rate their satisfaction with the effectiveness of OTFC at relieving migraine pain and other migraine symptoms at 120 minutes after starting self-administration, selecting 1 of 7 categories ranging from "very dissatisfied" through "very satisfied." Patients also recorded any adverse events (AEs).

Next Section

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CME/CE

Optimizing Opioid Treatment for Breakthrough Pain

Subtypes and Characteristics

Supported by an independent educational grant from:

of BTP

Consensus has not been reached on precise definitions of terms related to BTP. However, many clinicians consider BTP to comprise 3 subtypes (Figure 2).[6]

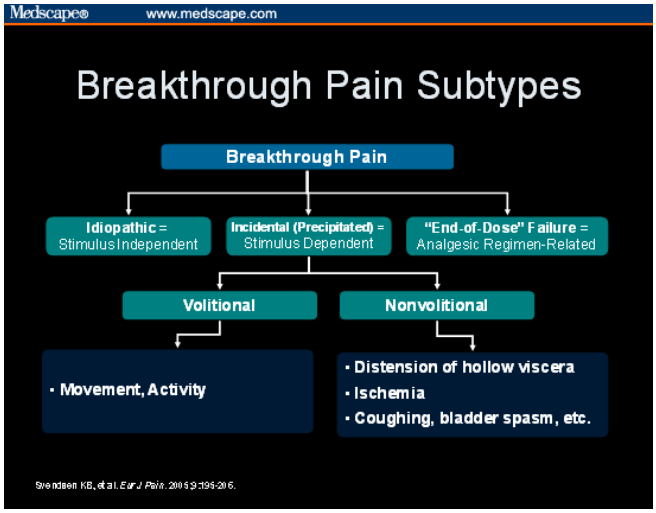

Figure 2. Breakthrough pain subtypes.

Idiopathic, or spontaneous, pain requires no precipitating stimulus. It comes on without warning and is marked by a sudden, often disabling crescendo. An example is the sharp, lancinating pain suffered during attacks of acute shingles or postherpetic neuralgia. Idiopathic BTP is common in neuropathic pain conditions.

Incident pain is associated with an identifiable cause whether volitional, as in pain caused by patient-precipitated movement, or nonvolitional, as in pain brought on by a bladder spasm after voiding.

End-of-dose failure pain results when the dose of drug drops below the analgesic

level. Pain experts do not agree about whether end-of-dose failure represents true BTP; however, it is a category of pain experienced separately from a background of otherwise controlled pain and requires management.

The unpredictability of BTP will strongly influence the choice of treatment. A BTP event sometimes can be predicted when an antecedent activity is identified as the precipitating factor. However, BTP may occur without warning in up to 48% of cases, as shown in Figure 3.[5]

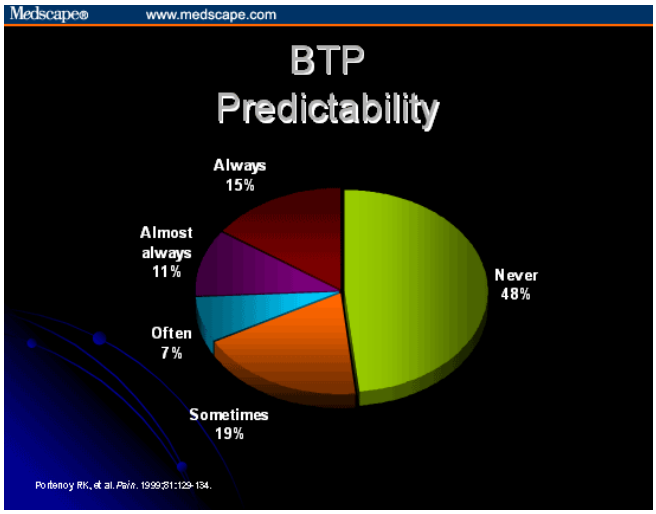

Figure 3. Predictability of breakthrough pain.

Incident pain caused by volitional activity is usually nociceptive and appears to be more prevalent than either stimulus-independent or end-of-dose pain. Of note, volitional incident pain can occur when there is no baseline pain. For example, a patient may experience pain only when walking because of severely arthritic knees. However, to satisfy the definition of BTP, persistent

background pain must also be present. Because volitional incident pain is relatively predictable, it is most likely to respond to preemptive treatment. By contrast, incident pain caused by nonvolitional activity is less predictable.

Question 1 of 2

A patient whose background of chronic back pain is well controlled with medication, but who experiences sudden flares of sharp, stabbing pain when cleaning house, is exhibiting:

- ◯ Nonvolitional incident pain
- ◯ Nonvolitional idiopathic pain
- ◯ Volitional incident pain
- ◯ Volitional idiopathic pain
- ◯ End-of-dose pain
- ◯ Chronic pain, not BTP

Question 2 of 2

Which of the following would you choose to treat this patient's BTP?

- ◯ RO opioid taken when the pain strikes
- ◯ SAO taken before she begins housecleaning
- ◯ Augment chronic pain treatment with an NSAID
- ◯ Higher dose of chronic pain treatment

SAVE AND PROCEED

EXHIBIT 90

Special REPORT

This activity is based on a symposium presented at the **International Association for the Study of Pain 12th World Congress on Pain,** held on August 20, 2008 in Glasgow, Scotland.

SELECT

STRATIFY. EXAMINE. LISTEN. EVALUATE. CONTROL. TAILOR.

Opioid-Based Management of Persistent and Breakthrough Pain

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Program Description/Statement of Need

The primary objective of this program is to educate health care professionals about a semi-structured approach to the opioid-based management of persistent and breakthrough pain (BTP). Particular emphasis will be placed on appropriate selection of patients for opioid therapy following comprehensive evaluation of the underlying chronic pain disorder and stratification of potential risks for medication misuse. Through a combination of evidence- and case-based discussions, the importance of identifying opioid-tolerant patients will be discussed, as will the need for continual assessment of therapeutic structure and efficacy.

Target Audience

This program is intended for physicians and other health care providers who treat patients with chronic pain, including pain specialists, primary care physicians, neurologists, surgeons, rheumatologists, internists, oncologists, psychologists, nurses, physical medicine and rehabilitation specialists, and pharmacists.

Learning Objectives

At the conclusion of this activity participants should be better prepared to:

❶ Select patients for opioid-based management of chronic pain based on individual assessment and evaluation of the benefits and risks of therapy.

❷ Initiate opioid trials and maintain or modify treatment by reassessing analgesia, patient function, adverse events, and adherence to the treatment plan.

❸ Discuss the appropriate roles of long-acting, short-acting, and rapid-onset opioids for the management of opioid-tolerant patients with persistent and breakthrough pain.

❹ Stratify and monitor patients based on their risk for aberrant medication use.

Disclaimer Statement

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of the Advanced Strategies in Medicine name implies review of educational format, design, and approach. Some medications and indications, including oral transmucosal fentanyl citrate and fentanyl buccal tablets for breakthrough pain in noncancer populations do not have marketing authorization for use in the United States. Please review the complete prescribing information for specific drugs or drug combinations, including indications, contraindications, warnings, and adverse effects, before administering pharmacologic therapy to patients.

Opioid Therapy for Chronic Pain: A Constructivist Approach

Chronic pain is a prevalent biopsychosocial condition associated with significant disability, reduced quality of life (QoL), and high costs to the patient and society.[1-3] As such, chronic pain requires assessment of multiple biomedical, psychological, social, cultural, and spiritual dimensions of an individual's pain experience. Potential diagnoses and treatment options are supported by information obtained through a detailed medical history, physical examination, and psychosocial evaluation.[4] Furthermore, the pain complaint itself should be characterized in terms of location, intensity, duration, quality, and aggravating and relieving factors. It is important to note that the clinical profile of chronic pain almost always is dynamic, with daily variations in pain levels, affective symptoms, and functional effects. Optimal assessment and treatment of chronic pain, therefore, requires consideration of its 2 temporal components: persistent baseline pain and breakthrough pain (BTP).[5-7] Fluctuations in baseline pain are common, requiring routine follow-up to monitor treatment effectiveness. Once the optimal regimen for baseline pain has been developed, ongoing assessment and treatment of BTP becomes an additional and equally important component of individualized patient care.

In some patients, persistent pain can be resolved by treating its underlying etiology. Common pain types amenable to direct care include neural decompression of a herniated disk; removal of a tumor associated with visceral, osseous, vascular, or neural impingent; and total joint replacement in cases of severe osteoarthritis (OA). Many non–self-limiting pain syndromes, however, require long-term treatment, typically with multimodal therapy encompassing behavioral, pharmacologic, and interventional strategies.[1,8] For each patient, clinicians should consider the benefits and risks of all available modalities, and advise that pain may persist despite aggressive treatment. When pain is severe enough to affect a patient's QoL and functional capacities, or when other therapies have not been satisfactory or are excessively risky (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] in older patients),[9-11] opioids may be required as a component of overall treatment for both baseline pain and BTP. Opioid prescribing requires careful consideration of patient-specific goals, the pathophysiologic mechanisms underlying the pain syndrome, and assessment of opioid-related risks and related capabilities of the clinician to structure therapy accordingly.[12-14]

Evidence supporting opioid-based therapy is well established in cancer-related pain but remains controversial in the context of chronic noncancer pain (CNCP). Well-designed published studies demonstrate that opioid medications may be safe and effective components of multimodal care, but most are short term (generally defined as less than 6 months in duration) and have been conducted in selected populations, thus limiting their relevance to the diverse population of patients with long-term chronic pain management needs. Treatment success in CNCP syndromes clearly requires careful patient selection; structured opioid prescribing; and ongoing monitoring of analgesic response, adverse events (AEs), adherence, and aberrant behaviors.

Clinically, broad classification of pain syndromes as either cancer- or noncancer-related has limited utility.[15] For example, many of the estimated 10.4 million patients classified as cancer survivors continue to suffer from debilitating somatic, visceral, or neuropathic pain syndromes resulting from tumor-induced tissue damage and/or cancer therapy.[16] This subpopulation highlights the need to assess and classify pain beyond its origins and to focus instead on relevant, presumed pathophysiologic processes causing pain—including nociceptive, neuropathic, or mixed mechanisms—whether initiated by metastatic disease or nonmalignant pain generators.[17] For example, despite their different pain diagnoses, patients with metastatic thoracic fractures and noncancer-related thoracic compression fractures experience pain via similar nociceptive signaling pathways and often require similar mechanism-based therapies.

Across all patient types and chronic pain syndromes, comprehensive assessment requires detailed reports of pain severity, character, and phenomenology, including its peaks and troughs; localization, radiation, and referral patterns; exacerbating and easing activities; and responses to therapy. Furthermore, the definition of realistic treatment goals should be based on the functional impact of pain and the psychosocial history of the patient, among other factors. Prior or current psychiatric conditions and/or substance abuse in patients or their immediate families are strong indicators of the potential for nonmedical opioid use—a significant concern with these medications. In addition, the psychosocial impact of pain on patient function predicates a multidisciplinary approach to facilitate the best possible functional outcome.

Clinical experience, published trial data, and professional societies increasingly support the use of opioid-based therapies for appropriately selected patients with CNCP conditions—at least in the short term.[18,19] Clinical trials demonstrate the safety and efficacy of opioids in the management of OA, chronic low back pain (LBP), and neuropathic pain, for example.[20-22] A systematic review of studies that evaluated opioid use in CNCP reported an average 30% reduction in pain levels,[23] a percentage previously suggested to be the threshold for clinically significant pain relief.[24] Including opioids as a component of multimodal care for CNCP is complicated, however, by the limited evidence base supporting long-term therapy. Randomized controlled trials of opioids typically evaluate patients for 16 weeks or less, report significant dropout rates during enrichment and treatment phases, and fail to address QoL outcomes.[25-27]

Importantly, prescription drug abuse—and in particular nonmedical use of opioids—has risen dramatically in recent years. This serious public health concern has been noted concomitantly with increased opioid prescribing for chronic pain.[28,29] That said, many clinicians, anxious about potentially deleterious long-term consequences and regulatory sanctions, are hesitant to prescribe opioids and unwittingly contribute to the ongoing undertreatment of pain in patients for whom this drug class may be beneficial.[30-33] Reconciliation of these dual and somewhat overlapping public health problems is best achieved by a "constructivist" approach to opioid prescribing through which clinicians employ a structured, iterative methodology for patient assessment and selection, opioid medication trials, and ongoing tailoring of therapy. By focusing on attainable treatment goals that reduce the adverse effects of pain on function, sleep, interpersonal interactions, mood, and self-view, while actively evaluating and mitigating risk, the constructivist approach may help resolve the tension between the benefits of opioid prescribing for appropriately selected patients and the inherent risk for nonmedical use of these medications. This approach seeks to determine the clinical utility of opioids based on a complete evaluation of available evidence, conventional practice for the pain syndrome, and potential opioid-related concerns in each individual, thus reducing harm to patients and potentially curtailing the current epidemic of drug abuse.

Rational Positioning of Opioid Therapy

All patients experiencing moderate to severe chronic pain associated with functional impairment or distress may be considered for a trial of opioid therapy.[34] Importantly, such a trial should be initiated with the understanding that chronic pain may persist for months or years; that medication may be required on a long-term basis; and that treatment may provide full, partial, or little symptomatic pain control.[34] As with any therapeutic modality, the decision to proceed with opioid therapy relies on an evaluation of the potential benefits and risks for the individual patient. As a framework for this risk–benefit analysis, the clinician may wish to consider the 4 critical questions outlined below.[34]

1. What is conventional practice for this type of pain or patient?

An understanding of conventional approaches and prevailing trends in one's regional and local pain-treating communities can inform the therapeutic decision-making process. Standard definitions of conventional practice presently are not available, however, and may vary depending on the extent to which various therapeutic strategies, including opioids, are used in a particular community. Nonmedical considerations—including, among others, cultural perceptions and availability of primary care and pain specialists in the community—may preclude a consensus view of what is or is not accepted as "routine care." Finally, there is a dearth of robust evidence comparing analgesic modalities, underscoring the primacy of clinician judgment in pain medicine and requiring physicians to look beyond their local communities at the global and national breadth of practice approaches pursuant to the patient's characteristics and chronic pain condition. Prescribing opioids outside what is usual and customary in a locale may not be contraindicated, but rather requires justification, meticulous documentation, and monitoring with appropriate clinical support to protect the patient and the prescriber. An opioid trial may be appropriate if the local environment supports the use of such therapy within the clinical context or if published evidence suggests that the pain syndrome at issue likely is opioid-responsive.

2. What other treatments have more favorable risk–benefit ratios than opioids for this patient?

Risk–benefit analysis of all medications on a patient-by-patient basis is a fundamental component of chronic pain management. Although the evidence for some treatment modalities is limited, the safety, tolerability, and efficacy of each analgesic and interventional strategy should be explored in the full context of the patient's pain syndrome, medical history, physical examination, laboratory findings, and psychosocial workup.

A detailed medical history of prior treatments may provide an understanding of therapeutic failure, partial response, and/or intolerable side effects. Inquiry into dosing, trial length, and patient self-evaluation of benefits and AEs may be particularly revealing. For example, on further investigation, a failed trial of a tricyclic antidepressant or anticonvulsant might have resulted from inadequate treatment duration, either insufficient or overly aggressive dosing, or unaddressed side effects. In such a case, retrial using a more appropriate therapeutic approach, may be beneficial.

Unaddressed AEs may lead to discontinuation of an agent despite proven analgesic efficacy. Patients receiving NSAIDs, for example, may experience relief of pain associated with nociceptive and inflammatory syndromes but also may be at increased risk for gastrointestinal and/or cardiovascular AEs. Similarly, treatment with serotonin norepinephrine reuptake inhibitors is associated with clinically important efficacy in neuropathic pain syndromes and generally well-tolerated side effects but requires regular monitoring, especially in older patients. Gabapentinoids provide effective relief in such neuropathic disorders as diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN), but their sedative effects require ongoing assessment. These and other nonopioid analgesics may provide only partial analgesia, often necessitating trials of multiple drugs targeting distinct sites along the neuraxis. An opioid trial may be appropriate

if a patient responds poorly to other therapies, including those with good risk–benefit profiles, or if a patient requires additional analgesia after a review of various potential pharmacologic and nonpharmacologic approaches.

3. Does the patient have a medical profile that suggests relatively high risks related to opioid pharmacology?

Opioids are associated with a significant side-effect profile that includes nausea and vomiting, sedation, bowel dysfunction, sleep-disordered breathing, respiratory depression, and with long-term use, potential immune and endocrine dysfunction.[35-37] Systematic reviews of opioid use in CNCP indicate that study populations often are enriched with responders and exclude those with significant AEs prior to randomization, thus increasing the difficulty of generalizing results to a broader population of patients with chronic pain.[23] Although AEs are reported in these trials, tolerance to opioid-related side effects develops rapidly.[23] Of note, however, constipation commonly persists, requiring treatment, and patients undergoing long-term opioid therapy should be evaluated (and treated, if necessary) for endocrine dysfunction.

When considering opioids for the treatment of CNCP, it is important to determine the patient's prior response to specific opioid medications. It should be noted, however, that a report of an inadequate analgesic response or intolerable side effects with one opioid formulation does not necessarily predict an unfavorable response to another, as is discussed in greater detail below.[38] In addition to pharmacodynamic and pharmacokinetic factors, clinicians should monitor patients specifically for comorbid psychiatric and medical disorders that may be affected negatively by opioid-based therapy. Patients should be considered at relatively high risk if they have a history of chemical dependency, serious psychiatric illness, cardiopulmonary disease, gastrointestinal disorders, sleep disorders (particularly untreated central sleep apnea), chronic encephalopathy, and/or hypogonadism. In these clinical circumstances, opioid therapy should be used only if it is considered to be the sole plausible means to control debilitating pain and in the context of consultation and comanagement with specialists who have expertise in the respective area.

4. Is the patient likely to manage his/her opioid therapy responsibly?

Emerging evidence and supporting statements from the American Pain Society, American Academy of Pain Medicine, and other associations provide a rationale for opioid-based therapy in patients with CNCP syndromes.[18,28] Regrettably, increased opioid prescribing has mirrored a concomitant rise in nonmedical use of these drugs. In 2000, the National Household Survey on Drug Abuse, for example, identified approximately 2 million people in the United States aged 12 years and older as new initiates to the nonmedical use of prescription opioids—a 400% increase from the mid-1980s.[39] Although the risks for opioid misuse, abuse, and addiction are low in most patients who do not have a current or past history of psychiatric or substance abuse disorder, it is impossible to identify all patients who will use their medication inappropriately.[40] This fundamental challenge in chronic pain management requires a structured, methodical evaluation of risk factors related to opioid misuse and abuse for every patient being considered for opioid therapy—a so-called "Universal Precautions" approach (Table 1).[41] Of primary interest in this risk assessment are personal or family history of substance abuse and significant psychiatric disorders.[34,41,42] In younger patients, nicotine use, history of physical or sexual abuse, chaotic social environment, and multiple motor vehicle accidents also may be relevant.[34,40,41]

Table 1. Universal Precautions[41]

1.	Establish diagnosis with the appropriate differential
2.	Conduct psychological assessment, including risk of addictive disorders
3.	Obtain informed consent
4.	Establish a treatment agreement
5.	Assess pain and function
6.	Initiate an opioid therapy trial
7.	Reassess pain, function, and behavior
8.	Regularly assess the 4 A's • **A**nalgesia • **A**ctivities of daily living • **A**dverse events • **A**berrant drug-taking behavior
9.	Periodically review pain diagnosis and comorbid conditions
10.	Document appropriately

Office-based risk assessment for potential opioid misuse may be facilitated by validated self-report tools, such as the Opioid Risk Tool and the revised version of the Screener Opioid Assessment for Patients with Pain (SOAPP-R).[41,42] Screening tools are designed to help clinicians stratify patients based on the risk for future aberrant drug-taking behaviors and include questions that address potential psychological issues and personal and family history of substance abuse. The SOAPP-R, for example, was derived empirically from a comprehensive listing of potentially predictive patient characteristics and circumstances. Each of the 24 items on this self-assessment questionnaire is scored between 0 (*never*) and 4 (*very often*), with questions addressing such predictors as social environment, impulsivity, and drug and alcohol use. The resulting score is used to stratify patients as at high, medium, or low risk for future aberrant behaviors.[42] Of note, the tools rely on candid patient self-report and thus are vulnerable to dishonesty; therefore, they should be used in the context of a comprehensive risk assessment. This may include interviews with family members; diligent use of prescription monitoring programs; and periodic, unannounced testing for prescribed and illicit substances in urine, saliva, blood, or hair.[43-45]

Patient stratification based on the results of these tests and tools helps shape the structure of treatment and degree of monitoring, including the identification of patients who can be treated without additional support, those who will require consultation with specialists, and those who should be referred to experts in pain and addiction medicine.[34] For patients with an active drug problem or those with significant risks for abuse, addiction, or diversion, an opioid trial may be inappropriate, appropriate only after all other therapeutic options have been exhausted, or appropriate only if performed or directed by addiction medicine specialists. Structured approaches for higher-risk patients include frequent office visits, pill counts, smaller prescription amounts, frequent unannounced urine drug testing, and psychiatric consultation.[43-45] Importantly, aberrant behaviors do not always indicate addiction or abuse; rather, each behavior requires a differential diagnosis addressing underlying motivations. Results from this continual assessment will dictate necessary adjustments to the treatment regimen.

Initiating Opioid-Based Therapy For Unremitting Baseline Pain

Like pharmacotherapy for most chronic conditions, opioids are prescribed initially on a trial basis to determine whether the balance between benefits and risks warrants continued treatment with the particular drug. Depending on the results of this trial, opioid therapy may be considered as a potentially long-term option. Alternatively, a lack of analgesic effect, development of intolerable AEs, or unsafe use, among other reasons, will necessitate discontinuation of the drug. Although the appropriate length of an opioid trial has not been standardized, a recent study of patients with chronic LBP demonstrated that the response to opioids at 1 month correlated significantly with response at 6 months, with a particularly strong relationship observed for insufficient analgesia.[46]

Initiation of therapy in both primary care and specialty settings often is accompanied by an opioid treatment agreement (OTA). If the clinician chooses a verbal treatment agreement, this must be noted appropriately in the patient's record. Many providers choose a written agreement. OTAs include information about the goals and risks of therapy, the rules and boundaries for treatment, and potential discontinuation strategies (often referred to as "exit strategies") to address inadequate analgesia, intolerable AEs, and/or nonadherence.[47] OTAs also may provide documentation of informed consent and a framework within which clinicians and patients can discuss and affirm their respective responsibilities. This structured process also helps reinforce the importance of trust, transparency, and adherence to the treatment plan.[48]

When initiating opioid therapy, key considerations include the clinical profile of the pain, characteristics and route of administration of the opioid medication, and the patient's previous experience with specific opioids (Figure 1).[34] Therapy traditionally is initiated with an immediate-release, short-acting opioid (SAO), beginning at a dose that is safe and likely to be effective[49] and titrating upward until an acceptable balance between analgesia and AEs is achieved. Titrating with SAOs rather than long-acting opioids (LAOs) seeks to minimize the risk for overdose and avoid extended periods of distress should AEs develop. After titration, patients often are transitioned to an equivalent daily dose of an LAO. These agents provide stable plasma drug levels that may translate to more consistent analgesia.[49] In addition, the longer dosing interval associated with LAOs may be more convenient for patients and thus may improve adherence to the dosing schedule. Like most aspects of opioid treatment, there is little if any evidence supporting the preferential use of LAOs for CNCP; patient-by-patient decision making is shaped largely by clinical experience. Knowledgeable prescribers may be comfortable initiating and titrating with an LAO, particularly in patients with prior exposure to specific opioids; such an approach, however, requires particularly vigilant monitoring for AEs.[50]

Response to opioids may differ markedly among individuals. This can be explained, in part, by the unique pharmacologic properties of each agent; patient-specific variation in opioid receptors that mediate analgesia, side effects, and related pharmacodynamic effects[50]; and the existence of cytochrome P-450 variants responsible for the metabolic degradation of the analgesic.[51,52]

Interpatient variability in response to opioids also presents a rationale for the establishment of a well-structured opioid trial that allows for opioid rotation. Switching the patient to a different opioid may help overcome inadequate analgesia and/or intolerable side effects. Importantly, an open and ongoing dialogue with the patient before and during an opioid trial provides the reasons for switching medications, without which patients may erroneously associate switching with treatment failure. A retrospective chart review of various CNCP conditions found that the first prescribed opioid was effective for 36% of patients, whereas 31% of those who required rotation because of side effects or ineffectiveness reported an adequate response with the second opioid.[52] Successive opioid rotations—in some cases as many as 5—identified an appropriate opioid in more than 80% of patients. There is no established limit on the maximum number of trials, and more studies are needed to help identify the best initiation, rotation, and discontinuation strategies.[52]

The effectiveness of opioids also can be enhanced using rationally constructed multidrug regimens.[53] Co-administration of drugs with different and potentially complementary mechanisms of action may result in additive or supra-additive (synergistic) analgesia, with lower dosing requirements for individual agents and fewer associated side effects. In a study comparing maximum tolerated doses of morphine, gabapentin, and the combination of gabapentin and morphine in patients with painful DPN or PHN, the combination treatment resulted in lower total scores on the Short-Form McGill Pain Questionnaire relative to either agent alone ($P<0.05$ for the combination vs placebo, gabapentin alone, or morphine alone).[54] In another study of patients with moderate to severe DPN who already were receiving a maximum tolerated dose of gabapentin, the addition of sustained-release oxycodone led to improved pain relief (average reduction in pain scores, 33%), less need for rescue medication, and fewer nights of disturbed sleep ($P<0.05$ for each domain compared with placebo).[55] Fundamental issues

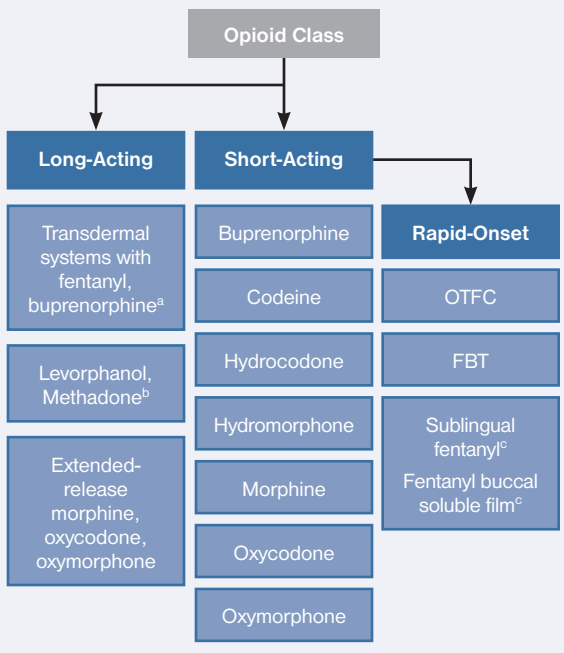

Figure 1. Opioid selection.[34]

[a] Transdermal buprenorphine available in Europe.

[b] Analgesic effects often are shorter-lived than effective metabolites.

[c] In development.

FBT, fentanyl buccal tablet; **OTFC,** oral transmucosal fentanyl citrate

remain—for example, whether sequential or concurrent addition of medications is preferable—and underscore the need for well-designed studies and a methodical approach based on clinical experience and practice-based evidence. A 10-step approach to designing rational multidrug therapeutic plans was devised recently to serve as a template for practicing clinicians, although it requires formal validation (Table 2).[53]

Assessing Treatment Outcomes For Baseline Pain

When monitoring patient outcomes, clinicians may want to consider the 4 A's of pain management: Analgesia, Activities of daily living, AEs, and Aberrant drug-taking behaviors.[43] Review of these domains can facilitate ongoing assessment and appropriate documentation as the clinician monitors treatment response and adherence. In this way, the aspects of successful patient outcomes extend beyond lowered pain intensity scores to include improved psychosocial functioning.[43] Patients also should be asked whether they experience intermittent periods during which their pain is uncontrolled.[56] Characterizing the dynamic profile of baseline pain can facilitate adjustments to the medication regimen that address the daily ebbs and flows in pain levels. For example, worsening of symptoms in the morning may represent cyclical opioid withdrawal in patients whose analgesic blood levels may wane at regular intervals.

Routine follow-up and monitoring of pharmacotherapy also facilitates side-effect management. Although tolerance to most opioid-related side effects develops quickly with ongoing therapy, opioid-induced bowel dysfunction, notably constipation, may persist.[57] In fact, among patients with cancer, opioid-induced constipation commonly causes more distress than the pain itself.[58] Proactive and prophylactic strategies may be needed to reduce this symptom; in addition to increased fluid and dietary fiber, patients may be prescribed a stimulant laxative and a stool softener.[59]

Patients also should be reassessed frequently to confirm appropriate use of medications. Assessment, interpretation, and differential diagnosis of aberrant drug-taking behaviors can be challenging, in part because of inconsistent nomenclature used to characterize prescription opioid abuse (Table 3).[44,61] Some behaviors, such as the acquisition of opioids from multiple prescribers or repeated requests for early refills, may be more indicative of significant abuse or addiction, whereas others, such as complaints about the need for more medication or a rare unilateral self-escalation of the dose, may suggest inadequate pain control.[44,61] Whatever the underlying reason, behaviors that do not conform to the treatment plan must be addressed quickly and openly, beginning with a nonjudgmental assessment of potential motives.[43] Such an approach seeks to facilitate a candid dialogue between the patient and the prescriber, which in turn informs an appropriate degree and structure of monitoring.

Table 2. Rational Multidrug Therapy[53]

1.	Conduct initial assessment, formulate appropriate diagnosis, prioritize treatments.
2.	Review past treatments, including over-the-counter preparations, complementary therapies, and previous drug combinations.
3.	Consider medications with evidence of efficacy for the disorder. When possible, also chose drugs to minimize adverse effects, end-organ effects, drug–drug interactions, and cost.
4.	Use a staring dose at the low end of the recommended range, and titrate slowly.
5.	Continually reassess therapeutic efficacy. Discontinue medications that do not provide clinically meaningful pain relief (eg, ≥30% reduction in pain) and functional improvement.
6.	Monitor adverse effects.
7.	If good efficacy is documented, but the patient reports intolerable side effects, consider rotating to a different medication with a similar mechanism of action. Alternatively, consider therapy to control side effects.
8.	In general, begin 1 drug at a time, titrating slowly while monitoring for efficacy and adverse effects until maximum benefit or usual therapeutic dose is reached.
9.	Co-administer drugs with differing mechanisms of action.
10.	When adding drugs, consider all previous steps as well as potential drug–drug interactions.

Table 3. Terminology Associated With Opioid Therapy[44,61]

Tolerance	• State of adaptation in which exposure to a given dose of a drug induces biologic changes that result in diminution of 1 or more of the drug's effects over time. • Need for escalating doses of a drug to maintain a given level of effect over time.
Physical dependence	• State of adaptation manifested by a drug class-specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, or administration of an antagonist.
Misuse	• Medical use of a medication for purposes other than directed or indicated.
Abuse	• Use of any illegal drug. • Intentional self-administration of a medication for a nonmedical purpose, such as altering consciousness.
Addiction	• A primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations and characterized by 1 or more of the following behaviors: – Impaired control over drug use – Compulsive use – Continued use despite harm – Craving
Diversion	• Intentional removal of a medication from legitimate distribution and dispensing channels.

Breakthrough Pain: From Phenomenology To Treatment

Although control of baseline persistent pain is necessary, it may be insufficient for optimal pain care in all patients. Severe fluctuations in baseline persistent pain require adjustments in the behavioral, cognitive, and/or pharmacologic treatment plan. Characterization of the epidemiology and phenomenology of severe, debilitating, and often unpredictable pain episodes continues to shape the definition of BTP. Originally identified in the oncology setting, the clinical construct of BTP was defined as a transitory increase in pain levels to greater than moderate intensity, superimposed on a baseline pain of moderate intensity or less, in patients receiving long-term opioid therapy.[5] The prevalence, etiology, temporal characteristics, and adverse consequences of BTP in patients with cancer are well described.[5,62] More recently, remarkably similar prevalence, patterns, and functional effects have been observed in patients with such CNCP conditions as OA, neuropathic pain, and LBP (Table 4).[63,64] Irrespective of the underlying etiology, independent assessment and treatment of BTP is associated with significant improvement in patient satisfaction, functional outcome, and QoL.

Results from epidemiologic surveys and well-controlled randomized studies in patients with chronic cancer-related pain and CNCP syndromes support a clinically refined definition of BTP as a transitory increase in pain that negatively affects function or QoL in patients with adequately controlled baseline pain who receive analgesic drug therapy on most days.[64,65] This more inclusive definition emphasizes the negative impact of BTP episodes and the importance of controlling baseline persistent pain. The "breakpoint" between generally uncontrolled baseline pain and dynamic exacerbations of otherwise controlled baseline pain is not well established and requires careful clinical assessment. In the absence of a consensus definition for controlled baseline pain, several investigators have suggested that re-evaluation of the baseline regimen may be required in patients reporting more than 4 daily BTP episodes.[7] Identifying these episodes demands continual monitoring of the peaks and troughs that characterize chronic pain, which may best be accomplished through use of patient diaries.[7]

Numerous studies have demonstrated the functional impact of BTP. Patients report decreased physical functioning and difficulty sleeping,[56] impaired mood, and significantly increased anxiety and depression.[62] A recent study of patients with CNCP found that BTP interferes with multiple QoL domains, including ability to work and interact with other people.[66] Such functional impairment and psychological distress imposes a financial burden on the individual and society as a whole. Patients with BTP, for example, have a higher frequency of hospital admissions (36.9% vs 22.5%) and higher estimated annual medical costs ($12,000 vs $2,400) related to hospitalizations, emergency room visits, and physician visits than those without BTP.[67]

Assessment of Breakthrough Pain

Effective management of BTP requires independent, comprehensive assessment. Like the evaluation of baseline pain, this begins with in-depth characterization of the pain profile and identification of correctable causes. Describing the intensity, duration, character, location, and potential precipitants of the BTP episodes helps shape the therapeutic plan. Importantly, the etiology and pathophysiology of the episodes often are related to the baseline persistent pain, suggesting that the same underlying disease mechanisms directly cause BTP.[5,62,63] In other cases, BTP may be an indirect consequence of a chronic condition (eg, deconditioning), a result of treatment (eg, chemotherapy-induced neuropathy), or a manifestation of concomitant illness.[68]

Categorizing the episodes based on predictability and underlying cause facilitates the management of BTP (Figure 2, page 8).[64,69] Idiopathic BTP is spontaneous, unpredictable, and independent of an identifiable precipitant. Incident (precipitated) BTP is associated with a known event, which can be volitional (eg, movement), nonvolitional (eg, sneezing), or procedural (eg, related to a therapeutic intervention).[56] End-of-dose failure occurs when the analgesic effects of the around-the-clock (ATC) medication wane, leading to gradually increased pain levels at the end of the dosing interval.

Failure to address and to treat BTP as an independent and clinically important construct often leads to unnecessary and potentially harmful increases in baseline medication doses intended to treat the patient's "worst pain." In other cases, therapy that is otherwise effective for the baseline pain may be wrongly discontinued if the patient continues to report periods of severe pain. Among challenges in the assessment of BTP, currently available clinical tools—including the Brief Pain Inventory, McGill Pain Questionnaire, and Neuropathic Pain Questionnaire—do not address pain fluctuations adequately. Self-report questionnaires specific to BTP have been developed, although some were designed for research purposes and are not used widely in practice.[5,70-73] Clinical experience supports the use of

Table 4. BTP in Patients With Cancer-Related and Noncancer Pain[62-65]

	Cancer BTP	Noncancer BTP
Subjects	227 (2 studies)	228
Prevalence, %	64-65	74
Frequency, episodes/d (range)	4-6 (1-3,600)[a]	2 (<1-12)
Duration, min (range)	30 (1-240)	60 (1-720)
Time to maximum intensity, min (range)	3 (0-30)	10 (0-180)
Identified precipitant, % of episodes	55-62	69
Pains that could never be predicted, %	48.2	45
QoL	Significant effects on BDI, BAI, and all domains of BPI	Adverse effects on multiple QoL domains

[a] Maximum observed in a lung cancer patient with cough-induced pain every minute from a broken rib.
BAI, Beck Anxiety Index; **BDI,** Beck Depression Inventory; **BPI,** Brief Pain Inventory; **BTP,** breakthrough pain; **QoL,** quality of life

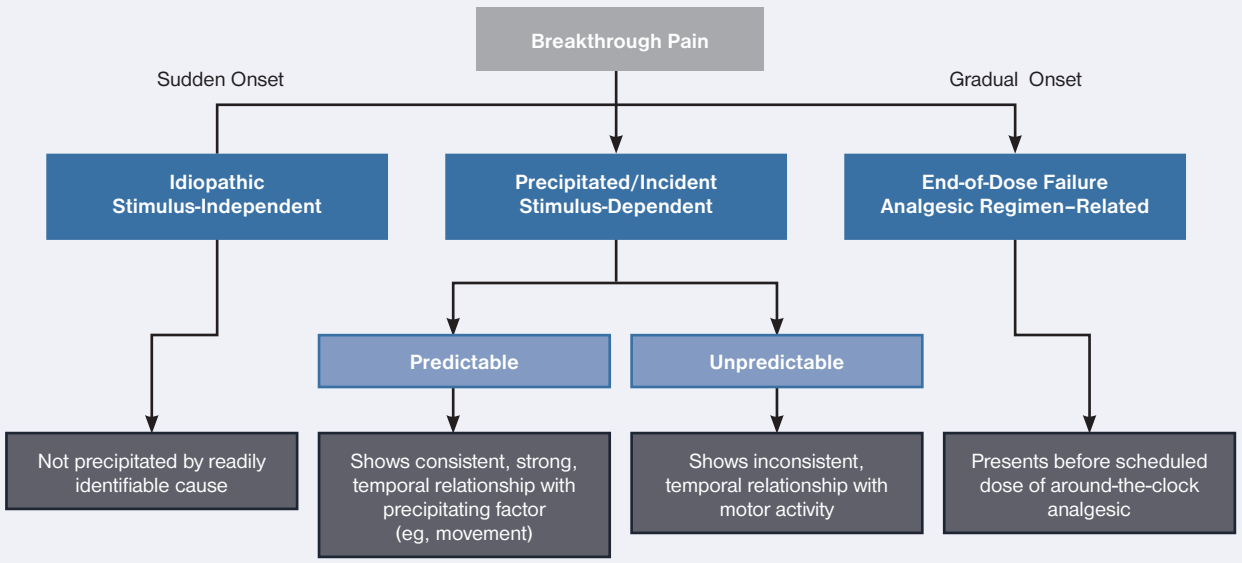

Figure 2. BTP subtypes.[64,69]

a structured approach to BTP assessment, comprising practical questions that characterize the potential etiologies and subtypes of the BTP episodes, their functional effects, and potential therapeutic interventions (Table 5).

Treatment of Breakthrough Pain

Optimal treatment of BTP targets the underlying disease or pathogenic mechanisms.[68] If disease-modifying therapy is not possible, symptomatic management, following the precepts of baseline pain control, is recommended. As such, individualized risk–benefit analysis of the range of potential treatments plays a central role in determining nonpharmacologic (eg, pacing of activities, heat and cold, patient education, relaxation, cognitive-behavioral techniques) and/or pharmacologic (eg, acetaminophen, NSAIDs, opioids, ketamine) modalities.[74]

Because BTP often is characterized by a time to peak pain intensity of just a few minutes, and the average duration of an episode is 30 to 60 minutes, the pharmacokinetic profile of any prescribed analgesic is of particular importance.[5,62,63] Ideal medications provide rapid pain relief, with a brief duration of effect to avoid unnecessarily long periods of drug exposure and increased risk for AEs.

Management strategies vary by subtype of BTP episode.[68] Incident BTP can be treated by targeting the precipitant directly, although this approach may not be feasible for many patients.[75] Predictable episodes of incident BTP may be ameliorated by proactive (ie, anticipatory) treatment with breakthrough medication prior to the precipitating activity.[70] Ideally, the pharmacokinetic profile of the drug approximates the onset of the precipitated pain.[74] Otherwise, the timing of the

Table 5. Assessment of Breakthrough Pain

Pain assessment	1	Do you have periods during the day when your pain is uncontrolled? If so, how often?
	2	How long is it from when you notice the pain until it is at its worst? How long do the episodes last?
	3	Can you predict when your pain will become uncontrolled? Does this occur at a particular time of day or with certain activities?
	4	Do the episodes feel like the same type of pain you usually have, or a different type? If they are different, how do they differ?
Function	5	Do the episodes affect your ability to handle daily responsibilities at home or work?
	6	To what extent does avoiding activities due to fear of a pain episode compromise your quality of life?
Palliation	7	Does anything help to lessen the severity of the episodes? What is effective? What is ineffective?

preemptive dose relative to the precipitating activity should be considered in light of the pharmacokinetics of the prescribed agent.[74] It should be noted that the frequency of precipitated BTP may increase as effective baseline and breakthrough therapy allows patients to become more active—an encouraging sign of treatment success—and may necessitate behavioral adjustments and additional treatment modalities.

Idiopathic or nonvolitional precipitated BTP can be addressed by adjusting the baseline regimen (eg, increasing the baseline dose or prescribing an additional ATC agent, both of which may be hampered by dose-related toxicity) or by adding a breakthrough medication.[34] The unpredictability of idiopathic episodes again highlights the importance of matching the mechanism and kinetics of the breakthrough medication with the onset of the BTP.

End-of-dose failure also is managed by adjusting the regimen for the background persistent pain,[75] either by increasing the baseline dose, which may be limited by the development of side effects, or switching to an agent with a longer duration of action. For example, modified-release opioids are designed to provide stable drug plasma levels for 8 to 72 hours, depending on the formulation. However, the duration of action of these medications varies among patients. A recent study found that 91% of patients treated for CNCP with controlled-release oxycodone required dosing more frequently than the twice-daily recommended for this formulation.[76] In such cases, shortening the dosing interval may be helpful.[77]

Opioid-Based Therapy for Breakthrough Pain

Idiopathic and incident BTP episodes often are managed by adding an SAO to the treatment regimen. This approach seeks to maximize analgesia during brief windows of increased pain while avoiding the side-effect burden that may result from increasing the baseline analgesic dose.[68] As with baseline therapy, an opioid may be considered for all patients experiencing BTP that impairs function or reduces QoL. The decision to proceed, therefore, requires an independent evaluation of the 4 critical questions discussed previously. These questions, now applied to BTP, advise the clinician to address conventional practices for the BTP, relative risk–benefit ratios for all potential modalities, specific risks related to opioid pharmacology, and concerns about responsible use of short-acting or rapid-onset rescue medication.[34]

If the decision is made to treat BTP with an opioid, comprehensive assessment and classification of the BTP subtype will guide the treatment strategy. Predictable BTP can be pretreated by administration of an SAO 30 to 40 minutes before the exacerbating activity. For episodes that occur spontaneously or are associated with an activity that prevents standardized pretreatment (eg, getting up to answer the door), clinicians may consider the subclass of rapid-onset opioids, which currently includes oral transmucosal fentanyl citrate (OTFC) and the fentanyl buccal tablet (FBT). Designed specifically to match the pharmacokinetics of the formulation with the temporal profile of a typical cancer-related BTP episode, OTFC and FBT are based on the synthetic opioid fentanyl.[78] This agent is highly potent and lipophilic—a property that promotes rapid distribution into tissues—and has an established safety profile when prescribed by practitioners knowledgeable in the use of schedule II opioids.[78] Transmucosal delivery of the active ingredient into the buccal capillary bed allows for a quick onset of action with some of the opioid bypassing the gastrointestinal tract and first-pass metabolism.[68] Both OTFC and FBT are FDA-approved for the treatment of opioid-tolerant patients with cancer-related BTP.[79,80]

Case Study: Owen

Owen is a 51-year-old mortgage broker who is married and has 1 teenaged son. One year ago, Owen received a diagnosis of small cell lung cancer. After aggressive treatment with chemotherapy (docetaxel), he developed a severe, debilitating, diffuse, peripheral neuropathy. Although it has been 6 months since he completed chemotherapy, Owen still suffers from continuous, severe pain that he rates as 8 to 9 on a scale from 0 (*no pain*) to 10 (*worst pain imaginable*).

Current treatment for Owen's painful peripheral neuropathy includes pregabalin 100 mg 3 times daily, which reduces his pain level to 6 to 7 out of 10. Escalation of the pregabalin dose is prevented by edema. Owen has no significant personal or family history of substance abuse and has been stratified as low risk for future aberrant drug-taking behaviors based on a comprehensive risk assessment, a score of 7 on the revised version of the Screener Opioid Assessment for Patients with Pain, and an office interview with him and his wife.

After signing an opioid treatment agreement, Owen is prescribed oxycodone/acetaminophen (APAP) 5/325 mg 2 tablets, up to 4 times daily in addition to pregabalin. He also receives specific instructions to lock up his medications to prevent access by anyone else, including his son and his son's friends. One week later, Owen reports that he has been taking 8 oxycodone/APAP tablets daily, and his pain level is 3 out of 10. He is transitioned to oxycodone extended-release (ER) 20 mg twice daily. Although this regimen causes some constipation, increased dietary fiber and senna at bedtime effectively manage this symptom. Owen is advised to return in 1 month.

When he returns for follow-up as scheduled, he reports that overall, his medication is working; however, there are times when he feels that his pain is "out of control." He cannot identify specific points in the day when his pain is more likely to flare up, and nothing he has tried prevents the episodes from occurring. His most severe pain during the previous week was rated 9 out of 10. He is not experiencing sedation or "mental clouding" with his current analgesics. Owen's wife recounts that he is neither snoring nor having apneic episodes.

Owen's dose of oxycodone ER is titrated up to 40 mg twice daily, and after 2 weeks, his baseline pain is reduced to 2 out of 10. Nevertheless, Owen still reports idiopathic breakthrough pain (BTP) episodes, often 3 or 4 times daily, reaching 9 out of 10 within 5 minutes and lasting for close to 1 hour. He is nervous about leaving the house because he does not want to be away from home when an episode strikes.

Owen is considered opioid-tolerant based on his daily opioid dose (oxycodone 40 mg twice daily), and he is prescribed fentanyl buccal tablet (FBT) 100 mcg to be taken up to 4 times daily. Owen is told that if a BTP episode is not relieved after 30 minutes, he may take only 1 additional dose for that episode and must wait at least 4 hours before treating another BTP episode with FBT. Eventually, Owen's dose is titrated up to 2 tablets of FBT 100 mcg (1 on each side of the mouth in the buccal cavity) for every BTP episode. The combined treatment regimen controls his baseline pain (2/10), quickly ameliorates his BTP episodes, and allows him regain "control of his life."

Several studies of OTFC in opioid-tolerant patients have demonstrated efficacy and safety,[66,81,82] as well as improvement in QoL measures—notably enjoyment of life, mood, and general activity level.[66] FBT causes an effervescent reaction that optimizes dissolution, membrane permeation, and ultimately early systemic exposure to fentanyl.[83] Placebo-controlled studies of this medication in opioid-tolerant patients with cancer-related or noncancer BTP demonstrated significant improvements in efficacy variables (eg, pain intensity differences) 10 minutes after dosing.[84,85] FBT provides approximately 30% to 50% greater bioavailability than OTFC, suggesting that FBT delivers the same amount of fentanyl using approximately two-thirds the dose required for OTFC.[86] Thus, FBT and OTFC are not interchangeable. Other oral transmucosal formulations of fentanyl, including sublingual sprays and dissolvable polymer discs, currently are in development.[68]

Opioid-based management of BTP in patients with CNCP raises several important issues. First, rapid-onset opioid medications are only to be used in patients who are opioid tolerant, because previous exposure to such medications reduces the risks for serious AEs such as respiratory depression and overdose; however, identification of patients who fit this description is complicated by interindividual variability in opioid responsiveness.[51] Threshold levels for the daily opioid dose required before prescription of a rapid-onset formulation, therefore, have been established (Table 6).[87] Vigilant monitoring of the patient during initial dosing and titration also is advised.

Table 6. Baseline Opioid Doses Considered Safe Before Initiating Rapid-Onset Opioids[87]

Patients are considered opioid tolerant when they are taking a minimum of the following for ≥1 wk	
a.	60 mg/d oral morphine
b.	25 mcg/h transdermal fentanyl
c.	30 mg/d oxycodone
d.	8 mg/d oral hydromorphone
e.	An equianalgesic daily dose of another opioid

Second, studies have shown that there is no correlation between the baseline opioid dose and the effective dose of the rapid-onset opioid; in an analysis of 3 clinical trials examining the role of OTFC for BTP, the breakthrough opioid dose ranged from 1% to 72% of the daily ATC dose.[88] Thus, breakthrough medications should be provided on an individualized basis, with a titration strategy separate from that used for the baseline medication.

Third, nonmedical use of prescription opioids poses significant risks to the individual, the prescriber, and society. Long-term opioid therapy in patients with CNCP requires scrutiny and vigilance among clinicians. Whether the risk for aberrant drug-related behaviors is heightened in patients with CNCP relative to cancer patients has not been shown. Similarly, the relative abuse liabilities of long-acting, short-acting, and rapid-onset opioids have yet to be determined. Still, certain patient subpopulations (individuals with active addiction, those in recovery for addictive disorders, or those biologically predisposed to the development of addictive disorders) may require more detailed assessment, tighter monitoring, comanagement, and/or specialist referral when prescribed an opioid—particularly one with a rapid onset of effect.

Finally, the variability and unpredictability of patient responses to opioid medications requires the application of an individualized paradigm similar to that used in other areas of medicine, such as oncology and empiric antibiotic therapy. Appropriate selection of a BTP medication considers a comparison of the onset of pharmacodynamic effect with the onset and predictability of BTP episodes, the desired duration of analgesia, and prescribers' level of comfort and experience administering available formulations. An "N-of-1" trial methodology, constructively established on comprehensive risk mitigation strategies is critical to treatment success. Careful patient selection, risk stratification, and structuring of therapy all provide a management framework within which goals of pain therapy and associated risk can be monitored longitudinally. Careful monitoring in turn leads to necessary adjustments across the full range of treatment modalities and, presumably, to improved outcomes.

Conclusion

Chronic pain is a debilitating biopsychosocial condition prevalent in both cancer and noncancer pain populations. Its optimal management requires comprehensive assessment and careful therapeutic management, including consideration of both the baseline and breakthrough components of the pain profile. Opioids have an established role in pain related to cancer and other advanced medical illnesses, as well as an increasing contribution to the long-term treatment of carefully selected and monitored patients with certain CNCP conditions. All individuals with chronic, moderate to severe pain associated with functional impairment should be considered for a trial of opioid therapy, although not all of them will be selected. The decision to proceed is supported by comprehensive assessment, analysis of conventional practice, an evaluation of the relative risks and benefits of the therapeutic options, and intention to treat on a long-term basis. The structure and degree of monitoring for long-term opioid therapy should reflect initial and ongoing assessment of the risk for aberrant medication use; and therapy should be tailored individually over time, through examination of analgesia, functional goals, side effects, and patient adherence to the prescribed regimen. Ongoing assessment may reveal the presence of BTP, necessitating a second methodical patient evaluation to position potential therapies appropriately, including short-acting and rapid-onset opioids.

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EXHIBIT 91

THE WORLD'S BIGGEST RISKS

The pain killer: A drug company putting profits above patients

Dina Gusovsky | @DinaGusovsky | 10:13 AM ET Wed, 4 Nov 2015

The United States' opiate drug problem isn't limited to illegal narcotics. The sale of dangerously addictive painkillers prescribed by our physicians has quadrupled in the past decade, and one company in particular is pushing pain to the legal edge of aggressive medical marketing.

According to criminal complaints, attorneys general reports and CNBC sources, specialty pharmaceutical company Insys Therapeutics — with the help of several physicians across the country now under investigation — is putting profits before patients as it makes millions off your pain.

Insys is subject to investigations regarding the sales and marketing practices of its main product — Subsys Fentanyl, a painkiller delivered as an oral spray — by both federal and state attorneys general offices in California, Massachusetts, Connecticut, Arizona and Illinois, according to its 10-Q filing.

"I've been investigating drug cases for about 15 years now, and the conduct that we saw in this case was among the most unconscionable that I've seen," said Oregon Assistant Attorney General David Hart, who led an investigation that resulted in the first state-level settlement with Insys and a detailed, published report on the company's practices. "There was harm done to patients on a level I'm not used to seeing," Hart said.

In a recent presentation obtained by CNBC, an officer from the Inspector General's Office of the United States Department of Health and Human Services placed Subsys on a list of "new diversion drugs of concern." Diversion is a form of medical fraud that can include doctors prescribing drugs for unintended uses.

CNBC

Subsys fentanyl sublingual spray

Scottsdale, Arizona-based Insys Therapeutics' revenue is almost entirely derived from the highly addictive opiate fentanyl, which it markets under the brand name Subsys Fentanyl. In the six months ended June 30, 2015, Subsys sales accounted for $147.2 million of $148.4 million in total revenue. (Insys is scheduled to report third-quarter earnings on Thursday morning.)

Fentanyl products are "the most potent and dangerous opioids on the market," said Dr. Andrew Kolodny, executive director of Physicians for Responsible Opioid Prescribing and chief medical officer of the Phoenix House Foundation. According to some physicians, fentanyl is about 100 times more powerful than morphine and gets into the bloodstream faster because it is sprayed under the tongue.

The potency of Subsys also comes with a high price tag. One package of 30 sprays can cost between $900 and $3,000, depending on the dosage, and those prices only seem to be increasing. The fentanyl class of drugs had an average prescription price of $160 last year, according to Express Scripts, the largest pharmacy benefits manager in the U.S.

The average price of 100 micrograms (mcg) of Subsys (the smallest dose) is 70 percent higher this year than the average 2014 price.

Express Scripts began excluding Subsys from its list of covered drugs this year. UnitedHealth Group also recently made the decision to exclude the drug in 2016, citing lower-cost options.

You'll never guess what's killing America's teens

The stock market has richly rewarded the Insys business plan. The company started marketing the drug in 2012, went public in May 2013 and went on to become that year's top-performing initial public offering. At press time, Insys shares were up over 600 percent since it began trading on the Nasdaq.

In October 2013, John Kapoor, chairman and founder of Insys, made the annual *Forbes* billionaire list for the first time, due to his various pharma-related investments and companies. In March of this year, Insys entered into a consulting agreement with Kapoor, paying him an additional $300,000 annually "to compensate Dr. Kapoor for his ongoing time and contribution to the company," the company stated in a filing. He also receives compensation as executive chairman of the board of directors of Insys. In 2014, Kapoor received a total of $228,472 for the board role.

How the company has achieved its results has come under scrutiny, with allegations that Insys is pushing the drug far beyond cancer patients and engaging in potentially fraudulent activities in the process.

Insys shares have been volatile in trading this year — up 37 percent year-to-date, but down 35 percent in the past three months through Nov. 3. Short interest — bets that the company's stock will decline — have tripled since late 2014, according to Nasdaq, and now represent roughly 75 percent of the public float, or the amount of company shares available for investors to trade.

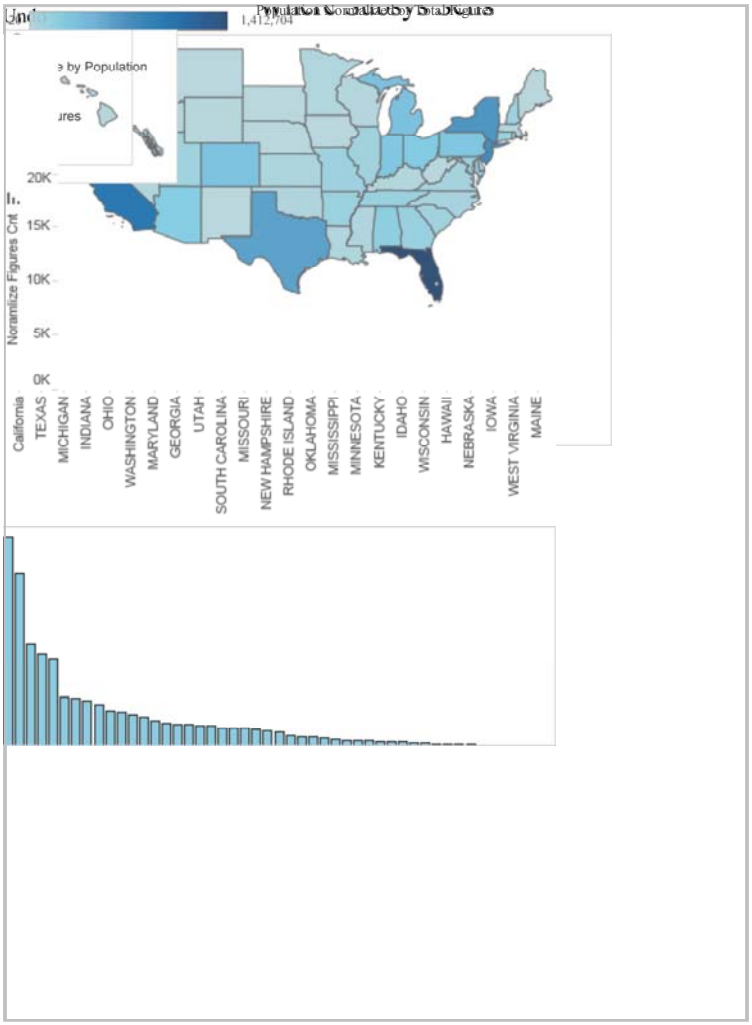
Relentless Rx

Subsys, according to FDA guidelines, is only meant to be used to treat late-stage cancer pain. In the 2012 FDA approval letter, the agency stated, "This new drug application provides for the use of Subsys (fentanyl sublingual spray) for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain."

Several sources — and emails obtained from current and former employees of Insys, as well as from physicians — show sales staff were under immense pressure, including threats of termination, to get

doctors to write more prescriptions and higher doses of Subsys for everything from neck pain to migraines.

Insys declined an on-camera interview and refused to respond to repeated requests for comment.



Shannon Walsh, a former Insys sales representative, resigned in October because of what she said is "the negative environment, the continued deception and the lack of managerial focus, ethics, transparency and direction" within the company.

Walsh was based in Oregon and said she had been excited to work for Insys, mainly because a drug like Subsys could have relieved the intense pain her father — who was fighting cancer for several years before he passed away — had experienced. When she approached her managers about reaching out to palliative-care offices to tell them about the drug, management replied that she shouldn't approach those types of facilities because "those patients would die soon anyway and couldn't titrate (increase their dosage)."

Walsh said she was shocked that the doctors Insys told her to target for Subsys prescriptions were mostly family doctors and internal and

general medicine physicians. "The physicians I spoke with had never heard of these fentanyl products. They also advised me that they would never have any occasion to use the products in this class, because they did not treat pain nor did they treat cancer," Walsh said.

The Southern Investigative Reporting Foundation's Roddy Boyd brought some of these issues to light earlier this year as well.

"I've been investigating drug cases for about 15 years now, and the conduct that we saw in this case was among the most unconscionable that I've seen."

-David Hart, Oregon Assistant Attorney General

In one instance, Insys allegedly hired the son of a pain-management doctor in an effort to persuade his father to write scripts, according to details from the Oregon settlement report.

In a text-message exchange between the son and father (names have been redacted because the doctor ended up not writing any scripts, since he had no cancer patients under care), it is implied the company targeted him in the hopes that his kin could convince him to do the wrong thing:

"These people from my company are relentless and it's kind of pissing me off. I have told them multiple times (starting with the interview) that you probably won't be writing my product due to the type of practice you have. ... I'm getting ready to tell them to **** off [expletive deleted]. Now they told me that Dr. Kapoor contacted you. I need you to help me to figure out what to say to them to calm them down."

The Oregon report also said that the company used "flirtation" in order to try to get doctors to write more scripts.

The doctor's son left the company after only three months. He did not respond to CNBC requests for comment.

While it is legal for physicians to prescribe medications for indications outside of FDA guidelines if they see fit, it is illegal for pharmaceutical companies to market a drug for off-label use.

Insys allegedly not only marketed Subsys off-label but also paid medical professionals in the hopes they would write more prescriptions of the drug.

Connecticut-based nurse practitioner Heather Alfonso pleaded guilty several months ago to accepting about $83,000 from Insys in return for prescribing the highly addictive Subsys, in what the Connecticut U.S. Attorney's office called kickbacks.

According to court transcripts of her plea agreement, the money was allegedly paid to Alfonso as part of Insys Therapeutics' speaker program, which was, in Alfonso's words, "basically dinner at a nice restaurant" with people who had no license to prescribe controlled substances like Subsys.

Thomas Carson, spokesman for the U.S. attorney's office in Connecticut, confirmed that the matter was still an ongoing investigation. Insys stated in its most recent 10-Q that it is currently investigating the matter.

The top prescriber nationally, according to a Health and Human Services Office of Inspector General Complaint, was Michigan-based Dr. Gavin Awerbuch.

The complaint questions whether Awerbuch should have even recommended Subsys for some of his patients, several of whom did not have cancer; some did not even report having severe pain.

Meet some of the doctors

DR. GAVIN AWERBUCH

Specialty Description: Neurology

Medicare Payment 2013: $6,443,778.33

Payments from INSYS 2013: $ 54,539.97

Payments from INSYS 2014: $28,875.49

HHS OIG criminal complaint filed on May 2, 2014. The investigation is continuing — a hearing date has been extended. Awerbuch did not respond to calls seeking comment.

Read more profiles:



Note: All three doctors are still working at pain clinics in their respective states.

Other doctors, like top Oregon Subsys prescriber James Gallant, were much more compliant with the company's insistence on writing more prescriptions with higher dosages.

The report said in at least one instance, Insys paid Gallant $2,400 to speak to his own physician's assistant about Subsys.

The Oregon report also said that "Gallant is not a pain specialist knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain."

Martin Shkreli Controversial CEO was accused of serious 'harassment'

According to the Oregon attorney general's report, Gallant's appeal to Insys may have been based upon the fact that he had a long history of getting into trouble with medical boards, including having his license suspended in 2014, in part because he misprescribed opioids.

CNBC made multiple attempts to contact Dr. Gallant, who is still employed at Corvallis Internal Medicine in Oregon, but calls were not returned.

The Insys way?

Sources and legal documents allude to the fact that much of Insys Therapeutics' ability to drive sales of Subsys had to do with its prior authorization unit. The company offered to intervene on behalf of the physician and patient in order to try to get Subsys approved by insurers. For doctors with minimal staff and resources, this service saves a lot of time and money. The catch, though, is that the patient must sign away all of his or her medical history and records to the company.

Oregon Assistant AG Hart told CNBC that while other pharmaceutical companies will sometimes pay patients' co-pays for a certain drug, he found it unusual that the company interjected itself into the whole process of obtaining insurance approval.

Insys often assisted with the prior authorization process for off-label prescriptions, according to legal documents.

In Oregon alone, out of the preauthorization forms submitted by Insys on behalf of patients, about 78 percent were for off-label uses, according to the Oregon report from its investigation.

Insys offers free units of Subsys and agrees to pay patients' out-of-pocket co-pay for up to $500 for each prescription, **an incentive the company still advertises**.

According to a class-action lawsuit brought by 68 Insys stock investors in October 2014, workers in its prior authorization department were "trained to pretend they worked in doctors' offices ... lie about medications the patient had already taken to obtain pain relief ... and ask for authorization for a three-month supply even if the doctor had only written the prescription for a one-month supply."

The suit alleges that "the Company's management was aware that only about 10% of prescriptions approved through the Prior Authorization Department were for cancer patients; the majority were written for peripheral neuropathy, lower back pain and sciatica." The lawsuit goes even further and alleges that there was "encouragement to doctors to disregard FDA mandated dosing, violation of patient privacy rights, fraudulent Medicare and private insurance claims, kickbacks to doctors, and nepotism."

Old dog, same tricks?

In 2008, biopharmaceutical company Cephalon settled with the U.S. government for $425 million in a suit against the company that alleged it marketed drugs, including one called Actiq, for unapproved uses (off-label). The FDA approved the drug for use only in opioid-tolerant cancer patients, yet the company allegedly promoted the drug for migraines, injuries and other things it wasn't supposed to be used for. (Teva bought Cephalon in 2011 at about a 41 percent premium.)

According to the Oregon settlement and class-action lawsuit, at least three employees involved in sales and/or marketing at Cephalon had moved over to Insys Therapeutics, including (now former) Insys vice president of sales Alec Burlakoff, as well as sales specialists Karen Hill and Joe Rowan.

Insys did not return CNBC's request for comment regarding these individuals.

The Oregon report also states that Insys deliberately targeted doctors who were already prescribing Actiq "and had already been exposed to Cephalon's unlawful off-label promotional campaign which was the subject of the federal criminal action."

Taxpayers Against Fraud's Patrick Burns told CNBC that kind of behavior was inevitable.

"It's amazing, but if you don't truly punish fraudsters, the fraud will never be extinguished. This is evidence of that," Burns said.

Ultimate consequences

Over the past decade, the amount of opioids prescribed and sold in the U.S. quadrupled, even though the amount of pain Americans reported had not changed, according to information provided by The Centers for Disease Control and Prevention.

Last year alone, more than 20,000 people died as a result.

But now, perhaps more than ever, doctors are taking a closer look at how to change the grim statistics.

Dr. Larry Epstein, a New-York based anesthesiologist who specializes in chronic pain management, told CNBC that doctors are now taking "hundreds and hundreds of patients off of these medications."

"We made a lot of addicted people. We ruined a lot of lives by prescribing a lot of medication. And now we're, I think, starting to recover from that and people are beginning to understand," Epstein

said. "But it's not so straightforward. And sometimes we don't know the answers until we make the mistakes."

A proposed settlement between Insys and plaintiffs in the class-action lawsuit of $6,125,000 is currently being offered, and a hearing is expected by Dec. 4 to determine (among other things) whether the settlement should be approved by the court and plaintiffs.

In August, Oregon and Insys entered into an Assurance of Voluntary Compliance (AVC) agreement in which the company agreed to pay the government $1.1 million. In settling the case, the company continued to deny all of the state's claims and did not admit any wrongdoing or liability. In a report accompanying the investigation, the state accused Insys of engaging in everything from kickback schemes to off-label marketing and encouraging some sales representatives to engage in inappropriate behavior with doctors, all in an effort to boost sales.

The settlement between Oregon and Insys may not seem like much money for a company with a market cap close to $2 billion. However, the fine is more than double Insys' $533,000 in Subsys sales in Oregon.

"If other states followed suit with similar conduct and obtained similar results, that would be a severe sanction for the company," Hart told CNBC. "Clearly, having to disgorge two times their income would be a deterrent and frankly perhaps a death sentence," he said.

On Oct. 29, the U.S. Food and Drug Administration granted Insys "Fast Track" designation — which expedites drug development, review and potential approval — for a sublingual spray to treat opioid intoxication or overdose, a growing nationwide problem that the company cited in a press release announcing the FDA decision.

The Southern Investigative Reporting Foundation's Roddy Boyd contributed to this report.

Is it time for your doctor to get a financial checkup?

It's not uncommon for pharmaceutical companies to pay physicians for things like speaking fees, but if you're suspicious about your own doctor or are curious about level of fees paid, you can give your doctor a financial checkup by doing a little research on the Centers for Medicare & Medicaid Services **Open Payments website**.

Dina Gusovsky
CNBC Reporter/Producer

EXHIBIT 92

DEPARTMENT OF JUSTICE

STATE OF OREGON

IN THE MATTER OF

INSYS THERAPEUTICS, INC,

Respondent.

NOTICE OF UNLAWFUL TRADE PRACTICES AND PROPOSED RESOLUTION

TO: Insys Therapeutics, Inc
444 South Ellis Street
Chandler, AZ 85224

c/o David Angeli
Angeli Unger Law Group LLC
121 SW Morrison Street, Suite 400
Portland, OR 97204

This notice is to inform you the Oregon Attorney General is authorized to file a lawsuit against you 10 days after you receive this notice. The Attorney General is required by statute to give you this notice. See Oregon Revised Statute 646.632.

To avoid the filing of a lawsuit against you, you may deliver an Assurance of Voluntary Compliance [AVC] to the Financial Fraud Section of the Oregon Department of Justice within 10 days after you receive this notice.

An AVC must be in writing and state what actions you intend to take to resolve the violations described below. The AVC is not an admission of violation of law and is submitted to a Circuit Court for the State of Oregon for approval and filing.

The Attorney General must approve and accept an AVC before an AVC is submitted to the Circuit Court. Once filed with the court, any willful violation of the terms of an AVC is a contempt of court which may result in punitive or remedial sanctions including confinement and civil penalties of up to $25,000 per violation.

DEPARTMENT OF JUSTICE
1515 SW 5th Ave Suite 410
Portland, OR 97222
PHONE: (971) 673-1880

This notice becomes a public record after 10 days have passed following your receipt of this notice.

The Attorney General sent you this notice because there are concerns you violated the Oregon Unlawful Trade Practices Act, ORS 646.605 through ORS 646.656, including but not limited to the following alleged conduct:

1) Implicitly misrepresenting to patients that Subsys® should be used to treat migraine, neck pain, back pain, and other off-label uses for which Subsys is neither safe nor effective. This implicit misrepresentation occurred when you paid patients' insurance co-payments even when you knew the prescription was off-label or contraindicated; when you arranged for free Subsys to be provided to patients even when you knew the free product was for an off-label or contraindicated use; and when you advocated to obtain insurance payments to patients for Subsys when you knew Subsys was to be used for an off-label or contraindicated use.
2) Implicitly misrepresenting to doctors that Subsys could be used to treat migraine, neck pain, back pain, and other off-label uses for which Subsys is neither safe nor effective.
3) Implicitly misrepresenting that the doctor whom you paid to teach Oregon physicians about Subsys was qualified to prescribe and teach about Subsys when in fact, he was not qualified.
4) Misrepresenting that a paper written by a well-known doctor supported the definition of break through cancer pain used by you to promote Subsys when in fact, the paper did not support the definition.
5) Misrepresenting that Subsys should be used to treat mild breakthrough cancer pain when in fact, the potential harm of using Subsys to treat mild pain far outweighs any possible benefit.
6) Employing an unconscionable tactic by making payments to doctors that you intended to be a kickback to incentivize the doctor to prescribe Subsys.

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7) Employing an unconscionable tactic by targeting Subsys promotion at doctors whom you knew, or should have known, misprescribed Schedule II opioid drugs such as Subsys.

8) Employing an unconscionable tactic by targeting doctors for Subsys promotion when you knew, or should have known, that the doctor only prescribed Subsys for off-label uses for which Subsys is neither safe nor effective.

9) Employing an unconscionable tactic by arranging for free Subsys to be provided to patients, and paying patients insurance co-payments for off-label uses of Subsys that you knew, or should have known, were neither safe nor effective.

10) Employing an unconscionable tactic by pressuring sales representative to solicit doctors to shorten the label mandated titration schedule designed to protect patients.

Background

Starting in January, 2012, Insys Therapeutics, Inc. (Insys) promoted and sold in Oregon the Schedule II opioid drug Subsys. Schedule II opioid drugs have a high potential for abuse and addiction. They can also have serious side effects which include respiratory depression and death.

Subsys consists of the powerful and highly addictive narcotic fentanyl administered through a sub-lingual (under the tongue) spray. Because it is absorbed rapidly into the bloodstream through the sub-lingual mucosa, Subsys has a rapid onset. Subsys is one of a class of drugs described as Transmucosal Immediate-Release Fentanyl ("TIRF").

To ensure that prescription drugs sold in the United States are safe and effective, the Food Drug and Cosmetic Act ("FDCA") requires drug manufacturers to submit a new drug application ("NDA") for all prescription drugs sold in the United States. The NDA must include clinical trials sufficient to prove to the U.S. Food and Drug Administration's ("FDA's") satisfaction that the drug is safe and effective for each and every indication (use) for which the drug is sold. If a manufacturer wants to market a drug for an indication not initially approved by FDA, the company must submit a supplemental new drug application ("sNDA") that

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demonstrates to FDA's satisfaction that the drug is safe and effective for the new indication. The Food Drug and Cosmetic Act ("DCA makes it unlawful for companies to promote drugs for indications FDA has not approved. Since FDA regulates drug manufacturers and the promotion of drugs, but not the practice of medicine, doctors are free to prescribe drugs for indications for which FDA has not determined that the drug is safe and effective. Such prescribing is described as "off-label," meaning outside the FDA-approved label.

Based on the Subsys NDA submitted by Insys, FDA determined that Subsys may only be lawfully promoted "for management of breakthrough pain in cancer patients 18 years of age or older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain."[1] Any other use would be off-label. FDA also determined that to ensure appropriate usage, Subsys is only intended to be prescribed by "pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain." The FDA-approved label also expressly provides that Subsys is "contraindicated" (should never be used) to treat migraine headaches.

Although not expressly contraindicated in the label, Subsys should also not be prescribed to treat most musculoskeletal pain, such as fibromyalgia, neck pain, and back pain, for which Subsys has not been shown to be safe or effective. In fact, prescribing of opioids for back and neck pain is often harmful and may ultimately lead to increased pain, dysfunction, and disability.

To help protect against Subsys' potentially fatal side effects, and to reduce the risk of misuse and abuse, FDA determined that doctors should use the lowest possible dose of Subsys that adequately treats a patient's symptoms. This is achieved through "titration" where the doctor initially prescribes 100 micrograms (unless the patient is already using another TIRF, in which case the starting dose can be slightly higher) and slowly increases to higher dosages at a specified schedule while waiting at each dose level to determine whether the patient's pain is adequately managed. While the highest dose of Subsys is 1600 micrograms, according to studies

[1] Subsys label.

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included in the FDA approved label, breakthrough cancer pain is well managed in approximately 25% of patients at 400 micrograms or less. Although patients benefit from using the lowest possible dose, Insys earns more money when a higher dose is prescribed, as do Insys sales representatives whose compensation is based on commission.

The first TIRF drug approved by FDA was Actiq®, which has the same FDA approved indications as Subsys. In 2008, Cephalon pleaded guilty to criminal and civil charges that it promoted Actiq for off-label uses and targeted physician specialties such as Physical Medicine and Rehabilitation doctors (" PM&R" or "Physiatrists") who do not usually treat cancer patients but commonly treat neck and back pain. Among other things, Cephalon admitted to promoting Actiq off-label to treat migraine headaches.

As a result of the federal enforcement action against Cephalon, even before Subsys was approved for sale, Insys knew that there was a problem with off-label use of TIRF drugs and that prescribers of Actiq, and PM&R doctors in particular, had been targeted with off-label messaging regarding TIRF drugs.

To reduce the risk of abuse, misuse, and diversion, FDA instituted a Risk Evaluation and Management Strategy ("REMS") for Subsys and other fentanyl products "to ensure that the benefit of the drugs outweigh the risk of the drug."[2] The purpose of this REMS was to educate "prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose" for this class of drugs.[3] Sadly, the REMS for fentanyl drugs is particularly necessary in Oregon which in 2012 led the nation in the estimated rate of nonmedical use of prescription opioids (6.4% versus the national mean of 4.6%).[4]

To address the opioid epidemic in Oregon, the Prescription Drug Taskforce, appointed by previous Governor Kitzhaber to study the problem, specifically recommended that among other

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[2] U.S.C. § 355-1.

[3] Press Release, *FDA Approves Shared system REMS for TIRF Products* (December 29, 2011), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm285345.htm.

[4] Substance Abuse and Mental Health Services Administration, *The NSDUH Report: State Estimates of Nonmedical Use of Prescription Pain Relievers* (2012).

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interventions, it is necessary to "educate prescribers and the public on the risks of opioid use and to reduce the amount of opioids in circulation.[5]

Unfortunately, rather than educate prescribers and the public about appropriate use of Subsys in order to reduce the risk of abuse, misuse and diversion, Insys did the very opposite. As alleged below, rather that promoting appropriate use of Subsys, Insys used unconscionable, false, and deceptive sales tactics which had the potential of increasing the misuse of Subsys in Oregon. When Insys began promoting Subsys in 2012, it consciously targeted prescribers of Actiq already predisposed to prescribe TIRF drugs off-label, with unconscionable and deceptive promotion of Subsys. Within two years of Subsys' release, it was reported that approximately 80% of Subsys prescriptions were for off-label uses.

Insys Promoted Subsys Off- Label for Non-Cancer Pain such as Back Pain and Neck Pain, Uses for which Subsys is Neither Safe Nor Effective

As discussed above, Subsys was never approved by FDA to treat back pain, neck pain, myalgia, migraine or any other non-cancer pain. Opioids in general are highly problematic for non-cancer chronic pain[6] and are often counter-productive for back pain.[7] TIRFs in particular are unsuited for treating these chronic conditions. Nonetheless, Insys promoted Subsys off-label to treat a back and neck pain and other off-label pain conditions. Subsys did so by targeting physicians who primarily treated the off-label pain but did not treat breakthrough cancer pain. Insys' goal was to get the doctor to prescribe Subsys even though the nature of the doctor's practice was to only treat non-cancer pain and use of Subsys could only be off-label.

Insys also worked with patients and doctors to get insurance to pay for Subsys for off-label conditions for which it is neither safe nor effective; provided economic incentives to its

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[5] Dennis McCarty et al., *Oregon's strategy to control prescription opioid misuse: a case study*, Journal of Substance Abuse Treatment (2014), *available at* http://dx.doi.org/10.1016/j.jsat.2014.07.012.

[6] Roger Chou et al., *The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain*, 162 Ann Intern Med. 276 (2015).

[7] Richard A. Deyo et al., *Opioids for low back pain*, 350 BMJ g6380(2015).

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sales reps to promote Subsys off-label for non-cancer pain; implicitly encouraged sales representatives to promote off-label for non-cancer; paid patient co-pays when Insys knew the Subsys prescription was for an off-label or even a contraindicated use; and gave free samples to patients when Insys knew that the drug was to be used off-label.

From the start, Insys made the strategic decision to target doctors who were already prescribing Actiq and other TIRFs and had already been exposed to Cephalon's unlawful off-label promotional campaign which was the subject of the federal criminal action. Only a minority of these physicians are oncologists likely to prescribe Subsys for the on-label indication of breakthrough cancer pain.

Rather than focus on oncologists, Insys targeted specialties like PM&R that rarely, if ever, treat breakthrough cancer pain but commonly treat neck and back pain. A good example of this was Insys' aggressive promotional campaign targeting Dr. Roy [redacted] a PM&R physician practicing at [redacted] in Tigard, Oregon. As described below, Insys targeted Dr. [redacted] even though Insys knew Dr. [redacted] does not treat patients with breakthrough cancer pain and could not prescribe Subsys on-label.

On September 19, 2013, Insys hired Jonathan [redacted] Dr. [redacted]'s son, as its Oregon Subsys sales representative. Jonathan [redacted] had no background in pharmaceutical sales or health care. Shortly after he was hired, Jonathan set up a dinner meeting between his father, Insys [redacted] and Stuart Rosenblum, an anesthesiologist with a long history of speaking on behalf of pharmaceutical companies about drugs, including drugs that were unlawfully promoted off-label to treat certain types of pain.[8] Rosenblum is a long-time acquaintance of Dr. [redacted]. The dinner took place October 21st, 2013 at Riccardo's Ristorante in Lake Oswego; it cost about $100 per person. Rosenblum was paid $1,600 to speak to Dr. [redacted] about Subsys at the dinner. Even before the dinner, Insys knew that Dr. [redacted] did not treat

[8] In 2009 Pharmacia & Upjohn Company pleaded guilty to a felony violation of the Food, Drug and Cosmetic Act for misbranding Bextra with the intent to defraud or mislead. Although FDA rejected the Bextra NDA for an acute pain indication, Pharmacia & Upjohn promoted it for this use anyway. Ultimately Bextra was totally withdrawn from the market for any use. Dr. Rosenblum was one of Pharmacia's top Bextra speakers in Oregon.

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patients with breakthrough cancer pain, and that the types of patients Dr. [redacted] treats would not benefit from Subsys. In fact, Insys had been told repeatedly that this was the case. On November 1, 2013 Jonathan [redacted] texted to his father:

> "These people from my company are relentless and it's kind of pissing me off. I have told them multiple times (starting with the interview) that you probably won't be writing my product due to the type of practice you have, but my manager just called me an[sic] told me that they were 'concerned' that I haven't gotten you tirf rems enrolled. I'm getting ready to tell them to **** off [expletive deleted]. Now they told me that dr kapoor[9] contacted you. I need you to help me to figure out what to say to them to calm them down."

When John [redacted] was asked during a sworn interview how many breakthrough cancer patients were treated by his father at [redacted] he replied "*None.*"

In addition to trying to use family relationships and old acquaintance to try to get Dr. [redacted] to prescribe Subsys off-label, Insys also used flirtation. On October 27th, 2013 Dr. [redacted] texted his son, asking if it "seemed weird " that he [Dr. [redacted] was getting texts from [redacted] proposing "tequila dates." In a sworn interview Jonathan [redacted] was asked:

> Q **What did you say in response to your father's question, "Does it seem weird to you"?**
>
> A Probably something along the lines of, She's a cougar and that's what she's going to do.
>
> Q **She is a cougar?**
>
> A Yeah. In the general term of cougarism.
>
> Q **So why was - - why - - just to continue with that, why was Beth sending these texts to your father?**
>
> A Yeah, I don't want to get down like a rabbit hole of speculation, but, you know, she -- you know, attractive lady. She thought she could use that to kind of sway doctors to write, and so she would send my dad text messages like that.

[9] Kapoor is the founder of Insys and the Executive Director of the Insys Board of Directors and has been closely involved with the development of Subsys.

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Insys also sought to influence Dr. [redacted] by offering to make him a Subsys promotional speaker even though Dr. [redacted] had never prescribed Subsys and did not treat the type of patients that would benefit from Subsys. On November 12th, 2013 Jon [redacted] wrote to Dr. [redacted] "This company really want to make you a speaker. Apparently Kapoor had good things to say about you. The VP of sales wants to come out and speak with you . . . I apologize for being pushy."

Insys knew that Dr. [redacted] did not treat cancer patients and could not prescribe Subsys on-label for the FDA approved indication. Nonetheless, Insys aggressively and persistently targeted Dr. [redacted] and other non-oncologist physicians in an attempt to increase prescribing of Subsys for off-label uses for which it is neither safe nor effective. Ultimately Insys' campaign to get Dr. [redacted] to prescribe Subsys off-label was unsuccessful: Dr. [redacted] wrote no prescriptions for Subsys. On December 19th, 2013, after only three months working as a Subsys sales representative, Jonathon [redacted] resigned.

While targeting doctors who could only prescribe Subsys off-label, Insys expected its sales representatives to implicitly promote Subsys for off-label uses. Although lip service was paid to not breaking the law, the expectation was that sales representatives would do just that. Jaimi Hooker was Insys' first and longest serving Oregon Subsys sales representative. In a sworn interview, she testified:

Q This was for a diagnosis of back pain. Was there a discussion in the monthly meeting about doctors writing prescriptions for SUBSYS for back pain?

A It would be, it would definitely be talked about. Like what are you seeing what providers write for? Definitely back pain came up.

Q Were you implicitly encouraged by your superiors to try to get docs to write for back pain?

A Yes. In like as on the label as you can kind of way, yes.

Q So the goal was to try to get docs to write for back pain but still technically not ask them to directly write for back pain?

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A Right. Or just like imply do you have any patients that experience breakthrough cancer pain.

Q It was marketing for off-label uses by implication, is that correct?

A I would say that that's fair to say.

In another portion of the interview, Hooker indicated that Insys managers expected reps to ask for all of a doctor's TIRF business – including off-label uses.

Q This is another exchange involving Karen Hill and Richard Simon. If we go to the second page of this document there is an email from December 14, 2012 from Rich to Karen. And again, they are talking about you and an assessment of Jamie[sic]**, and they talk about you asking doctors to write to their capabilities. What does it mean to have a doctor write to their capability?**

A I think it means that they were probably writing for our competitors, our competitor, so maybe it meant to get all of that business and also write more. They probably felt like they had patients, like these providers had patients that could be written that would be provided with SUBSYS.

Q A few more lines down Rich says that "she, "meaning you, "is at the point where her doctors truly like HER" -- cap HER -- to have the difficult conversations and try to move them. What's the difficult conversation?

A I think the difficult conversation was to ask them to write more.

Q Why would that be difficult?

A Because it would be asking them to take business from our competitors who they probably have a relationship with like the other reps. But also it would probably imply writing more off-label. I think that that's kind of what that means. It's like trying to find patients.

Insys also pressured sales representative to circumvent the Subsys label, even parts of the label relating to safety and titration. As already discussed, the Subsys label expressly instructs prescribers to start at the lowest possible dose and titrate slowly upward in a way that would allow for the doctor to determine the lowest possible effective dose. However, whenever a doctor followed the label and started low, Insys sent an email to the doctor's sales representative that was copied to top management which instructed the rep to "*report back to*

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your manager within 24 hours on WHY the low dose was used and HOW the doctor plans to titrate the patient to effective dose." The clear implication of these communications was to pressure the sales representative to try to get the doctor to prescribe a higher dose – even before it had been determined whether the lower dose is effective.

Sales representatives also had an economic incentive for doctors to prescribe a high dose and to prescribe Subsys off-label since Insys' compensation plan paid sales representatives based on the value of the prescriptions written by the sales representatives' doctors and the price of Subsys was based on the size of the dose. The higher the dose, the higher the price and the higher the commission. Moreover, sales reps received their commission even when Insys knew that the prescription was for an off-label or contraindicated use.

Insys often knew when a prescription was for an off-label or contraindicated use because Insys provided reimbursement assistance to patients with insurance prior authorization requests. For example, when sports medicine doctor Jimmy D. Huebert of the Sports and Spine Center in Tualatin prescribed Subsys for a patient with a herniated disc, Insys filled out the prior authorization form on behalf of the doctor and actively assisted in submitting the form. Insys did the same when James Gallant (discussed further below) prescribed Subsys for a diagnosis of "Back Pain," and then again when Gallant prescribed Subsys for "neck pain." Insys similarly assisted with the prior authorization process for at least five off-label prescriptions written by Stuart Rosenblum which list diagnoses of spinal stenosis, osteoarthrosis, myalgia, myositis, post laminectomy syndrome, neuralgia neuritis and radiculitis - but not for breakthrough cancer pain. Insys also submitted reimbursement forms for at least five other Oregon patients with diagnoses such as chronic pain syndrome. As discussed further below, Insys even went so far as to provide pre-authorization assistance and reimbursement assistance when Insys knew that the prescription was for a contraindicated use. Moreover, under the Insys Subsys "Patient Savings Program," these patients who Insys knew were prescribed Subsys for off-label uses were eligible to receive up to 60 free units of Subsys. Insys also paid the patients' out-of-pocket copay for up to $500 for

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each prescription. All told, out of 18 preauthorization forms submitted by Insys on behalf of Oregon patients that are known to DOJ, 14 (78%) were for off-label uses related to chronic, non-cancer pain such as chronic pain syndrome, joint pain involving multiple sites, and degeneration of lumbar or lumbosacral intervertebral discs. Insys was fully aware that its reimbursement assistance program was unconscionably assisting in the misuse of Subsys. Moreover, by providing reimbursement assistance, Insys implicitly misrepresented to patients, payors, and physicians, that Subsys was appropriate for these off-label uses.

Insys Unconscionably Targeted Roy Blackburn, a Problem Doctor who Misprescribed Opiates, With Aggressive Subsys Promotion and Facilitated His Prescribing of Subsys for Contraindicated Uses.

On November 7th, 2013, Dr. Roy Blackburn entered into an Interim Stipulated Order with the Oregon Medical Board to cease prescribing of controlled substances for chronic pain patients pending the completion of the Board's investigation into his ability to safely and competently practice medicine. On June 3rd, 2014, the Oregon Medical Board issued a Complaint against Dr. Roy Blackburn that describes gross or repeated acts of negligence; prescribing of controlled substances without a legitimate medical purpose; and prescribing of controlled substances without following accepted procedures for examination of patients. In July 2014, Blackburn agreed to a stipulated order which, among other things, prohibited him from prescribing Schedule II drugs, or from prescribing any drug for chronic pain to a patient for more than 30 days in a one year period. Blackburn is a physiatrist and not a pain specialist who would be knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain. Blackburn treats chronic non-cancer pain patients. Nonetheless, he was the target of aggressive Subsys promotion during the time period described in the Board of Medicine Complaint. He was the third most heavily detailed (visited) doctor by Subsys sales representatives in Oregon.

Blackburn and his office were visited by Insys sales representatives at least 80 times; on at least 28 of those visits, the sales representative brought coffee and/or snacks. On October 23, 2012, Insys paid Dr. James Gallant $2,400 to speak to Blackburn and one of his employees at a

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catered lunch at Blackburn's office. At this lunch, Gallant promoted Subsys for among other things, treatment of mild breakthrough cancer pain (discussed further below). On November 26, 2012, Insys paid Dr. Stuart Rosenblum $1,600 to give the same promotional talk to Blackburn and two other doctors at Marche, a French restaurant in Eugene. Insys knew, or should have known, that Dr. Blackburn is not a pain specialist knowledgeable and skilled in the use of schedule II opioids to treat cancer pain. In fact, Insys knew that Blackburn prescribed Subsys for migraine, an expressly contraindicated use, and helped Blackburn obtain third party payment for the contraindicated use.

On February 18th, 2013, Insys Prior Authorization Specialist Liz Gurrieri wrote Blackburn's Subsys sales representative Jaimi Hooker "FYI . . .I received a duplicate opt in for Dr Blackburn's pt [name redacted] for 600 mcg. He is requesting 240 units per month for migraines. I do not think we can get it approved but we can try . . ." On February 6th, 2013, Gurrieri wrote to Hooker (copied to, among others, Director of Sales Rich Simon and Vice President of Sales Alec Burlakoff) that she had received the request. On March 28th, 2013 Hooker wrote to Blackburn, "Hi Dr B! I tried forwarding you an email about [name redacted]. I just wanted to let you know that he is now reapproved for Subsys and our company called the pharmacy and spoke with Aaron to run a dummy script and it went through!" In addition to being unconscionable, the sum total of this conduct was to misrepresent to the patient and the third party payor that Subsys is appropriate for the treatment of migraines.

Insys Unconscionably Targeted James Gallant, A Problem Doctor who Misprescribed Opiates, With Aggressive Subsys Promotion. Despite Gallant's Lack of Qualifications, Insys Hired Gallant to Teach Other Doctors about Subsys. The Payments made to Gallant and other Doctors were intended to be Kickbacks to Increase Prescribing of Subsys.

Dr. James Gallant is a medical doctor who has never been board certified by any medical specialty. Except for a four-day commercial continuing education program in Las Vegas, he lacks post graduate training in pain management. In October 2014, based in part on Gallant's misprescribing of opioids, the Oregon Medical Board suspended Gallant's license for 90 days,

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formally reprimanded him, imposed a $10,000 civil penalty, placed him on probation for 10 years, ordered him to complete an assessment and education or remediation plan, a course in medical ethics, and a course in prescribing, and ordered him to refrain from treating chronic pain. Gallant has a long history of receiving letters of concern and formal reprimands from the Board of Medicine, and in1997 he was formally reprimanded and his license was suspended after it was determined that he had euthanized a patient. Gallant is not a pain specialist knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain. Nonetheless, Insys hired Gallant as its top Oregon consultant to train doctors about safe usage of Subsys.

Gallant was Insys' top Oregon Subsys consultant. He was paid up to $2,400 to give short promotional talks about Subsys. The amount Insys paid Gallant for his talks was 50% more than the amount paid Stuart Rosenblum, the second most frequent Oregon Subsys speaker who is a board certified anesthesiologist. Gallant was also a paid member of a Insys "Advisory Board and was paid to attend speaker training programs, including $2,500 to attend a speaker training program in San Francisco that occurred after he stopped doing Subsys talks. In 2012 and 2013, Gallant's office was visited by Insys sales representatives over 100 times, more than any other doctor in Oregon. On at least seven occasions, the sales rep brought lunch or breakfast for the office. Gallant was also repeatedly taken out for meals by Insys sales representatives.

Some of the talks paid for by Insys were shams that were essentially an excuse to make a payment to Gallant to encourage increased prescribing of Subsys. On one occasion, Gallant was paid $2,400 plus expenses to speak to his own physician assistant over a meal at an expensive restaurant. In sworn testimony, Subsys sales representative Jaimi Hooker testified that this sham talk was expressly approved by Director of Sales Rich Simon, who knew the only attendee at the talk was Gallant's assistant.

Such sham talks were not unique to Gallant. For example, Stuart Rosenblum was paid $1,600 to speak at what was essentially a social event and an opportunity for Rosenblum to market his practice to other doctors. As Rosenblum wrote in an invitation to the event (that was

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copied to Jaimi Hooker): "*you are invited to a social event this Friday at 1530 SE 7th (near Hawthorne) Vie de Boehme. Phone 503-360-1233 at 8PM. We are having food and drinks supplied by Jamie*[sic] *of Insys. Wives and girlfriends are invited. Scott's band will be playing. They start about 9pm. I hope to see you there.*"

In a subsequent email that Rosenblum wrote to his clinic staff: "*I have rescheduled our dinner event. . .Our pain clinic staff and our wives are invited. Please feel free to invite any referring physicians and we can use this for marketing as well. Dinner is sponsored by Insys and I will give a brief informal presentation. Otherwise the evening will be for socializing and networking. RSVP to Jamie* [sic]. . ."

Insys was well aware that payments made to Gallant and Rosenblum were not for bona fide educational events but rather were an attempt to buy good will and an obligation to prescribe Subsys.

Insys fully intended that its payments to Gallant and Rosenblum would cause the doctors to write more Subsys prescriptions. For example, after Subsys sales executive Karen Hill did a site visit to Oregon and accompanied sales representative Jaimi Hooker on visits to Drs Gallant and Rosenblum, Hill wrote to Vice President of Sales Alex Burlakoff and CEO Michael Babich "*I managed to meet her speakers and challenged each of them (we are paying these guys* [Gallant and Rosenblum] *and not seeing a return on our investment.*"

In another email from District Sales Manager Crystal Skelton (who had responsibility for Oregon) to Director of Sales Rich Simon, which was subsequently forwarded to a number of other sales representatives (including Oregon Sales Representative Jaimi Hooker), Skelton wrote that she had confronted one of her speakers for failing to write a sufficient number of Subsys prescriptions. She further wrote that "*[h]is response was 'thank you for telling me this. It is a privilege to be a speaker and an advocate for you and if I'm not giving you a full return on investment then I want you to hold me accountable.*"

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In another e-mail Simon wrote that Gallant and Rosenblum "*are on a short string with me.*" When asked under oath why Gallant was on a short string with Simon, Hooker testified that "*he felt like Dr. Gallant could have been writing more prescriptions.*" When asked if "*the problem [was]that the return on investment for payments to Dr. Gallant was low,*" Hooker responded, " *I would say yes.*"

Gallant himself confirmed Hooker's observation. In a sworn response to an interrogatory, Gallant wrote: "*As a result of my prescribing numbers being considered too low for the company, I was told that I would not be used as a speaker again.*"

Through its payments to Gallant and Rosenblum, Insys unconscionably sought to increase prescriptions written for Subsys. Gallant was chosen as a speaker not because he was qualified to speak to doctors about Subsys – he was not - but to incentivize him to prescribe Subsys. Nonetheless, Insys deceptively held Gallant out as a qualified speaker and sought out Oregon physicians to attend his talks. Although Gallants prescribing of Subsys failed to meet Insys' expectations, Gallant was the top prescriber of Subsys in Oregon. Out of the total of $511,000 worth of Subsys sold in Oregon, Gallant wrote prescriptions worth almost $250,000, including $95,800 paid by the Public Employee Benefits Board (PEBB). In 2013, Gallant and Rosenblum were responsible for approximately 80% of all Subsys prescriptions filled in Oregon. For the years 2012 and 2013, Gallant, Rosenblum, and Blackburn were responsible for 78% of all Oregon Subsys prescriptions.

Insys Deceptively Misrepresented that Subsys Should Be Used to Treat Mild Pain

The definition for breakthrough cancer pain ("BTCP") was critical for Insys because it determined the breadth of the only FDA approved use for which, under federal law, Subsys could be lawfully promoted. The broader the definition of BTCP, the wider the potential market for Subsys. To broaden the approved indication of BTCP, Insys defined BTCP to include mild pain. However, Subsys should never be prescribed solely to treat mild pain because Subsys' risks far outweigh its benefits for this use. To achieve its goal of a broad definition of BTCP that

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includes mild pain, Insys knowingly fabricated a false citation to a paper written by RK Portenoy, a well-known researcher and clinician.

As early as January 2011, the Insys Board of Directors considered two possible definitions for BTCP. The first definition came from the National Cancer Institute and defined BTCP as "*intense increases in pain* that occur with rapid onset even when pain control medication is being used." (Emphasis added). The second definition considered was a "transitory exacerbation, or flare, of *moderate-to-severe intensity* over persistent pain in patients receiving chronic opioid medication" and cited to a paper by RK Portenoy which defined BTCP as a "transitory increase in pain to *greater than moderate intensity* which occurred on a baseline pain of moderate intensity or less (that is, to *an intensity of 'severe' or 'excruciating'*). . ." [10] (Emphasis added).

Insys considered these two definitions at consultant meetings prior to product launch and chose to use the Portenoy definition. At the time of Subsys' launch in March 2012, Subsys promotional materials accurately cited the Portenoy definition. However, starting in June 2012, began to falsely cite Portenoy to define BTCP as "a flare of mild–to-severe pain in patients with otherwise stable persistent pain." Despite the fact that Portenoy's definition expressly excluded mild and moderate pain and covered only severe or excruciating pain, Insys falsely cited Portenoy to include mild pain. The clear implication of Insys' deceptive citation to Portenoy was that it was appropriate and acceptable for doctors to prescribe Insys to treat even mild breakthrough pain. However, it is never appropriate and acceptable to prescribe Subsys to treat mild breakthrough pain because the potential harm to patients far exceeds any potential benefit. These harms include addiction, diversion, and death. Improper use of opioids to treat mild pain can actually make pain worse, a condition known as opioid-induced hyperalgesia.

Insys trained its sales representatives to use the deceptive definition of BTCP and to falsely cite Portenoy. Between June 2012 and September 2013, a deceptive Subsys Core Visual

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[10] Portnoy, RK, et al, Breakthrough pain: definition, prevalence, and characteristics, 41 273-281).

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Aid was used by Insys sales representative to detail Oregon health care professionals. Sales representatives were expected to use the Core Visual Aid whenever they detailed Subsys to a health care provider or a provider's office. Between June 2012 and September 2013, Subsys sales representatives engaged in at least 830 such sales visits. Each time a sales representative used the deceptive BTCP definition in an Oregon presentation is a separate and distinct violation of the UTPA.

Between October 12th, 2012 and November 26th, 2013, the deceptive BTCP definition was used in a slide that was presented at all Subsys promotional talks in Oregon. There were at least at least 23 presentations by four different speakers during this time period. Each time the slide was used is a separate and distinct violation of the UTPA.

***

If the Attorney General files a lawsuit, the Attorney General will allege that among other violations, this conduct violated the Oregon Unlawful Trade Practices Act, ORS 646.605 through ORS 646.656 by:

1) Implicitly misrepresenting to patients that Subsys should be used to treat migraine, neck pain, back pain and other off-label uses for which Subsys is neither safe nor effective. This implicit misrepresentation occurred when you paid patients' insurance co-payments even when you knew the prescription was off-label or contraindicated; when you arranged for free Subsys to be provided to patients even when you knew the free product was for an off-label or contraindicated use; and when you advocated to obtain insurance payments to patients for Subsys when you knew Subsys was to be used for an off-label or contraindicated use.

2) Implicitly misrepresenting to doctors that Subsys could be used to treat migraine, neck pain, back pain, and other off-label uses for which Subsys is neither safe nor effective.

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3) Implicitly misrepresenting that the doctor whom you paid to teach Oregon physicians about Subsys was qualified to prescribe and teach about Subsys when in fact, he was not qualified.

4) Misrepresenting that a paper written by a well-known doctor supported the definition of break through cancer pain used by you to promote Subsys when in fact, the paper did not support the definition.

5) Misrepresenting that Subsys should be used to treat mild breakthrough cancer pain when in fact the potential harm of using Subsys to treat mild pain far outweighs any possible benefit.

6) Employing an unconscionable tactic by making payments to doctors that you intended to be a kickback to incentivize the doctor to prescribe Subsys.

7) Employing an unconscionable tactic by targeting Subsys promotion at doctors who you knew, or should have known, misprescribed Schedule II opioid drugs such as Subsys.

8) Employing an unconscionable tactic by targeting doctors for Subsys promotion when you knew, or should have known, that the doctor only prescribed Subsys for off-label uses for which Subsys is neither safe nor effective.

9) Employing an unconscionable tactic by arranging for free Subsys to be provided to patients, and paying patients insurance co-payments for off-label uses of Subsys that you knew, or should have known, were neither safe nor effective.

10) Employing an unconscionable tactic by pressuring sales representative to solicit doctors to shorten the label mandated titration schedule designed to protect patients.

If the Attorney General files the lawsuit, the Attorney General will ask the court to order you to pay:

1) Civil penalties of up to $25,000 for each violation;

2) Restitution to anyone harmed by your acts; and

3) Our reasonable attorney's fees, costs and disbursements.

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In addition, the Attorney General may ask the court to permanently enjoin you from conducting any aspect of any trade or commerce in the State of Oregon.

Dated this 10th day of July, 2015.

David A. Hart OSB #002750
Assistant Attorney-in-Charge
Health Fraud Unit/Consumer Protection Section
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EXHIBIT 93

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BUSINESS DAY

Doubts Raised About Off-Label Use of Subsys, a Strong Painkiller

By KATIE THOMAS MAY 13, 2014

Almost overnight, a powerful new painkiller has become a $100 million business and a hot Wall Street story.

But nearly as quickly, questions are emerging about how the drug is being sold, and to whom.

The drug, Subsys, is a form of fentanyl, a narcotic that is often used when painkillers like morphine fail to provide relief. The product was approved in 2012 for a relatively small number of people — cancer patients — but has since become an outsize moneymaker for the obscure company that makes it, Insys Therapeutics. In the last year, the company's sales have soared and its share price has jumped nearly 270 percent.

Behind that business success is an unusual marketing machine that may have pushed Subsys far beyond the use envisioned by the Food and Drug Administration. The F.D.A. approved Subsys only for cancer patients who are already using round-the-clock painkillers, and warned that it should be prescribed only by oncologists and pain specialists. But just 1 percent of prescriptions are written by oncologists, according to data provided by Symphony Health, which analyzes drug trends. About half of the prescriptions were written by pain specialists, and a wide range of doctors

prescribed the rest, including general practice physicians, neurologists and even dentists and podiatrists.

Interviews with several former Insys sales representatives suggest the company, based in Chandler, Ariz., has aggressively marketed the painkiller, including to physicians who did not treat many cancer patients and by paying its sales force higher commissions for selling higher doses of the drug.

Under F.D.A. rules, manufacturers may market prescription drugs only for approved uses. But doctors may prescribe drugs as they see fit. Over the last decade, pharmaceutical companies have paid billions of dollars to settle claims that they encouraged doctors to use drugs for nonapproved treatments, or so-called off-label uses, to increase sales and profits.

Drug-safety experts said the range of medical professionals who appeared to be prescribing Subsys was troubling, particularly given concerns about the widespread use — and abuse — of narcotic painkillers. In December, Insys disclosed that it had received a subpoena from the federal health department's Office of the Inspector General for documents related to its sales and marketing practices. The company has said it is cooperating with the investigation.

Medicine aside, Subsys is, much as anything, a Wall Street story. The explosive growth of Insys was fanned first by Wall Street investors betting the company's sales and share price would rise. Now, other investors are betting the stock will decline. Over the last week, shares of Insys have lost roughly a third of their value, after the arrest on federal fraud charges of a Michigan neurologist who was a top prescriber of Subsys. In a statement, Insys said it took patient safety seriously and was committed to working with doctors to ensure its products were used properly.

Drug-safety experts said it was crucial that products like Subsys be marketed responsibly because the drugs are powerful, and powerfully addictive.

"You're essentially spreading the accessibility to a very potent, rapid-onset narcotic to a large number of people, and a number of them may get addicted," said Dr. Sidney M. Wolfe, founder and senior adviser to the Public Citizen Health Research Group, a consumer organization.

Oral fentanyl products like Subsys have a history of being broadly prescribed. In 2008, the drug company Cephalon pleaded guilty to a criminal charge and paid $425 million in fines for inappropriate marketing of its products, including Actiq, a fentanyl lollipop, which federal officials said was being promoted for a range of unapproved uses, including treatment of migraines.

In 2007, Cephalon sought approval from the F.D.A. to market a newer fentanyl product, a dissolving pill called Fentora, for use in people without cancer. At the time, F.D.A. officials cited data showing the product was already being widely used by noncancer patients and they later denied the company's application. Cephalon was acquired by Teva Pharmaceutical Industries in 2011.

Dr. Margaret A. Hamburg, the F.D.A. commissioner, said the agency did not regulate how doctors practice medicine. Still, she acknowledged that the widespread prescribing of oral fentanyl products for off-label uses was troubling, especially given the agency's efforts to restrict the use of fentanyl and other opioids in the face of painkiller abuse. In the case of products like Subsys, prescribers must undergo training about the drug's risks, pass a test and register in a national database. Patients must sign an agreement with their doctor before being prescribed the drug.

"It is frustrating, and we are in a process of continually assessing how our approaches are unfolding in the real world," Dr. Hamburg said.

Several doctors said products like Subsys, which is sprayed under the tongue, fill an important role for seriously ill cancer patients, who may need the drug if their condition worsens or if their standard painkiller regimen occasionally fails to work.

"You want it to work as quickly as possible," said Dr. Joshua R. Wellington, a pain specialist at Indiana University Health University Hospital. He is a paid speaker for Insys and said he prescribed it only to cancer patients. "In my mind, that's what sets it apart."

Still, Subsys has sold surprisingly well given the drug is approved only for cancer pain, and given that only a small number of oncologists, who are typically responsible for treating their patients' pain, appear to be prescribing it. In addition to pain specialists and anesthesiologists, who together made up about half of all

prescriptions, a significant number were written by neurologists and physical medicine and rehabilitation specialists, who often treat patients with a variety of pain conditions.

The former sales employees said that while the company targeted some oncologists, it placed more focus on high prescribers of competing products like Actiq and Fentora, regardless of whether those doctors treated cancer patients. They also said they were trained to mention the restriction to cancer pain at the beginning of the sales pitch and then to move on to a more general discussion of "breakthrough pain" in the doctors' other patients.

Dr. Wellington said while he did not prescribe the drug off-label, he understood why some colleagues did. "Cancer pain is not a unique pain syndrome," he said. "Pain is pain."

Others disagreed.

Dr. Lewis S. Nelson, a medical toxicologist at the New York University School of Medicine, said such drugs might be appropriate for a terminally ill cancer patient, but fentanyl, like other opiates, carries a high risk of dependency. It can also cause respiratory distress — and death — if it is taken by people who are not using painkillers regularly.

"If you're waiting to die, you should die in comfort and dignity," Dr. Nelson said. "It's very different than if you're attempting to have a functional life, because these drugs are relatively incompatible with having a functional life."

At least part of Insys's business strategy appears to rely on the assumption that patients will eventually need more of the drug, along with higher doses. Higher doses are more expensive than lower doses.

Comments from a Wall Street analyst underscore that view. "As Subsys grows more mature, we expect the number of experienced patients to grow," Michael E. Faerm, an analyst for Wells Fargo, wrote last year in a note to investors. "As the experienced patients titrate higher, the average dose per prescription should increase."

The former Insys sales representatives said they were paid more for selling higher doses.

Pratap Khedkar, who oversees the pharmaceutical practice at ZS Associates, a global sales and marketing firm, said such a practice was highly unusual because "most companies feel that is the doctor's decision because it is very patient-specific."

Many of the sales representatives were new to the pharmaceutical industry and were paid low base salaries, about $40,000 a year, compared with the industry standard of about $80,000, as an added incentive to rack up higher sales commissions, they said. Some said they were told they could make hundreds of thousands by selling aggressively.

Michael L. Babich, the chief executive of Insys, has attributed his company's sales to its ambitious compensation structure. "We believe this is the most effective way to motivate our sales team," he told analysts during an earnings call last fall.

On Tuesday, the company reported that Subsys sales continued to grow in the first quarter of this year, to $40.7 million, from $9.7 million a year ago.

Meanwhile, the company's plans for Subsys are only just getting underway: Earlier this year, Insys announced that it intended to seek approval to market the product for a broader range of uses, including for children and burn patients, and to treat acute pain in emergency rooms.

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EXHIBIT 94

United States Department of Justice

THE UNITED STATES ATTORNEY'S OFFICE
DISTRICT of MASSACHUSETTS

U.S. Attorneys » District of Massachusetts » News

Department of Justice

U.S. Attorney's Office

District of Massachusetts

FOR IMMEDIATE RELEASE Thursday, December 8, 2016

Pharmaceutical Executives Charged in Racketeering Scheme

BOSTON – Several pharmaceutical executives and managers, formerly employed by Insys Therapeutics, Inc., were arrested today on charges that they led a nationwide conspiracy to bribe medical practitioners to unnecessarily prescribe a fentanyl-based pain medication and defraud healthcare insurers.

The indictment alleges that Michael L. Babich, 40, of Scottsdale, Ariz., the former CEO and President of the company; Alec Burlakoff, 42, of Charlotte, N.C., former Vice President of Sales; Richard M. Simon, 46, of Seal Beach, Calif., former National Director of Sales; former Regional Sales Directors, Sunrise Lee, 36, of Bryant City, Mich. and Joseph A. Rowan, 43, of Panama City, Fla.; and former Vice President of Managed Markets, Michael J. Gurry, 53, of Scottsdale, Ariz., conspired to bribe practitioners in various states, many of whom operated pain clinics, in order to get them to prescribe a fentanyl-based pain medication. The medication, called "Subsys," is a powerful narcotic intended to treat cancer patients suffering intense episodes of breakthrough pain. In exchange for bribes and kickbacks, the practitioners wrote large numbers of prescriptions for the patients, most of whom were not diagnosed with cancer.

The indictment also alleges that the now former corporate executives charged in the case conspired to mislead and defraud health insurance providers who were reluctant to approve payment for the drug when it was prescribed for non-cancer patients. They achieved this goal by setting up the "reimbursement unit" which was dedicated to obtaining prior authorization directly from insurers and pharmacy benefit managers.

"Patient safety is paramount and prescriptions for these highly addictive drugs, especially Fentanyl, which is among the most potent and addictive opioids, should be prescribed without the influence of corporate money," said United States Attorney Carmen M. Ortiz. "I hope that today's charges send a clear message that we will continue to attack the opioid epidemic from all angles, whether it is corporate greed or street level dealing."

“As alleged, top executives of Insys Therapeutics, Inc. paid kickbacks and committed fraud to sell a highly potent and addictive opioid that can lead to abuse and life threatening respiratory depression,” said Harold H. Shaw, Special Agent in Charge of the Federal Bureau of Investigation, Boston Field Division. “In doing so, they contributed to the growing opioid epidemic and placed profit before patient safety. These indictments reflect the steadfast commitment of the FBI and our law enforcement partners to confront the opioid epidemic impacting our communities, while bringing to justice those who seek to profit from fraud or other criminal acts.”

“We take allegations of paying kickbacks to physicians in exchange for prescribing medically unnecessary painkillers extremely seriously,” said Special Agent in Charge Phillip Coyne of the U.S. Department of Health and Human Services, Office of the Inspector General. “Working closely with our law enforcement partners, we will continue to protect the health of Medicare beneficiaries and the integrity of the nation’s healthcare system.”

The defendants were arrested this morning in their respective states and will appear in U.S. District Court in Boston at a later date. Babich is charged with conspiracy to commit racketeering, conspiracy to commit wire and mail fraud and conspiracy to violate the Anti-Kickback Law; Burlakoff, Simon, Lee and Rowan are charged with RICO conspiracy, mail fraud conspiracy and conspiracy to violate the Anti-Kickback Law; Gurry is charged with RICO conspiracy and wire fraud conspiracy.

The indictment also alleges that the conspiracy to bribe practitioners and to defraud insurers generated substantial profits for the defendants, their company, and for the co-conspirator practitioners.

“Causing the unnecessary use of opioids by current and retired U.S. military service members shows disregard for their health and disrespect for their service to our country,” said Special Agent in Charge Craig Rupert of the Defense Criminal Investigative Service (DCIS), Northeast Field Office. “DCIS will continue to partner with the DOJ and our fellow law enforcement agencies to address conduct such as this and protect America's Warfighters.”

“EBSA is very pleased to had the opportunity work collaboratively with our law enforcement partners in this important investigation,” said Susan A. Hensley, Regional Director of the U.S. Department of Labor, Employee Benefits Security Administration, Boston Regional Office.

“I commend the exceptional work performed by our criminal investigators and their law enforcement partners,” said Scott Rezendes, Special Agent in Charge of the U.S. Office of Personnel Management, Office of Inspector General, Office of Investigations. “It is utterly unacceptable to risk the safety and well-being of patients in order to increase profits. This office will continue to vigorously pursue any and all cases that may jeopardize the health of Federal employees, annuitants, and their families.”

“U.S. Postal Inspection Service is committed to protecting the nation’s mail system from criminal misuse,” said Shelly Binkowski, Inspector in Charge of the U.S. Postal Inspection Service. “This investigation is an excellent example of a partnership between government agencies working together to dismantle prescription drug practices that directly contribute to the ongoing opioid abuse epidemic.”

"The United States Postal Service, Office of Inspector General will continue to vigorously investigate companies that engage in improper relationships with medical providers for the purpose of increasing market share as alleged in this case," said Eileen Neff, Special Agent in Charge of the U.S. Postal Service Office of Inspector General. "We thank our law enforcement partners for their help in preventing this type of fraud against the healthcare programs of the American public and the Postal Service."

"Misrepresenting a patient's diagnoses and using kickbacks to prescribing doctors to inflate drug sales is fraudulent activity," said Donna L. Neves, Special Agent in Charge of the U.S. Department of Veterans Affairs, Office of Inspector General, Northeast Field Office. "Targeting veterans' dependents using CHAMPVA with these type techniques is unacceptable. We are pleased to have contributed to this outstanding multi-agency criminal investigation and will continue to pursue allegations of health care fraud that put our veterans and their families at risk."

On the charges of conspiracy to commit RICO and conspiracy to commit mail and wire fraud, the charging statute provides a sentence of no greater than 20 years in prison, three years of supervised release and a fine of $250,000, or twice the amount of pecuniary gain or loss. On the counts of conspiracy to violate the Anti-Kickback Law, the charging statute provides a sentence of up to five years in prison, three years of supervised release and a $25,000 fine. Actual sentences for federal crimes are typically less than the maximum penalties. Sentences are imposed by a federal district court judge based upon the U.S. Sentencing Guidelines and other statutory factors.

The investigation was conducted by a team that included the FBI; HHS-OIG; FDA Office of Criminal Investigations; the Defense Criminal Investigative Service; the Drug Enforcement Administration; the Department of Labor, Employee Benefits Security Administration; the Office of Personnel Management; the U.S. Postal Inspection Service; the U.S. Postal Service Office of Inspector General; and the Department of Veterans Affairs. The U.S. Attorney would like to acknowledge the outstanding cooperation and assistance of the U.S. Attorney's Offices around the country engaged in parallel investigations, including the District of Connecticut; the Eastern District of Michigan; the Southern District of New York; and the Southern District of Alabama. The efforts of the Central District of California and the Civil Fraud Section of the Department of Justice are also greatly appreciated.

Assistant U.S. Attorneys K. Nathaniel Yeager, Chief of Ortiz's Health Care Fraud Unit, and Susan M. Poswistilo, of Ortiz' Civil Division, are prosecuting the case.

The details contained in the indictment are allegations. The defendants are presumed innocent unless and until proven guilty beyond a reasonable doubt.

Attachment(s):
Download Insys Indictment

Topic(s):
Healthcare Fraud

Component(s):

USAO - Massachusetts

Updated December 9, 2016

EXHIBIT 95

SEALED

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

UNITED STATES OF AMERICA, v. (1) MICHAEL L. BABICH (2) ALEC BURLAKOFF (3) MICHAEL J. GURRY (4) RICHARD M. SIMON (5) SUNRISE LEE (6) JOSEPH A. ROWAN Defendants.	CRIMINAL NO. 16cr 10343 VIOLATIONS: 18 U.S.C. § 1962(d) (Racketeering Conspiracy) 18 U.S.C. § 1349 (Mail Fraud Conspiracy) 18 U.S.C. § 1349 (Wire Fraud Conspiracy) 18 U.S.C. § 371 (Conspiracy) 18 U.S.C. §§ 1963, 982(a)(7) and 981(a)(1)(C); 28 U.S.C. § 2461(c) (Forfeiture)

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THE GRAND JURY CHARGES THAT:

INTRODUCTION TO ALL COUNTS

At all times material hereto, unless otherwise alleged:

I. Overview

A. The Defendants

1. The defendant **MICHAEL L. BABICH** ("**BABICH**") resided in Scottsdale, Arizona. At various times relevant to the indictment **BABICH** was President and Chief Executive Officer ("CEO") of a publicly traded entity located in Arizona ("the Company"). At various times between in or about March 2012 and December 2016, the Company manufactured, marketed, and sold a fentanyl spray ("Fentanyl Spray") in interstate commerce, including in the District of Massachusetts. As President and CEO of the Company, **BABICH** was responsible for managing the development, promotion, distribution, and sale in interstate commerce of the Fentanyl Spray.

2. The defendant **ALEC BURLAKOFF** ("**BURLAKOFF**") resided in Charlotte, North Carolina. At various times relevant to the indictment **BURLAKOFF** held executive management positions at the Company, including Regional Sales Manager for the Southeast Region and Vice President of Sales.

3. The defendant **MICHAEL J. GURRY** ("**GURRY**") resided in Scottsdale, Arizona. At various times relevant to the indictment **GURRY** held executive management positions at the Company, including Vice President of Managed Markets.

4. The defendant **RICHARD M. SIMON** ("**SIMON**") resided in Seal Beach, California. At various times relevant to the indictment **SIMON** held executive management

positions at the Company, including Regional Sales Manager for the Central Region and National Director of Sales.

5. The defendant **SUNRISE LEE** ("**LEE**") resided in Byron Center, Michigan. At various times relevant to the indictment **LEE** held executive management positions at the Company, including Regional Sales Manager for the Mid-Atlantic Region, Regional Director for the Central Region, and Regional Director for the West Region.

6. The defendant **JOSEPH A. ROWAN** ("**ROWAN**") resided in Panama City, Florida. At various times relevant to the indictment **ROWAN** held various positions at the Company, including Regional Sales Manager for the Southeast Region and Regional Director for the East Region.

B. Co-Conspirator Practitioners

7. Licensed medical practitioners who were registered with the Drug Enforcement Administration ("DEA") and able to prescribe opioids in the usual course of professional practice for a legitimate medical purpose, owed a fiduciary duty to their patients to refrain from accepting or agreeing to accept bribes and kickbacks in exchange for prescribing any drug. At times relevant to the indictment certain licensed medical practitioners associated with the Company ("the co-conspirator practitioners") conspired with the Defendants and other persons and entities known and unknown to the Grand Jury to engage in various criminal activities as described below. These medical practitioners included the following whose identities are known to the Grand Jury:

a. Practitioner #1 was a physician licensed to practice in Alabama.

b. Practitioner #2 was a physician licensed to practice in Alabama.

c. Practitioner #3 was a physician licensed to practice in Michigan.

d. Practitioner #4 was a physician licensed to practice in Florida.

e. Practitioner #5 was a physician licensed to practice in Texas.

f. Practitioner #6 was a physician licensed to practice in Illinois and Indiana.

g. Practitioner #7 was an Advanced Practice Nurse ("APRN") licensed to practice in Connecticut.

h. Practitioner #8 was a Physician Assistant licensed to practice in New Hampshire.

i. Practitioner #9 was a physician licensed to practice in Florida.

j. Practitioner #10 was a physician licensed to practice in Arkansas.

C. Summary of the Allegations

8. In or about late March of 2012, the Company launched the Fentanyl Spray, a powerful, and potentially dangerous, rapid onset opioid approved to treat breakthrough cancer pain, into a small, crowded, and tightly controlled market.

9. From in or about June 2012 and continuing until in or about December 2015, **BABICH**, **BURLAKOFF**, **SIMON**, **LEE**, and **ROWAN**, the co-conspirator practitioners, and other co-conspirators known and unknown to the Grand Jury, sought to profit by devising and fostering a scheme to bribe practitioners who were licensed to practice in various states, many of whom ran pain clinics. In exchange for those bribes and kickbacks, the practitioners wrote large numbers of Fentanyl Spray prescriptions, most often for patients who did not have cancer. The bribes and kickbacks took different forms, but were most frequently disguised as fees the Company paid the practitioners for marketing events.

10. While the bribery scheme succeeded at generating new Fentanyl Spray prescriptions, insurers, private sector employer-sponsored employee benefit plans (referred to herein as "insurers"), and their agents, were reluctant to approve payment for the Fentanyl Spray

when it was prescribed for patients without cancer. The potential for profits generated by the bribes could not be fully realized unless insurers authorized payment. Accordingly, in or about November 2012, **BABICH** and **GURRY**, together with co-conspirators known and unknown to the Grand Jury, created and fostered a scheme to mislead insurers, and the agents of insurers, into authorizing payment for the Fentanyl Spray.

11. Each of the Defendants directed Company employees, including sales force employees, to obtain information necessary to defraud insurers. From a call center at corporate headquarters, Company employees, acting at the direction of **BABICH** and **GURRY**, and co-conspirators known and unknown to the Grand Jury, defrauded insurers by disguising the identity and location of their employer, and by lying about patient diagnoses, the type of pain being treated, and the patient's course of treatment with other medication.

12. By bribing practitioners to write prescriptions for the Fentanyl Spray, and then defrauding, insurers, the Defendants and co-conspirators known and unknown to the Grand Jury, dramatically increased the volume of prescriptions written for the Fentanyl Spray, and thereafter, the rate at which insurers approved payment for the drug, generating substantial profits for the Company, the Defendants, and co-conspirators known and unknown to the Grand Jury, including the co-conspirator practitioners.

II. The Fentanyl Spray

13. Opioids were a therapeutic class of drugs used to relieve pain. Fentanyl and analogues of fentanyl were among the most potent opioids available for human use. Fentanyl produced effects that were practically indistinguishable from the opioids morphine and heroin, but fentanyl had a greater potency and a shorter duration of action. Fentanyl was rapidly distributed to the brain, heart, lungs, kidneys and spleen.

14. The Fentanyl Spray was a liquid formulation of fentanyl to be applied under the tongue, also called a sublingual spray.

The Fentanyl Spray Label

15. Every manufacturer of a new drug was required to obtain approval of a new drug application (NDA) from the United States Food and Drug Administration ("FDA") before introducing its new drug into interstate commerce, unless subject to an exemption not applicable here. To obtain approval of an NDA, the manufacturer had to demonstrate to FDA that the new drug was safe and effective for its intended uses. Labeling on the drug also had to be truthful, accurate and non-misleading.

16. On or about March 4, 2011, the Company submitted an NDA to the FDA seeking approval of its Fentanyl Spray. The FDA approved the Fentanyl Spray in or about January 2012 for the management of breakthrough pain in patients with cancer, 18 years of age or older, who were already receiving and who were already tolerant to opioid therapy for their underlying persistent cancer pain. The label for the Fentanyl Spray warned that the drug posed risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors. Explicit warnings on the Fentanyl Spray label included that as an opioid agonist the drug could be abused in a manner similar to other opioid agonists, legal or illicit.

The TIRF REMS Access Program

17. The FDA determined that the Fentanyl Spray was in a category of drugs it called Transmucosal Immediate Release Fentanyl ("TIRF") products, which included other fentanyl-based rapid onset opioids. Each of the TIRF drugs was indicated for the management of breakthrough pain in patients with cancer, 18 years of age or older, who were already receiving and who were already tolerant to opioid therapy for their underlying persistent cancer pain.

18. Each of the TIRF drugs was approved subject to a risk evaluation and mitigation strategy ("REMS") in order to ensure that the benefits of the drug outweighed the risks associated with the drug, including the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors. Consequently, the FDA required the Company to submit, and ultimately to implement, a REMS strategy for the Fentanyl Spray called the TIRF REMS Access Program.

19. The TIRF REMS Access Program included several elements designed to protect patients from the risks associated with TIRF drugs. The program required, among other things, that TIRF medicines only be dispensed to an outpatient when the practitioner prescribing the drug, the patient, and the pharmacy dispensing the TIRF medicine had each been educated about the risks associated with the drug.

Schedule II

20. Titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended, 21 U.S.C. §§ 801-971, were collectively referred to as the "Controlled Substances Act" or the "CSA." The CSA and its implementing regulations identified drugs and other substances defined by federal law as "controlled substances," and classified every controlled substance into one of five schedules based in part upon its potential for abuse, its currently accepted medical use in treatment in the United States, and the degree of dependence the drug or other substance might cause. To be placed in "Schedule II," a drug had to have, among other things, a high potential for abuse.

21. Fentanyl, including the Fentanyl Spray, was a Schedule II controlled substance.

III. The Market for the Fentanyl Spray

22. The Company began selling the Fentanyl Spray in or about March 2012. From the beginning, the Fentanyl Spray faced a number of market challenges.

Crowded TIRF Market

23. In or about 2012, there were an estimated one to two million patients in the United States suffering from breakthrough cancer pain.

24. At the time of its launch, the Fentanyl Spray was the fourth new branded drug in the TIRF market in four years. While the Fentanyl Spray was the first TIRF product to be delivered as a spray for sublingual administration, each of the TIRF formulations delivered fentanyl rapidly via the oral mucosa in a variety of dosage forms.

25. In the first year after the Fentanyl Spray was launched, fewer than 1,900 practitioners wrote approximately 90 percent of all TIRF product prescriptions in the United States. Approximately 30 percent of all TIRF prescriptions were written by fewer than 200 practitioners nationwide.

Insurance

26. The Fentanyl Spray, like other TIRF drugs, was expensive. Depending upon the dosage and number of units prescribed, a prescription for the Fentanyl Spray usually cost thousands of dollars each month.

27. Most patients relied upon commercial insurance to subsidize the cost of taking prescribed TIRF medicines. Publicly funded insurance also subsidized the costs of prescribed TIRF medication for its enrollees. Federal health care benefit programs that subsidized payment for the cost of the Fentanyl Spray included, among others, the Medicare program ("Medicare") and the Medicaid program ("Medicaid").

Managed Care

28. Many insurers controlled the costs of health care by managing the form and substance of care provided to their enrollees and by employing organizations that specialized in managing the costs of prescription pharmaceuticals, called pharmacy benefit managers. Insurers and pharmacy benefit managers controlled the costs of prescription drugs by using, among other restrictions, prior authorizations.

29. In the six years before the launch of the Fentanyl Spray, managed care restrictions dramatically reduced the market for branded TIRF medications in favor of generics, the most affordable of the TIRF drugs. When the Fentanyl Spray was launched in 2012, the generic forms of TIRF medicines retained nearly two-thirds of the market for TIRF drugs.

Prior Authorizations

30. While their specific requirements varied, almost all insurers required patients to obtain prior authorization of TIRF medications, including the Fentanyl Spray, before agreeing to pay for a prescription. In general, patients had to have a specific medical diagnosis before the insurer would authorize payment for the medication. Many insurers and pharmacy benefit managers would not pay for an expensive drug until the patient had tried and failed certain other preferred medications.

31. If prior authorization was granted, the insurer paid most, but not all, of the cost of the drug. Without prior authorization, the prescription was not filled unless the patient or a third party paid for the entire cost of drug.

IV. Bribing Practitioners and Defrauding Insurers

32. Beginning in or about June 2012 and continuing until in or about December 2015, **BABICH**, **BURLAKOFF**, **GURRY**, **SIMON**, **LEE**, and **ROWAN**, the co-conspirator

practitioners including those described in paragraph 7, and other persons and entities known and unknown to the Grand Jury, conspired with one another to use bribes and kickbacks, as well as materially false and fraudulent pretenses, representations, and promises, to gain influence over and control of market demand, and ultimately payment, for the Fentanyl Spray.

A. Bribery of Practitioners

The Speaker Program

33. In or about March 2012 through in or about August 2012, the Company planned and funded a marketing program (the "Speaker Program") purportedly intended to increase brand awareness using peer-to-peer educational lunches and dinners (the "events"). Company policy required sales representatives, also called Specialty Sales Professionals, to recruit licensed practitioners to lecture regarding the use of the Fentanyl Spray for the treatment of breakthrough cancer pain in opioid tolerant patients. Company policy also required speakers to be chosen and approved based upon various criteria, including skill in the use of opioids, experience with the Fentanyl Spray, geography, prominence, and experience as speakers. In exchange for practitioners speaking to other prescribers about the Fentanyl Spray, the Company agreed to pay each speaker a fee, also referred to as an "honoraria," for each event.

34. Speakers were required to sign written agreements with the Company, which, among other things, required them to attend organized training sessions. Sales representatives began looking for qualified speakers during the second quarter of 2012. The Company began training speakers in or about June and July 2012.

Using The Speaker Program to Pay Bribes

35. April through June 2012 was the first full fiscal quarter during which the Fentanyl Spray was sold in the United States. By the end of June 2012, the Company's leadership had

grown dissatisfied with sales of the Fentanyl Spray. **BABICH**, the President and CEO, began making personnel changes within the Company.

36. In or about late June 2012, approximately one month before the Company was to begin conducting Speaker Program events, **BABICH** replaced the Company's Southeast Regional Sales Manager with **BURLAKOFF**.

37. On or about June 27, 2012, approximately one week after **BURLAKOFF** joined the Company, **BABICH** sent an email to his sales managers, including **BURLAKOFF**. The email, entitled "Live Speaker Targets," compelled **BURLAKOFF** and the other managers to ensure that sales representatives understood "the important nature of having one of their top targets as a speaker. It can pay big dividends for them."

38. Almost immediately **BURLAKOFF** began using in-person meetings, telephone calls, and texts to inform sales representatives that the key to sales was using the Speaker Program to pay practitioners to prescribe the Fentanyl Spray. **BURLAKOFF** texted one sales representative, telling her not to worry about the communication skills of practitioners speaking about the Fentanyl Spray: "[t]hey do not need to be good speakers, they need to write a lot of [Fentanyl Spray prescriptions]."

39. Sales in the Southeast District increased under **BURLAKOFF**. In or about September 2012, approximately three months after he was hired, **BURLAKOFF** was promoted to Vice President of Sales for the Company. In that role, **BURLAKOFF** supervised all of the Company's sales managers and sales representatives.

40. **BABICH** and **BURLAKOFF** hired new sales employees throughout the summer and autumn of 2012, including **SIMON**, **ROWAN**, and **LEE**.

41. **SIMON** was promoted to Director of Sales for the Company in or about July of 2013. As Director of Sales, **SIMON** directly reported to **BURLAKOFF** and was responsible for supervising the Company sales force, which was organized into East, Central, and West regions. **LEE** and **ROWAN** were promoted to Regional Directors, responsible for supervising all of the sales managers and sales representatives working in their respective regions. As Regional Directors, **LEE** and **ROWAN** reported directly to **SIMON**.

Quid Pro Quo

42. Using pharmacy data acquired from third parties, **BABICH**, **BURLAKOFF**, **SIMON**, **LEE**, and **ROWAN**, and other co-conspirators known and unknown to the Grand Jury, tracked the success of competitor brands in the TIRF market and circulated to interested staff lists of practitioners who had written prescriptions for TIRF products, including the Fentanyl Spray. The lists ranked practitioners in groups (called "deciles") one to ten, according to the number of TIRF prescriptions written by each. A practitioner who wrote the fewest TIRF prescriptions was a "decile 1," while a practitioner who wrote the most TIRF prescriptions was a "decile 10." The Company sales force targeted "high decile" practitioners.

43. On his first day as Vice President of Sales for the Company, in September 2012, **BURLAKOFF** emailed a newly hired sales representative, with copies to all Regional Sales Managers and **BABICH**, as follows:

> …it all starts with choosing the right LOCAL speaker. Your local speaker should be your 'business partner'. You do not work for him, nor does he work for you. You are <u>partners</u> in this endeavor, if your speaker does not see it this way…… (then it is time to identify another speaker).

44. **BABICH**, **BURLAKOFF**, **SIMON**, **LEE**, and **ROWAN**, and other co-conspirators known and unknown to the Grand Jury, tracked and circulated the total number of planned Speaker Program events for each speaker, the number of Speaker Program events completed, the

number of Fentanyl Spray prescriptions written by the speaker, the percentage of Fentanyl Spray prescriptions versus its competitor drugs written by the speaker, the net revenue of profit the Company earned from each speaker, and the total amount of honoraria paid to the speaker, and for a time, explicitly calculated the ratio of return on investment for each speaker.

45. In return for bribes and kickbacks paid to co-conspirator practitioners, **BABICH**, **BURLAKOFF**, **SIMON**, **LEE**, and **ROWAN**, and other co-conspirators known and unknown to the Grand Jury, expected the co-conspirator practitioners to prescribe the Fentanyl Spray to their patients. If a co-conspirator practitioner did not write an appropriate number of prescriptions, the Defendants and their co-conspirators reduced the number of scheduled Speaker Programs for which the co-conspirator practitioner was to be paid (or canceled the Speaker Programs), unless and until the practitioner wrote more prescriptions for the Fentanyl Spray.

46. In or about November 2013, **BABICH** received a list that identified medical practitioners, including co-conspirator practitioners, who had written prescriptions for a competitor drug.

47. In response, **BABICH** sent an email to **BURLAKOFF** and others. In the email **BABICH** indicated that a quid pro quo with co-conspirator practitioners was expected, "I thought we owned the high decile folks? Lot of big names on there."

Targeting Pain Clinics

48. **BABICH**, **BURLAKOFF**, **SIMON**, **LEE**, and **ROWAN**, and other co-conspirators known and unknown to the Grand Jury, knew from tracked data that physicians focused on treating cancer were not high decile prescribers. As a result, **BABICH**, **BURLAKOFF**, and **SIMON**, and other co-conspirators known and unknown to the Grand Jury, continuously

targeted practitioners who prescribed TIRF medicines not just for breakthrough cancer pain, but for all pain.

49. On one occasion, **SIMON** texted a sales representative stating,

> I need confirmation from YOU that you had a conversation with… [the practitioner] where he will not ONLY promote for cancer patients. If he does this he will single handedly take down the whole company. He MUST creatively share how docs write this product everywhere. Please get back to me ASAP with confirmation that he will share with our other speakers how effective … [the Fentanyl Spray] will be to treat ALL BTP [Breakthrough Pain].

50. Likewise, at a national sales meeting, in or about 2014, **BURLAKOFF** told the Company's assembled sales force,

> [t]hese [doctors] will tell you all the time, well, I've only got like eight patients with cancer. Or, I only have, like, twelve patients that are on a rapid-onset opioids [sic]. Doc, I'm not talking about any of those patients. I don't want any of those patients. That's, that's small potatoes. That's nothing. That's not what I'm here doing. I'm here selling [unintelligible] for the breakthrough pain. If I can successfully sell you the [unintelligible] for the breakthrough pain, do you have a thousand people in your practice, a thousand patients, twelve of them are currently on a rapid-onset opioids [sic]. That leaves me with at least five hundred patients that can go on this drug.

51. The discipline of pain medicine is an accepted and recognized medical subspecialty practiced by physicians throughout the United States. Legitimate pain medicine specialists used a multi-disciplinary approach to treat patients suffering from chronic pain. Other such specialists knowingly engaged in illicit commercial drug distribution in order to profit. At times, pain clinics engaged in illicit drug distribution were colloquially called "pill mills."

52. **BABICH**, **BURLAKOFF**, **SIMON**, **LEE**, and **ROWAN**, and other co-conspirators known and unknown to the Grand Jury, actively recruited practitioners known to have questionable prescribing habits as potential co-conspirators in their bribery and kickback scheme.

Other Bribes and Kickbacks

53. Fees paid to speakers were the most common form of bribes and kickbacks paid to co-conspirator practitioners. **BABICH, BURLAKOFF, SIMON, LEE,** and **ROWAN** sought to and did use other forms of bribes and kickbacks to reward co-conspirator practitioners. In exchange for Fentanyl Spray prescriptions:

a. **BABICH, BURLAKOFF, SIMON, LEE,** and **ROWAN** sought to employ friends and family members of co-conspirator practitioners.

b. **BABICH, BURLAKOFF, SIMON, LEE,** and **ROWAN** sought to schedule Speaker Program events at and to purchase food from establishments owned or operated by practitioners, and their families or friends.

c. **BABICH, BURLAKOFF, SIMON, LEE,** and **ROWAN** sought to use the food and drink furnished at Speaker Program events as bribes and kickbacks. Speaker Program events were often just social gatherings at high-priced restaurants that involved no education and no presentation. Frequently, Speaker Program events involved the same repeat attendees, who were often friends of the co-conspirator practitioner. Speaker Program events also frequently did not have attendees who were licensed to prescribe the Fentanyl Spray, but rather only included support staff employed by the speaker. Many speaker events had no attendees at all. When this occurred, sales representatives were told to falsify the names of attendees and their signatures on Company sign-in sheets. Sham Speaker Program events occurred at restaurants within the District of Massachusetts and elsewhere, and functioned as a bribe in the form of a free dinner with friends.

Administrative Support as Kickbacks

54. Obtaining prior authorizations was time-consuming and costly for practitioners. A practitioner had to dedicate support staff, and the money necessary to compensate them, to navigate the prior authorization processes and associated paperwork.

55. Co-conspirator practitioners who wrote large numbers of Fentanyl Spray prescriptions were given the benefit of Area Business Liaisons ("ABLs") and Business Relations Managers ("BRMs"). ABLs and BRMs were support staff, employed and compensated by the Company, to work (in most cases) at the office of certain co-conspirator practitioners. Several of the ABLs and BRMs employed by the Company were family or friends of co-conspirator practitioners.

56. **BABICH**, **BURLAKOFF**, **GURRY**, **SIMON**, **LEE**, and **ROWAN**, and other co-conspirators known and unknown to the Grand Jury, required sales representatives and ABLs to assist the office staff of co-conspirator practitioners with filling out and faxing prior authorization paperwork and other documentation. The Defendants used this, and other administrative support from the ABLs and BRMs as a bribe and kickback to compensate co-conspirator practitioners for writing Fentanyl Spray prescriptions.

B. Defrauding Insurers and Pharmacy Benefit Managers

57. After targeting pain clinics and bribing practitioners, **BABICH**, **BURLAKOFF**, and **SIMON** began to see an increase in the number of new Fentanyl Spray prescriptions. **BABICH**, **BURLAKOFF**, and other co-conspirators known and unknown to the Grand Jury knew, however, that the Company still needed insurers and pharmacy benefit managers to authorize payment for the new prescriptions.

58. At or about the end of the second quarter of 2012, **BABICH** began to focus more attention on prior authorizations. In or about August 2012, **BABICH** hired **GURRY** as Vice President of Managed Markets. In or about September 2012, **BABICH**, **GURRY**, **BURLAKOFF**, and other co-conspirators known and unknown to the Grand Jury sought to create a comprehensive plan to increase profits generated by prior authorizations.

The Reimbursement Unit

59. In or about October 2012, **BABICH**, **GURRY**, and other co-conspirators known and unknown to the Grand Jury launched the Prior Authorization Tracking Program ("PA Tracking program"). The program tracked several types of information, including comprehensive data regarding prior authorizations. In or about the same month, **BABICH** and **GURRY** hired a "prior authorization specialist" ("PA specialist").

60. In or about November 2012, the PA Tracking program demonstrated that insurers and pharmacy benefit managers only approved payment for approximately 30 to 33 percent of all prescriptions for the Fentanyl Spray. **BABICH**, **GURRY**, and other co-conspirators known and unknown to the Grand Jury began planning a pilot program to increase the percentage of successful prior authorizations.

61. As part of the pilot program, **BABICH** and **GURRY** directed the PA specialist, who worked at corporate headquarters in Arizona, to seek prior authorizations directly from insurers and pharmacy benefit managers on behalf of patients from select practitioners based in several locations around the country. After the first week, the prior authorization rate for prescriptions handled by the PA specialist increased to 46 percent.

62. Using information learned from the pilot program, in or about January 2013 through in or about December 2015, **BABICH**, **GURRY**, and other co-conspirators known and unknown

to the Grand Jury created and operated a Company-based unit dedicated to obtaining prior authorizations directly from insurers and pharmacy benefit managers. The name of the unit (referred to as the "Reimbursement Unit") changed a number of times, but its purpose and functions remained roughly the same.

63. Practitioners using the Reimbursement Unit were required to fill out "Opt-In" forms, which sought patient identifiers and other confidential information such as name and date of birth, insurer information, prescriber information, pharmacy information, and the medical diagnosis and corresponding codes associated with the diagnosis. **BABICH, BURLAKOFF, GURRY, SIMON, LEE,** and **ROWAN**, and co-conspirators known and unknown to the Grand Jury, directed Company employees to obtain, and to assist practitioners in obtaining the information required to fill out Opt-In forms, including, at times, the medical records of patients.

64. Completed Opt-In forms and medical records were faxed or emailed from the offices of practitioners to the Reimbursement Unit in Arizona by staff employed by practitioners and by employees of the Company, including sales representatives, ABLs, and BRMs. The Reimbursement Unit, in turn, became the entity that sought prior authorization directly from the insurer and pharmacy benefit manager.

The Gate

65. **BABICH**, **GURRY**, and other co-conspirators known and unknown to the Grand Jury created a pay structure for Reimbursement Unit employees that rewarded prior authorization approvals with substantial financial bonuses. Every week **GURRY**, together with another co-conspirator, set a weekly minimum threshold, called a "gate," for the whole Reimbursement Unit. A Reimbursement Unit employee, no matter how productive, could not qualify for a bi-weekly bonus until the entire Reimbursement Unit reached each week's threshold number of

approvals. Once the Reimbursement Unit met its threshold, an employee could earn a bonus based upon the number of prior authorizations obtained.

Defrauding Insurers and Pharmacy Benefit Managers

66. **GURRY**, and other co-conspirators known and unknown to the Grand Jury, held team meetings with Reimbursement Unit employees, in which the group shared best practices for obtaining authorizations from insurers and pharmacy benefit managers. The practices included materially false and fraudulent pretenses, representations, and promises used to obtain payment from insurers and pharmacy benefit managers. Reimbursement Unit employees were taught how to mislead and deceive insurers regarding their employment, patient diagnoses, and tried and failed medications. **BABICH**, **GURRY**, and other co-conspirators known and unknown to the Grand Jury approved and fostered the use of these fraudulent practices.

67. In or about December 2013, approximately one year after it was created, the Reimbursement Unit handled prior authorization requests for practitioners nationwide. At or about the same time, the Reimbursement Unit reported that insurers and pharmacy benefit managers granted prior approval for more than 85 percent of all prescriptions handled by Reimbursement Unit employees.

V. Examples

68. The schemes to profit from using bribes and kickbacks to gain influence over and control of market demand for the Fentanyl Spray, and to obtain money and property by means of materially false pretenses, representations, and promises made to insurers and pharmacy benefit managers, included, but are not limited to, the criminal activities described below.

A. Examples of Bribing Medical Practitioners

Practitioner #1

69. Practitioner #1 and Practitioner #2 owned and co-directed a pain management clinic in two locations in or around Mobile, Alabama. Practitioner #1 and Practitioner #2 also owned a pharmacy, which was next to one of their clinic locations.

70. In or about March of 2012, a Company sales representative approached both Practitioner #1 and Practitioner #2 because both had been identified as pain specialists who wrote a substantial number of prescriptions for TIRF drugs. Practitioner #1 and Practitioner #2 began writing Fentanyl Spray prescriptions soon after it was launched. By the end of the second quarter of 2012, in or about the week of June 30, 2012, Practitioner #1 averaged approximately 2.2 Fentanyl Spray prescriptions per week. Practitioner #2 averaged roughly one Fentanyl Spray prescription every other week.

71. Within weeks of joining the Company as the Regional Manager for the Southeast, **BURLAKOFF** hired defendant **ROWAN**. **BURLAKOFF** and **ROWAN** had previously worked together selling a TIRF drug for a competitor pharmaceutical company. **BURLAKOFF** assigned **ROWAN** to call on a single physician, Practitioner #1.

72. On or about July 28, 2012, **BURLAKOFF** emailed **ROWAN** that the previous sales representative assigned to Practitioner #1,

> …made 7K off… [Practitioner #1] last quarter. He wrote … 26 prescriptions. So, thats [sic] basically 1 script every 3rd day for 60 days. If he wrote just 1 script every day ... you would make 22k. If he does 2 …[Fentanyl Spray prescriptions] a day for one straight quarter, you would make at least 40 grand for the quarter!"

73. Approximately two weeks after **ROWAN** joined the Company, Practitioner #1 participated in his first two Speaker Program events. During the same week Practitioner #1

wrote 18 Fentanyl Spray prescriptions. By on or about September 28, 2012, the end of the third quarter of 2013, Practitioner #1 averaged approximately 11 Fentanyl Spray prescriptions per week.

74. On or about December 20, 2012, **BURLAKOFF** sent an email to the Southeast District sales team in which **BURLAKOFF** addressed **ROWAN** directly, stating, "Joe…Congrats, you are now officially #1 in the company (with only one doctor). I am pretty sure your formula worked, you may want to pass it along to your team." Between his first Speaker Program event in or about August 2012 and the first week of December 2012, the Company paid Practitioner #1 approximately $24,000 in bribes and kickbacks.

75. Between in or about August 2012 and in or about May 2015, many of the Speaker Program events attended by Practitioner #1 were sham events that were mere social gatherings also attended by friends and office staff of Practitioner #1.

76. Between in or about August 2012 and in or about May 2015, payment was authorized for approximately 2,148 Fentanyl Spray prescriptions written by Practitioner #1.

77. Between in or about August 2012 and in or about May 2015, for the purpose of executing their scheme and artifice to defraud and for obtaining money and property, the Defendants, and other co-conspirators known and unknown to the Grand Jury, sent and caused to be sent to Practitioner #1 checks totaling approximately $229,640.00 for Speaker Program bribes and kickbacks.

Practitioner #2

78. At or around the end of the first quarter of 2013, Practitioner #2 wrote approximately two to three prescriptions for the Fentanyl Spray each week.

79. In April 2013 **BURLAKOFF** and **ROWAN** hired a new sales representative to serve Practitioner #2. **ROWAN**, who supervised the new sales representative, agreed with her that the "ultimate goal" was to get Practitioner #2 to write Fentanyl Spray prescriptions as Practitioner #1 did.

80. The new sales representative immediately sought to use the Speaker Program to pay Practitioner #2 bribes and kickbacks. Practitioner #2 began speaking more regularly during the second quarter of 2013. By on or about July 19, 2013, Practitioner #2 averaged approximately 6.8 Fentanyl Spray prescriptions each week.

81. On or about August 1, 2013, **ROWAN** sent an email to **BURLAKOFF** stating that where the new sales representative "has taken… [Practitioner #2] is out of this world. He is now a top seven prescriber for… [the Company]."

82. Between in or about February 2013 and May 2015, many of the Speaker Program events attended by Practitioner #2 were sham events that were mere social gatherings also attended by the friends and office staff of Practitioner #2.

83. Between in or about February 2013 and May 2015 insurers and pharmacy benefit managers authorized payment for approximately 984 Fentanyl Spray prescriptions written by Practitioner #2.

84. Between in or about February 2013 and May 2015, for the purpose of executing their scheme and artifice to defraud and for obtaining money and property, the Defendants, and other co-conspirators known and unknown to the Grand Jury, sent and caused to be sent to Practitioner #2 checks totaling approximately $103,350.00 for Speaker Program bribes and kickbacks.

Practitioner #3

85. Practitioner #3 owned and operated a pain management clinic in Saginaw, Michigan. The clinic, which served more than 5,000 patients, also had ancillary clinics in several locations throughout Michigan.

86. Practitioner #3 began prescribing the Fentanyl Spray the month after it was launched. By on or about September 28, 2012, Practitioner #3 averaged approximately four Fentanyl Spray prescriptions each week.

87. **BURLAKOFF** was not satisfied with the number of Practitioner #3's Fentanyl Spray prescriptions. In or about the first week in October 2012, **BURLAKOFF** traveled to Michigan and took Practitioner #3 to dinner. The next day **BURLAKOFF** sent an email to **BABICH**, **LEE** and another, telling them, "expect a nice 'bump' fellas…."

88. During the next year and a half, **BABICH**, **BURLAKOFF**, and **LEE** used the Speaker Program, and other Company resources, to pay bribes and kickbacks to Practitioner #3 in exchange for Fentanyl Spray prescriptions.

89. During the seven months between the launch of the Fentanyl Spray and the day before his first Speaker Program event in or about October 11, 2012, Practitioner #3 wrote approximately 94 Fentanyl Spray prescriptions. Within approximately one month of the dinner with **BURLAKOFF**, Practitioner #3 had attended two Speaker Program events and was scheduled to "speak" at six more. In the roughly two months between his dinner with **BURLAKOFF** and the end of November 2012, Practitioner #3 wrote approximately 120 Fentanyl Spray prescriptions.

90. By on or about January 11, 2013, Practitioner #3 was averaging approximately 19 Fentanyl Spray prescriptions each week. The Company paid Practitioner #3 for 18 Speaker Program events during the first quarter of 2013.

91. Many of the Speaker Program events attended by Practitioner #3 were sham events that were mere social gatherings also attended by the friends and office staff of Practitioner #3. At times, the Speaker Program events attended by Practitioner #3 included no attendees at all.

92. Between in or about November 2012 through in or about June 2014, insurers and pharmacy benefit managers authorized payment for approximately 2,847 Fentanyl Spray prescriptions written by Practitioner #3.

93. Between in or about November 2012 through in or about June 2014, for the purpose of executing their scheme and artifice to defraud and for obtaining money and property, the Defendants, and other co-conspirators known and unknown to the Grand Jury, sent and caused to be sent to Practitioner #3 checks totaling approximately $138,435.07 for Speaker Program bribes and kickbacks.

94. The bribes and kickbacks paid to Practitioner #3 were not limited to Speaker Program events. By the spring of 2013, Practitioner #3's office staff were overwhelmed with prior authorization requests. On or about May 2, 2013, a Reimbursement Unit employee sent an email to **BURLAKOFF** and **GURRY** stating that the Reimbursement Unit had 153 charts of Practitioner #3's, "in progress, … and … 88 charts that we have not worked on yet."

95. **BABICH**, **BURLAKOFF**, **GURRY**, **SIMON**, **LEE**, and **ROWAN**, and other co-conspirators known and unknown to the Grand Jury, recognized the lost profits caused by having so many prescriptions awaiting prior authorizations. In or about June 2013, **BABICH**, **BURLAKOFF**, **SIMON**, and **GURRY** created the ABL (Area Business Liaison) position.

ABLs were paid by the Company, but worked inside the medical offices of high prescribing co-conspirator practitioners. The ABL was responsible for providing the Reimbursement Unit with all of the patient information needed to navigate the prior authorization process.

96. In or about September 2013, the Company sought to hire an employee working in one of Practitioner #3's clinics as an ABL. On or about September 12, 2013, **LEE** emailed the Company's Human Resource Generalist ("HR"), copying **BURLAKOFF**, **SIMON**, and another, to ask, "please tell me what the status is for the new Detroit ABL, …She is very anxious." **BURLAKOFF** responded with an email to HR, copying **BABICH**, stating, "[a]s a point of reference, Mike Babich described this hire as "strategic" …. This is [Practitioner #3's] … niece. …Mike understands our rational [sic] for this ABL…" While the new ABL was not in fact Practitioner #3's niece, she was a woman close to Practitioner #3. **BABICH** approved the hire the same day.

97. The volume and forms of bribes and kickbacks paid to Practitioner #3 were considered a model within the Company. In or about September 2013 **BURLAKOFF** sent an email to his regional managers, including **LEE** and **ROWAN** with copies to **SIMON**, **BABICH**, and **GURRY**, in which he wrote, "[l]ets make some money, and stop playing BS games trying to manage rookies. It's the [Practitioner #3s] of the world that keep us in business, lets [sic] get a few more and the rest ...of this job is a 'joke.'"

Practitioner #4

98. Practitioner #4 operated a pain management practice in south Florida. On his first day working for the Company, **BURLAKOFF** joined the sales representative assigned to the south Florida District. After explaining that Practitioner #4 was first and foremost a business

man, **BURLAKOFF** directed the sales representative to use the Speaker Program as a way to pay Practitioner #4 for writing Fentanyl Spray prescriptions.

99. At or about the beginning of August 2012, when the Speaker Program was set to begin, Practitioner #4 averaged 0.8 Fentanyl Spray prescriptions each week. A month earlier, **BURLAKOFF** had acknowledged to the South Florida sales representative that Practitioner #4 was a good speaker, but that "even the docs he spoke to won't write."

100. Between the first week in August 2012 and the first week in December 2012, **BABICH**, **BURLAKOFF**, and co-conspirators known and unknown to the Grand Jury paid Practitioner #4 $36,000 for 15 Speaker Program events.

101. By in or about early January 2013, Practitioner #4 averaged approximately 3.3 Fentanyl Spray prescriptions per week. This was an improvement, but **BABICH**, **BURLAKOFF**, and **ROWAN** believed Practitioner #4 had potential to write many more Fentanyl Spray prescriptions.

102. On or about January 18, 2013, **BABICH**, **BURLAKOFF**, and **ROWAN** invited Practitioner #4 to corporate headquarters in Arizona. During the trip **BURLAKOFF** and **ROWAN** took Practitioner #4 to a club. The next morning **BURLAKOFF** sent the sales representative a text stating, "went fantastic last night. … [Practitioner #4] and I got back around 4AM. He had to have had one of the best nights of his life."

103. One week later, the sales representative assigned to Practitioner #4 informed **BURLAKOFF** and **ROWAN** that Practitioner #4 had written 17 Fentanyl Spray prescriptions in less than a week. The same day, **ROWAN** texted Practitioner #4, "we appreciate you more than you could believe. Leaving that meeting Alec and I felt very confident and [sic] what was going

to happen. And … you show loyalty to us like no other. You need anything at all, it is done. Thank you for being you."

104. Practitioner #4 continued to receive Speaker Program bribes and kickbacks, and by July of 2013 averaged approximately five prescriptions per week. By January 2014, Practitioner #4 averaged approximately seven Fentanyl Spray prescriptions per week.

105. Between in or about August 2012 and November 2015, insurers and pharmacy benefit managers authorized payment for approximately 2,030 Fentanyl Spray prescriptions written by Practitioner #4.

106. Between in or about August 2012 and November 2015, for the purpose of executing their scheme and artifice to defraud and for obtaining money and property, the Defendants, and co-conspirators known and unknown to the Grand Jury, sent and caused to be sent to Practitioner #4 checks totaling approximately $260,050.00 for Speaker Program bribes and kickbacks.

Practitioner #5

107. Practitioner #5 owned and operated two pain management clinics in Texas, one in Laredo and the other in Corpus Christi. During the 12 weeks between on or about July 27, 2012 and on or about October 5, 2012, Practitioner #5 wrote eight Fentanyl Spray prescriptions and was paid for only one Speaker Program event.

108. In or about October 8, 2012, **SIMON**, acting as sales manager, sent his sales team an email entitled "Speakers Not Used," instructing his sales force to schedule as many office or dinner programs "as possible with your top/targeted physicians." The next day, the sales representative for Practitioner #5 requested that the Company schedule a Speaker Program event for the doctor, describing him to **BURLAKOFF** and **SIMON** as a "local speaker for the San

Antonio territory, D[ecile]10." **BURLAKOFF** responded, copying **SIMON**, **ROWAN** and **LEE**, "[e]xcellent work! Keep them coming fast and furious..." Before the end of 2012, Practitioner #5 was scheduled to speak at seven more paid Speaker Program events and averaged more than two Fentanyl Spray prescriptions each week.

109. **BABICH**, **BURLAKOFF**, and **SIMON**, and co-conspirators known and unknown to the Grand Jury, focused significant financial resources on Practitioner #5 during the first quarter of 2013. On or about March 19, 2013 **BURLAKOFF** sent an email to the entire Company sales force lauding the top selling sales representatives, one of whom was the sales representative for Practitioner #5. **BURLAKOFF** wrote, "[t]he below 5 names mentioned at the top of the company rankings literally have their entire business being driven by basically 1 customer." **BURLAKOFF** concluded the email, "[o]wn your territory, own a doctor, and own your destiny."

110. Speaker Program events were a vehicle by which **BABICH**, **BURLAKOFF**, and **SIMON** sought to pay Practitioner #5 bribes and kickbacks.

111. Most of the Speaker Program events attended by Practitioner #5 were sham events that were mere social gatherings also attended by the friends and office staff of Practitioner #5. For example, during the first week of May 2013, **BURLAKOFF** and **SIMON** traveled to Texas to meet with Practitioner #5. One week later, on or about May 9, 2013, while identifying his planned speakers for the third quarter of 2013, the sales representative for Practitioner #5 informed **SIMON** that to date the doctor had not "influenced any physicians to write." The sales representative noted, however, that Practitioner #5 was "available to speak at dinners Monday-Thursdays."

112. By the end of the third quarter of 2013, Practitioner #5 averaged more than 12 Fentanyl Spray prescriptions each week. Between in or about January 2013 and January 2014, insurers and pharmacy benefit managers authorized payment for approximately 527 Fentanyl Spray prescriptions written by Practitioner #5.

113. Between in or about January 2013 and January 2014, for the purpose of executing their scheme and artifice to defraud and for obtaining money and property, the Defendants, and co-conspirators known and unknown to the Grand Jury, sent and caused to be sent to Practitioner #5 checks totaling approximately $123,185.10 for Speaker Program bribes and kickbacks.

114. **BABICH**, **BURLAKOFF**, and **SIMON** expected more than just a large volume of prescriptions from co-conspirator practitioners in exchange for their bribes and kickbacks. The bonus structure for sales representatives rewarded not just the number of prescriptions written, but also the dosage and the number of sprays, or "units," prescribed.

115. On or about March 11, 2013, **SIMON** sent an email to the sales representative for Practitioner #5 complaining that "3 out of the 4 scripts he wrote were refills and were still LOW units." **SIMON** instructed the sales representative to admonish office staff for Practitioner #5, "[d]rill into …[his] head that every refill has to be 180-240 etc. and that … [Practitioner #5] agreed to do this."

Practitioner #6

116. In or about 2012, Practitioner #6 practiced at a pain management clinic in Illinois. While Practitioner #6 frequently wrote prescriptions for rapid onset opioids throughout 2012, he did not write any prescriptions for the Fentanyl Spray during its first five months on the market.

117. On or about September 17, 2012, a sales representative in the Chicago area sent an email to **BABICH** to update him on her efforts with specific practitioners located in her territory, including Practitioner #6:

> I call on …[him] sometimes twice a week. …[He] runs a very shady pill mill and only accepts cash. He sees very few insured patients but does write some … [prescriptions for a competitor product]. He is extremely moody, lazy and inattentive. He basically just shows up to sign his name on the prescription pad, if he shows up at all. I have been working more with his MA ["Medical Assistant"] who is the one that knows what is going on in his office. He has agreed to try and help me out but I know that he is afraid of [the doctor's] …outbursts and is reluctant to input. I think that being in the office at the right time, when the right patient walks in, on a day [the doctor] …is in a good mood is the only way I will get him to write. This is the reason I call on him frequently.

118. Despite concerns about his prescribing practices, Practitioner #6 remained a sales target for **BABICH, BURLAKOFF**, and **SIMON**. Less than a month after the sales representative assigned to Practitioner #6 warned **BABICH** that Practitioner #6 was running a "pill mill," **LEE**, who was then the newly appointed sales manager in the Chicago area, asked the sales representative to set up a lunch with Practitioner #6. The sales representative and **LEE** took Practitioner #6 to lunch in or about early October 2012. At the conclusion of the lunch, **LEE** handed her business card to Practitioner #6 and told him to call if he wanted to discuss the Fentanyl Spray "in private."

119. Practitioner #6 arranged for drinks with **LEE** at a popular rooftop bar in downtown Chicago. A few days later, **LEE** called the assigned sales representative and told her that Practitioner #6 was going to start writing Fentanyl Spray prescriptions.

120. On or about October 18, 2012, **LEE** sent an email, copying **BURLAKOFF**, nominating a number of practitioners to be speakers, including Practitioner #6, and canceling further Speaker Program events for practitioners who had not written prescriptions or shown "interest" in the Fentanyl Spray. The next day, on or about October 19, 2012, **BURLAKOFF**

forwarded **LEE**'s email to **BABICH** and all of the Company's sales managers, noting, "[g]reat example of how we need to pro-actively manage our speaker data base by both adding and soft deleting speakers on an ongoing basis…."

121. Practitioner #6's first Speaker Program event occurred in or about November 2012. By in or about the last week of November 2012, Practitioner #6 was averaging approximately two Fentanyl Spray prescriptions per week. By in or about the second week of January 2013, Practitioner #6 averaged 3.6 Fentanyl Spray prescriptions each week.

122. In or about December 2012, the Company changed the way it disbursed bribes and kickbacks to co-conspirator practitioners. The change delayed, until early 2013, the payment of Practitioner #6's first "honoraria" from the Company. Practitioner #6 thus received bribes in exchange for his increasing number of prescriptions from in or about February 2013 through in or about July 2015. By May 2014 Practitioner #6 averaged approximately 10.3 Fentanyl Spray prescriptions each week.

123. Between in or about February 2013 and July 2015, many of the Speaker Program events attended by Practitioner #6 were sham events that were mere social gatherings also attended by friends and office staff of Practitioner #6.

124. Between in or about February 2013 and July 2015, insurers and pharmacy benefit managers authorized payment for approximately 1,601 Fentanyl Spray prescriptions written by Practitioner #6.

125. Between in or about February 2013 and July 2015, for the purpose of executing their scheme and artifice to defraud and for obtaining money and property, the Defendants and co-conspirators known and unknown to the Grand Jury, sent and caused to be sent to Practitioner #6 checks totaling approximately $70,800.00 for Speaker Program bribes and kickbacks.

Practitioner #7

126. Practitioner #7 practiced as an Advanced Practice Nurse ("APRN") for a pain management practice with offices in Derby and Meriden, Connecticut. In or about August of 2012, after speaking with Practitioner #7 about the Fentanyl Spray, the sales representative sent **BABICH** and the sales manager an email, to inform them that Practitioner #7, "expressed interest in becoming a speaker for us and I told her I would let her know as soon as we had another training scheduled."

127. In or about October 2012, Practitioner #7 signed a speaker agreement with the Company. In or about November 2012, **BURLAKOFF** emailed the manager for Connecticut, "[t]his clinician is writing, she has experience… She needs to speak ASAP." The manager responded,

> [d]amn Right [sic]. I know she was all fired up to get trained on the last training session. She definitely wants to speak, … [the assigned sales representative has] been in there working to get her dates and places lined up, she got wacked by the storm so that put things back. That's why I told him to plan it, TELL her when and where. And done. It's not rocket science.

128. By in or about March of 2013, Practitioner #7 averaged approximately 0.9 Fentanyl Spray prescriptions per week. In or about April 2013, in a private meeting, the sales representative promised Practitioner #7 payment for additional Speaker Program events in exchange for writing more prescriptions for the Fentanyl Spray.

129. On or about April 12, 2013, the sales representative for Practitioner #7 emailed his manager, stating,

> [y]ou and I both know my goals for … [Practitioner #7] and what she is verbally agreeing to do. … on Monday I will email you to get the … [Speaker Program] when she gives me a firm agreement on what we discussed earlier this week.

130. On or about June 5, 2013, the sales manager for Connecticut expressed frustration with Practitioner #7 in an exchange of emails with the assigned sales representative. The manager wrote,

> [w]hat I am concerned about is you and I spoke about 6 weeks ago when we were giving her this extra program and asked if her finding 1 new patient a week was a reasonable expectation and something to be accountable to. You told me she said yes and that you would be able to hold her accountable to that. In looking at 1 new patient in April and just 1 in May it is clear that is not happening.
>
> Keep in mind these emails are for you and me, not her. But our conversation was very clear about what had to happen. I am not sure why from the tone of your reply you now are seeming to hedge off of that commitment?
>
> Very simply when I look at return on investment as she has not motivated any new prescriber as of yet and she is not significantly increasing her own business, I am going to have tremendous difficulty in justifying more programs.

131. By on or about July 19, 2013, Practitioner #7 had increased her Fentanyl Spray prescriptions to an average of approximately 2.3 each week. By on or about September 27, 2013, Practitioner #7 averaged approximately three Fentanyl Spray prescriptions each week.

132. Between in or about December 2012 and April 2015, many of the Speaker Program events attended by Practitioner #7 were sham events that were mere social gatherings also attended by the friends and office staff of Practitioner #7.

133. Between in or about December 2012 and April 2015, insurers and pharmacy benefit managers authorized payment for approximately 556 Fentanyl Spray prescriptions written by Practitioner #7.

134. Between in or about December 2012 and April 2015, for the purpose of executing their scheme and artifice to defraud and for obtaining money and property, the Defendants and co-conspirators known and unknown to the Grand Jury, sent and caused to be sent to Practitioner #7 checks totaling approximately $78,758.25 for Speaker Program bribes and kickbacks.

Practitioner #8

135. Practitioner #8 practiced as a Physician Assistant at a pain management clinic in Somersworth, New Hampshire. In or about late April 2013, a sales representative for the Company catered a lunch at Practitioner #8's pain clinic.

136. On or about July 15, 2013, the sales representative encouraged Practitioner #8 to forward his resume to the Company for consideration as a paid speaker. Practitioner #8 forwarded his resume the same day.

137. Practitioner #8's resume did not reflect that he had ever published a scholarly article regarding TIRF drugs or pain management, nor did it indicate any previous speaking roles related to TIRF drugs and rapid onset opioids.

138. The Fentanyl Spray had been on the market for more than a year when Practitioner #8 wrote his first prescription for the drug on or about June 27, 2013. Just over one month later, on or about August 2, 2013, **BURLAKOFF** emailed the Company employee responsible for scheduling Speaker Program events and endorsed Practitioner #8 as a speaker:

> I noticed that … [Practitioner #8] out of the Manchester, NH territory has expressed a true passion and enthusiasm for … [the Fentanyl Spray] that I have not seen or felt in a very long time.
>
> These are the exact type of clinicians we want to put in front of a local audience. Often times we look for the most well-known speakers, however, with this type of product—I believe passion supersedes all!
>
> With this being said, I would like to note my desire to see this clinician have a significant increase in speaking opportunities-ASAP.
>
> In my brief phone conversation with … [Practitioner #8], I could literally feel this clinician's excitement coming through the phone.
>
> His excitement, made me excited / this is undoubtedly what we need.

139. On or about August 8, 2013, Practitioner #8 signed a Speaker Agreement with the Company. Between in or about August 2013 and the end of the year, Practitioner #8 was paid for speaking at seven Speaker Program events.

140. During the 12 weeks after his nomination as a speaker, Practitioner #8 wrote approximately 124 Fentanyl Spray prescriptions. He continued to write a large number of Fentanyl Spray prescriptions throughout the remainder of 2013. By in or about the second week of January 2014, Practitioner #8 averaged 11.8 Fentanyl Spray prescriptions per week.

141. Between in or about August 2013 and November 2014, many of the Speaker Program events attended by Practitioner #8 were sham events that were mere social gatherings also attended by the friends and office staff of Practitioner #8.

142. Between in or about August 2013 and November 2014, insurers and pharmacy benefit managers authorized payment for approximately 672 Fentanyl Spray prescriptions written by Practitioner #8.

143. Between in or about August 2013 and November 2014, for the purpose of executing their scheme and artifice to defraud and for obtaining money and property, the Defendants, and co-conspirators known and unknown to the Grand Jury, sent and caused to be sent to Practitioner #8 checks totaling approximately $44,000.00 for Speaker Program bribes and kickbacks.

144. The number of Fentanyl Spray prescriptions written by Practitioner #8 generated enough demand on his support staff that he requested the sales representative to handle the administrative work associated with obtaining prior authorization from his patient's insurers and pharmacy benefit managers. To accomplish this, Practitioner #8 routinely assembled the medical charts of each patient for whom he prescribed the Fentanyl Spray and gave them to the

sales representative, or to a Company employee assisting the sales representative. The sales representative then took the patient charts to her apartment in Boston, in the District of Massachusetts, where she or her assistant filled out the required prior authorization paperwork and faxed it to the Reimbursement Unit in Arizona.

Practitioner #9

145. Practitioner #9 owned and managed a pain management practice in southwest Florida. Practitioner #9 wrote a large volume of TIRF prescriptions. By at or about the end of the second quarter of 2012, Practitioner #9 averaged 1.9 Fentanyl Spray prescriptions per week.

146. Shortly after joining the Company, **BURLAKOFF** and the sales representative assigned to southwest Florida met with Practitioner #9 at his office. Following the meeting **BURLAKOFF** told the sales representative that the Speaker Program would help the Company get more prescriptions from practitioners paid as speakers.

147. Practitioner #9 was made a speaker for the Company in or about the end of July 2012. On or about August 1, 2012 **BABICH** sent the sales representative assigned to Practitioner #9 an email stating, "I have listed your top targets below and need a brief weekly email summarizing how, if and when the doctor will write, if he is already and can he be a bigger doctor to you." **BABICH** included Practitioner #9 as a top target.

148. On or about August 20, 2012, the sales representative assigned to Practitioner #9 sent **BABICH** a weekly update email, copying **BURLAKOFF,** stating that prescriptions from Practitioner #9 had:

> dropped off as he has told me some of his patients are preferring … [a competitor]. … But he continues to tell me he will continue to prescribe … [the Fentanyl Spray] whenever he can. I think using him as a speaker will cause things to pick back up again. I have two programs planned so far.

149. By the end of November of 2012, Practitioner #9 was averaging 1.6 Fentanyl Spray prescriptions per week.

150. In or about December of 2012, **BABICH**, **BURLAKOFF**, **SIMON**, and **ROWAN** hired a new sales representative for southwest Florida.

151. By in or about February of 2013, the new sales representative was using the Speaker Program to pay bribes and kickbacks to doctors in his territory in exchange for Fentanyl Spray prescriptions. **BABICH**, **BURLAKOFF**, and **ROWAN,** and other co-conspirators, began investing more financial resources in Practitioner #9.

152. **BABICH**, **BURLAKOFF**, and **ROWAN** knew that during the first quarter of 2013, Practitioner #9 wrote prescriptions for approximately 328 rapid onset opioids, 90 of which were for the Fentanyl Spray.

153. On or about March 12, 2013, **BURLAKOFF** sent an email to **ROWAN** and the sales representative for Practitioner #9,

> [w]here is … [Practitioner #9], we cannot go a single day with out [sic] a prescription from … [Practitioner #9]. I do not want to hear excuses, we pay good money here (we need 1 a day from …[Practitioner #9]).

154. By in or about the middle of July 2013, Practitioner #9 averaged approximately 6 Fentanyl Spray prescriptions per week.

155. Bribes and kickbacks paid to Practitioner #9 were not limited to Speaker Program honoraria. In or about September 2013, **BABICH**, **BURLAKOFF**, and **ROWAN** hired a woman known to be the girlfriend of Practitioner #9 as an ABL for his practice. By the last week of September 2013, Practitioner #9 was averaging 7.5 Fentanyl Spray prescriptions each week.

156. **BURLAKOFF** was not satisfied with the increase in the number of Fentanyl Spray prescriptions Practitioner #9 wrote each week through 2013. On or about October 3, 2013, **BURLAKOFF** sent an email to the assigned sales representative explicitly describing what was expected in exchange for bribes and kickbacks paid to Practitioner #9:

> Where is … [Practitioner #9]?
> Not even close to meeting anyone's expectations thus far, perhaps- We had failed in setting our expectations?
> We were looking to go from 40 percent market share to 90 percent?
> …I have to sit in the corporate office and answer these questions face to face. It is not fun, and the recent move we made on an ABL appears as if it is potentially not worth it?

157. Between in or about August 2012 and in or about August 2015, insurers and pharmacy benefit managers authorized payment for approximately 1,178 Fentanyl Spray prescriptions written by Practitioner #9.

158. Between in or about August 2012 and in or about August 2015, for the purpose of executing their scheme and artifice to defraud and for obtaining money and property, the Defendants, and co-conspirators known and unknown to the Grand Jury, sent and caused to be sent to Practitioner #9 checks totaling approximately $275,550.00 for Speaker Program bribes and kickbacks.

Practitioner #10

159. Practitioner #10 owned and managed a pain management clinic in Sherwood, Arkansas, where he saw as many as 75 to 100 patients a day. As early as 2012, **BABICH**, **BURLAKOFF**, and **SIMON**, and co-conspirators known and unknown to the Grand Jury, identified Practitioner #10 as an important priority. **BABICH**, **BURLAKOFF**, and **SIMON** knew that Practitioner #10 wrote TIRF prescriptions and believed he had potential to write even more.

160. As they had with other co-conspirator practitioners, **BABICH**, **BURLAKOFF**, and **SIMON**, and co-conspirators known and unknown to the Grand Jury, sought to use Speaker Program bribes and kickbacks to compel Practitioner #10 to write Fentanyl Spray prescriptions.

161. In or about September 2012 the sales representative assigned to Arkansas sent a weekly territory update to **BABICH**, **SIMON,** and **BURLAKOFF,** in which he mentioned Practitioner #10:

> 9/7 – Spoke to staff and they informed me … [Practitioner #10] would like to be taken off my call list. They would not give reason and I have been unable to reach … [Practitioner #10] or his office manager for at least a month. The pharmacy which is located in the same stand alone building was shut down due to the high percentage of opioids being dispensed. It has recently been opened but is unable to stock opioids. I spoke to … [my sales manager] and we are both under the opinion that they may be under investigation. I will follow up in 3-4 weeks to let things settle down.

162. On a different date the same sales representative told **BABICH** and **SIMON** that Practitioner #10 was,

> [v]ery pleased with … [the Fentanyl Spray]. Has had difficulty with insurance coverage lately. Pharmacy located within same building cannot order CII Rx from distributors due to ratio of opioids to other Rx. See once every week.

163. **BABICH**, **BURLAKOFF**, and **SIMON** continued to pursue Practitioner #10. On or about October 8, 2012, the sales representative assigned to Practitioner #10 sent **BABICH** and **SIMON** another update:

> 10/5-RSM Rich Simon and I took … [Practitioner #10] and his office manager to dinner and turned things around 180 degrees. We set out a plan to conduct dinner programs for … [Practitioner #10] to speak at his request. … [Practitioner #10] was not able to receive schedule two drugs in his buildings pharmacy which prevented his writing our drug. Rich Simon and I have been speaking to [the] pharmacist, … [the Director of Trade and Distribution for the Company] & … [Practitioner #10] to resolve the issue but have a guarantee from … [Practitioner #10] to have "more scripts than we can handle" once the pharmacy issue is resolved and begins to speak."

164. Beginning in or about November 2012, despite concerns about a potential investigation, the Company began paying Practitioner #10 for Speaker Program events.

165. While Practitioner #10 began receiving speaker payments from the Company, he did not increase the number of prescriptions he wrote for the Fentanyl Spray. In or about April 2013, the manager for the Arkansas territory had grown frustrated with Practitioner #10. In an email to the assigned sales representative, copied to **BURLAKOFF**, the manager explained that she had canceled scheduled Speaker Programs for Practitioner #10 because the doctor was not giving the Company enough business.

166. In or about July 2013, the manager sent another email to the assigned sales representative, this time copying both **BURLAKOFF** and **SIMON**,

> "[Practitioner #10] never wrote in Q2 and so far he has not written in Q3. I truly don't believe he is worth any more of your time especially since he is in AR. I am perplexed by his prescribing habits."

167. By the end of 2013, Practitioner #10 was writing approximately one Fentanyl Spray prescription each week. **BURLAKOFF**, **SIMON**, and **ROWAN** hired a new sales representative who had a pre-existing relationship with Practitioner #10, and assigned him to the Company's Arkansas territory.

168. In or about December 2013, **BURLAKOFF** transferred responsibility for Practitioner #10 to the newly hired sales representative. When the manager complained, **BURLAKOFF** responded,

> [t]he current rep did not eat what he killed. He did not KILL anything, he merely braised the doctor! … I need and want the business TODAY. I need to see if … [the new sales representative] can bring me what the other rep could not. I need … [the new sales representative] to make his living off this doctor. This is my job.

169. Working with his new sales representative and a new manager, Practitioner #10 wrote large numbers of Fentanyl Spray prescriptions in exchange for Speaker Program bribes

and kickbacks. Practitioner #10 was paid for eight Speaker Program events during the first quarter of 2014. By in or about the end of March 2014, Practitioner #10 was writing as many as 30 Fentanyl Spray prescriptions in one week.

170. By in or about March of 2014, Practitioner #10 had gone from having Speaker Program events canceled for lack of prescriptions, to an increase in the amount of the honoraria paid to him for Speaker Program events.

171. Many of the Speaker Program events attended by Practitioner #10 were mere social gatherings also attended by friends and office staff of Practitioner #10 and involved no presentation regarding the Fentanyl Spray.

172. Between in or about November 2012 and in or about June 2015 insurers and pharmacy benefit managers authorized payment for approximately 1,454 Fentanyl Spray prescriptions written by Practitioner #10.

173. Between in or about November 2012 and in or about June 2015, for the purpose of executing their scheme and artifice to defraud and for obtaining money and property, the Defendants, and co-conspirators known and unknown to the Grand Jury, sent and caused to be sent to Practitioner #10 checks totaling approximately $143,253.89 for Speaker Program bribes and kickbacks.

B. Examples of Defrauding Insurers and Pharmacy Benefit Managers

Disguising the Reimbursement Unit

174. After the Reimbursement Unit launched, in or about January of 2013, **BABICH**, **GURRY**, and other co-conspirators known and unknown to the Grand Jury learned that insurers and pharmacy benefit managers were often unwilling to engage a third party such as the Reimbursement Unit in the prior authorization process.

175. **BABICH, GURRY**, and other co-conspirators known and unknown to the Grand Jury responded to this problem by seeking to conceal the identity of Reimbursement Unit employees communicating directly with insurers and pharmacy benefit managers. **BABICH, GURRY**, and other co-conspirators known and unknown to the Grand Jury promoted the Reimbursement Unit to practitioners as a free source of additional administrative support, but the existence of the unit was deliberately shielded from insurers and pharmacy benefit managers.

176. **BABICH, GURRY**, and other co-conspirators known and unknown to the Grand Jury instructed Reimbursement Unit employees to lead agents of insurers and pharmacy benefit managers to believe that they were calling from the office of the practitioner, as if they were employees of the practitioner. Initially, **BABICH, GURRY**, and other co-conspirators told Reimbursement Unit employees to tell agents of insurers and pharmacy benefit managers that they were calling "from" the doctor's office. Later, employees were instructed to tell agents of insurers and pharmacy benefit managers that they were calling "on behalf of" a specific doctor, and were "with" a specific doctor's office. Even after this change **GURRY** and another co-conspirator instructed Reimbursement Unit employees to hang up when agents of insurers and pharmacy benefit managers pursued the identity of their employer. **GURRY** and another co-conspirator told Reimbursement Unit staff to call back later, in hopes of connecting with a new, less persistent agent. **BABICH** was also aware of, and approved of, the practice.

177. **BABICH, GURRY**, and other co-conspirators known and unknown to the Grand Jury also sought to mask the geographical location from which Reimbursement Unit employees were calling. **BABICH, GURRY**, and other co-conspirators set up the Reimbursement Unit phone system to block access to the unit's number, so that agents of insurers and pharmacy benefit managers would not notice that the Reimbursement Unit employees were calling from an

area code different than the area code of the prescribing practitioner. Employees at the Reimbursement Unit did not identify the Company when answering the phone.

Breakthrough Pain

178. While practitioners acting in the usual course of professional practice possessed the authority to write a prescription for any legitimate medical purpose, **BABICH**, **GURRY**, and a co-conspirator known to the Grand Jury knew that insurers and pharmacy benefit managers were less likely to authorize payment for a drug prescribed for a use that was not recognized on the drug's label.

179. All of the co-conspirator practitioners worked at pain clinics. While a few of their patients did in fact have cancer, none of the co-conspirator practitioners were oncologists. **BABICH**, **BURLAKOFF**, **GURRY**, **SIMON**, **LEE**, and **ROWAN**, and co-conspirators known and unknown to the Grand Jury, knew that the Company would lose substantial profits if insurers and pharmacy benefit managers only authorized payment for the Fentanyl Spray when it was prescribed according to its label – for the management of breakthrough pain in patients with cancer, 18 years of age or older, who were already receiving and who were already tolerant to opioid therapy for their underlying persistent cancer pain.

180. **GURRY**, and co-conspirators known to the Grand Jury directed Reimbursement Unit employees, when agents of insurers and pharmacy benefit managers asked if a patient was being treated for breakthrough cancer pain, to answer using a written script, sometimes called "the spiel":

> 'The physician is aware that the medication is intended for the management of breakthrough pain in cancer patients. The physician is treating the patient for their pain (or breakthrough pain, whichever is applicable).'

181. **GURRY** and co-conspirators known to the Grand Jury approved different versions of "the spiel."

Fake diagnoses

182. Even with the identity of the Reimbursement Unit disguised, insurers and pharmacy benefit managers reacted differently to prior authorization requests. For some insurers and pharmacy benefit managers, the Reimbursement Unit's use of the term "breakthrough pain," rather than "breakthrough cancer pain," was enough to gain payment for the Fentanyl Spray. But when agents of insurers and pharmacy benefit managers asked for additional information, Reimbursement Unit employees, following the directions of **GURRY** and co-conspirators known to the Grand Jury, made additional misleading statements and misleading omissions to agents of insurers and pharmacy benefit managers in order to gain prior authorization.

183. Medical facilities, practitioners, insurers and pharmacy benefit managers, government entities, and pharmacies employed a set of codes to classify diseases and injuries. The codes, which were recognized around the world, were called the International Statistical Classification of Disease and Related Health Problems 9th Revision ("ICD-9"), and later International Classification of Diseases, 10th Revision ("ICD-10"). Both revisions, ICD-9 and ICD-10, are referred to herein as ICD-9. There was a recognized ICD-9 code for each medical diagnosis.

184. Insurers and practitioners used ICD-9 codes to communicate about prior authorizations. Information sought by the Company Opt-In forms included a description of the diagnosis for which the Fentanyl Spray was prescribed, as well as the corresponding ICD-9 code.

185. **BABICH**, **GURRY**, and co-conspirators known and unknown to the Grand Jury tracked communications with agents of insurers and pharmacy benefit managers to learn why insurers and pharmacy benefit managers denied specific claims. **GURRY** and co-conspirators known and unknown to the Grand Jury used that information to instruct Reimbursement Unit employees regarding when and how to deceive insurers and pharmacy benefit managers.

i. Dysphagia

186. As a sublingual spray, the Fentanyl Spray was not swallowed, but absorbed into the blood stream after being applied beneath the tongue. **BABICH**, **GURRY**, and co-conspirators known and unknown to the Grand Jury learned that insurers and pharmacy benefit managers were more willing to grant prior authorization when a patient was diagnosed with dysphagia, or difficulty swallowing. **GURRY** and co-conspirators known and unknown to the Grand Jury instructed Reimbursement Unit employees to add the diagnosis of dysphagia when communicating with insurers and pharmacy benefit managers regardless of whether the patient in fact had difficulty swallowing.

187. The Company supplied practitioners with model letters of medical necessity, to be used when appealing a denied authorization. Use of the dysphagia code became so common that difficulty swallowing was included as part of the Company's model letter of medical necessity:

> I have treated (Full name) in my clinic since (xx/xx/xxxx). (Mr. /Mrs.). Is a (age) year old (man/woman) with severe (Diagnosis). (He/She) has difficulty swallowing and digesting oral medications, and (he/she) is in almost constant severe pain. The pain gives Mr. /Mrs. (Name) a significantly limited quality of life. (He/She) is unable to sit, stand, walk or reach- which includes participating in family life and riding in automobiles - for more than 2 to 3 hours per day.

188. At a Company leadership meeting, **BABICH**, **GURRY**, and **BURLAKOFF** were presented the dysphagia diagnosis and the procedures the Reimbursement Unit used to gain prior authorization from insurers and pharmacy benefit managers using the dysphagia diagnosis.

ii. A Diagnosis of Cancer

189. **GURRY** and co-conspirators known and unknown to the Grand Jury also used false cancer diagnoses to deceive insurers and pharmacy benefit managers to obtain payment for the Fentanyl Spray. **GURRY** and co-conspirators known and unknown to the Grand Jury directed Reimbursement Unit employees to review the medical history of patients in order to determine if the patient had ever been diagnosed with cancer. If a patient was previously treated for cancer, **GURRY** and co-conspirators known and unknown to the Grand Jury told Reimbursement Unit employees to tell insurers and pharmacy benefit managers that the Fentanyl Spray was prescribed to treat the previously diagnosed cancer, using the specific form of cancer previously diagnosed. At times co-conspirators known and unknown to the Grand Jury also instructed Reimbursement Unit employees to assert a cancer diagnosis regardless of the patient's history and regardless of whether the practitioner had prescribed the Fentanyl Spray for a different diagnosis.

Tried and Failed Medications

190. **BABICH**, **GURRY,** and co-conspirators known and unknown to the Grand Jury knew that insurers and pharmacy benefit managers often required patients to have tried and failed with other TIRF drugs before granting a prior authorization. The medications required before authorization was granted varied among insurers and pharmacy benefit managers. **GURRY,** and co-conspirators known and unknown to the Grand Jury tracked communications with agents of insurers and pharmacy benefit managers to learn the tried and failed medications

for specific insurers and pharmacy benefit managers. **GURRY** and co-conspirators known and unknown to the Grand Jury used that information to instruct Reimbursement Unit employees regarding when and how to deceive insurers and pharmacy benefit managers. Reimbursement Unit employees routinely falsely confirmed lists of tried and failed medications to insurers and pharmacy benefit managers in order to obtain prior authorization for the Fentanyl Spray. The practice was discussed and approved at Company leadership meetings attended by **BABICH**, **BURLAKOFF**, and **GURRY**.

The Calls

191. After the Reimbursement Unit received the Opt-In forms and accompanying medical records, Reimbursement Unit employees placed telephone calls to insurers and pharmacy benefit managers located in several different states. Relying in part on the Opt-Ins and accompanying documents, Reimbursement Unit employees misled and deceived insurers regarding their employment, patient medical history, patient diagnoses, and tried and failed medications during those calls.

CRIMINAL COUNTS

COUNT 1
(18 U.S.C. § 1962(d) – Racketeering Conspiracy)

[DEFENDANTS (1) BABICH, (2) BURLAKOFF, (3) GURRY, (4) SIMON, (5) LEE, and (6) ROWAN]

192. The allegations contained in paragraphs 1 through 191 are re-alleged and incorporated herein by reference.

193. At all times relevant to the Indictment, within the District of Massachusetts and elsewhere, **(1) BABICH, (2) BURLAKOFF, (3) GURRY, (4) SIMON, (5) LEE,** and **(6) ROWAN**, the co-conspirator practitioners described in paragraph 7 ("co-conspirator practitioners"), the Company, and other persons and entities known and unknown to the Grand Jury, collectively constituted an "enterprise," as defined in Title 18, United States Code, Section 1961(4), that is, a group of individuals and entities associated in fact. The enterprise constituted an ongoing organization whose members functioned as a continuing unit for a common purpose of achieving the objectives of the enterprise.

194. The enterprise was engaged in, and its activities affected, interstate commerce. The enterprise operated in the District of Massachusetts and elsewhere.

195. From in or about June 2012 and continuing until in or around December 2015, within the District of Massachusetts and elsewhere, **(1) BABICH, (2) BURLAKOFF, (3) GURRY, (4) SIMON, (5) LEE,** and **(6) ROWAN**, being persons employed by and associated with the enterprise described in paragraph 193 above, which engaged in, and the activities of which affected, interstate commerce, knowingly conspired with one another and with others known and unknown to the Grand Jury, to violate Title 18, United States Code, Section 1962(c), that is, to conduct and participate, directly and indirectly, in the conduct of the affairs of such enterprise

through a pattern of racketeering activity, as defined in Title 18, United States Code, Sections 1961(1) and (5).

196. The pattern of racketeering activity through which **(1) BABICH, (2) BURLAKOFF, (3) GURRY, (4) SIMON, (5) LEE,** and **(6) ROWAN**, along with others known and unknown to the Grand Jury, agreed to conduct and participate, directly and indirectly, in the conduct of the affairs of the enterprise consisted of multiple acts indictable under:

(a) Title 18, United States Code, §§ 1341 and 1346 (mail fraud, including honest services mail fraud);

(b) Title 18, United States Code, § 1343 (wire fraud); and

(c) Title 18, United States Code, § 1952 (interstate and foreign travel or transportation in aid of racketeering);

and multiple acts involving bribery in violation of Connecticut General Statutes Annotated (C.G.S.A.) § 53a-160 (commercial bribery); Florida Statutes Annotated (F.S.A.) § 838.16 (commercial bribery); Revised Statutes Annotated of the State of New Hampshire (N.H. Rev. Stat. § 638.7 (commercial bribery); and Vernon's Texas Statutes and Codes Annotated (V.T.C.A.) § 32-43 (commercial bribery).

197. It was part of the conspiracy that each defendant agreed that a conspirator would commit at least two acts of racketeering activity in the conduct of the affairs of the enterprise.

All in violation of Title 18, United States Code, Section 1962(d).

COUNT 2

18 U.S.C. § 1349 – Mail Fraud Conspiracy
(Scheme to Defraud Patients of Honest Services)
[DEFENDANTS (1) BABICH, (2) BURLAKOFF, (4) SIMON, (5) LEE and (6) ROWAN]

198. The allegations contained in paragraphs 1-2, 4-56, and 69-173 are re-alleged and incorporated herein by reference.

199. From in or about June 2012 until in or about December 2015, within the District of Massachusetts and elsewhere, **(1) BABICH, (2) BURLAKOFF, (4) SIMON, (5) LEE,** and **(6) ROWAN**, along with others known and unknown to the Grand Jury, did knowingly conspire with one another to commit mail fraud in violation of 18 U.S.C §§ 1341 and 1346, that is, having devised and intending to devise a scheme and artifice to defraud patients of honest services and to obtain money and property by means of materially false and fraudulent pretenses, representations and promises, for the purpose of executing such scheme and artifice to defraud, placed and caused to be placed in any post office and authorized depository for mail matter a matter and thing, to wit, checks and honoraria payments, to be sent and delivered by the United States Postal Service, and deposited and caused to be deposited a matter and thing, to wit, checks and honoraria payments, to be sent and delivered by a private and commercial interstate carrier.

All in violation of Title 18, United States Code, Section 1349.

COUNT 3
18 U.S.C. § 1349– Wire Fraud Conspiracy
(Scheme to Defraud Insurers and Pharmacy Benefit Managers)
[DEFENDANTS (1) BABICH, and (3) GURRY]

200. The allegations contained in paragraphs 1, 3, 7- 32, 57-68, and 174-191 are re-alleged and incorporated herein by reference.

201. From in or about December 2012 and continuing until in or around December 2015, within the District of Massachusetts and elsewhere, **(1) BABICH** and **(3) GURRY**, along with others known and unknown to the Grand Jury, did knowingly conspire to commit wire fraud in violation of 18 U.S.C §1343, that is, having devised and intending to devise a scheme and artifice to defraud insurers and pharmacy benefit managers and to obtain money and property by means of materially false and fraudulent pretenses, representations and promises, for the purpose of executing such scheme and artifice, transmitted and caused to be transmitted by means of wire communication in interstate commerce, writings, signs, signals, pictures, and sounds, to wit: telephone communications, and facsimile communications.

All in violation of Title 18, United States Code, Section 1349.

COUNT 4
18 U.S.C. § 371--Conspiracy to Violate the Anti-Kickback Law
[DEFENDANTS (1) BABICH, (2) BURLAKOFF, (4) SIMON, (5) LEE and (6) ROWAN]

202. The allegations contained in paragraphs 1-2, 4-56, and 69-173 are re-alleged and incorporated herein by reference.

203. From in or about June 2012 until in or around December 2015, within the District of Massachusetts and elsewhere, **(1) BABICH, (2) BURLAKOFF, (4) SIMON, (5) LEE,** and **(6) ROWAN** knowingly conspired with others known and unknown to the Grand Jury, to commit an offense against the United States, that is, to knowingly and willfully offer and pay remuneration, directly and indirectly, overtly and covertly, in cash and in kind, that is, kickbacks and bribes, from the Company, to induce physicians and other health care professionals to purchase, order, and arrange for goods, services and items, that is, prescriptions for the Fentanyl Spray, for which payment may be made in whole and in part by a federal health care program, in violation of Title 42, United States Code, Section 1320a-7b(b)(2).

All in violation of Title 18, United States Code, Section 371.

RACKETEERING FORFEITURE ALLEGATION
(18 U.S.C. § 1963)

204. Upon conviction of the offense in violation of Title 18, United States Code, Section 1962(d), set forth in Count One of this Indictment,

(1) BABICH, (2) BURLAKOFF, (3) GURRY,

(4) SIMON, (5) LEE and (6) ROWAN,

the Defendants herein, shall forfeit to the United States, jointly and severally, pursuant to Title 18, United States Code, Section 1963:

a. any interest acquired or maintained in violation of Title 18, United States Code, Section 1962;

b. any interest in, security of, claim against, or property or contractual right of any kind affording a source of influence over, any enterprise established, operated, controlled, conducted, or participated in the conduct of, in violation of Title 18, United States Code, Section 1962; and

c. any property constituting, or derived from, any proceeds obtained, directly or indirectly, from racketeering activity in violation of Title 18, United States Code, Section 1962.

The property to be forfeited includes, but is not limited to:

a. any and all securities, salaries, bonuses, stock distributions, retirement contributions and accounts, health and life insurance benefits including premium payments, and any and all other benefits obtained through employment by and association with the entities named in the racketeering enterprise alleged in Count One from 2012 through October 2016; and

b. forfeiture money judgment equal to the amount of proceeds obtained as a result of the offense alleged in Count One of the Indictment;

205. If any of the property described in Paragraph 204, above, as being forfeitable pursuant to Title 18, United States Code, Section 1963, and Title 28, United States Code, Section 2461(c), as a result of any act or omission of the Defendants –

a. cannot be located upon the exercise of due diligence;

b. has been transferred or sold to, or deposited with, a third party;

c. has been placed beyond the jurisdiction of the court;

d. has been substantially diminished in value; or

e. has been commingled with other property that cannot be divided without difficulty,

it is the intention of the United States, pursuant to Title 18, United States Code, Section 1963(m), to seek forfeiture of any other property of the Defendants up to the value of the property described in paragraph 204.

All pursuant to Title 18, United States Code, Section 1963.

MAIL AND WIRE FRAUD FORFEITURE ALLEGATIONS
(18 U.S.C. § 981(a)(1)(C) and 28 U.S.C. § 2461(c))

206. Upon conviction of one or more of the offenses in violation of Title 18, United States Code, Section 1349, set forth in Counts Two and Three of this Indictment,

(1) BABICH, (2) BURLAKOFF, (3) GURRY,

(4) SIMON, (5) LEE and (6) ROWAN,

the Defendants herein, shall forfeit to the United States, jointly and severally as to each of Count Two and Count Three, pursuant to Title 18, United States Code, Section 981(a)(1)(C), and Title 28, United States Code, Section 2461(c), any property, real or personal, which constitutes or is derived from proceeds traceable to the offense. The property to be forfeited includes, but is not limited to the following:

a. forfeiture money judgment equal to the amount of proceeds obtained as a result of the offenses alleged in Count Two and Count Three of the Indictment.

207. If any of the property described in Paragraph 206, above, as being forfeitable pursuant to Title 18, United States Code, Section 981(a)(1)(C), and Title 28, United States Code, Section 2461(c), as a result of any act or omission of the defendants –

(a) cannot be located upon the exercise of due diligence;

(b) has been transferred or sold to, or deposited with, a third party;

(c) has been placed beyond the jurisdiction of the Court;

(d) has been substantially diminished in value; or

(e) has been commingled with other property which cannot be divided without difficulty;

it is the intention of the United States, pursuant to Title 28, United States Code, Section 2461(c), incorporating Title 21, United States Code, Section 853(p), to seek forfeiture of any other property of the Defendants up to the value of the property described in Paragraph 206 above.

All pursuant to Title 18, United States Code, Section 981(a)(1)(C), and Title 28, United States Code, Section 2461(c).

CONSPIRACY TO VIOLATE THE ANTI-KICKBACK LAW
FORFEITURE ALLEGATIONS
(18 U.S.C. § 982(a)(7))

208. Upon conviction of Conspiracy to Violate the Anti-Kickback Law, in violation of Title 18, United States Code, Section 371, set forth in Count Four of this Indictment,

(1) BABICH, (2) BURLAKOFF, (4) SIMON,

(5) LEE and **(6) ROWAN,**

the Defendants herein, shall forfeit to the United States, jointly and severally as to each of Count Four, pursuant to Title 18, United States Code, Section 982(a)(7), any property, real or personal, which constitutes or is derived from proceeds traceable to the offense. The property to be forfeited includes, but is not limited to the following:

b. forfeiture money judgment equal to the amount of the proceeds of the offense alleged in Count Four of the Indictment.

209. If any of the property described in Paragraph 208, above, as being forfeitable pursuant to Title 18, United States Code, Section 982(a)(7), as a result of any act or omission of the defendants –

(f) cannot be located upon the exercise of due diligence;

(g) has been transferred or sold to, or deposited with, a third party;

(h) has been placed beyond the jurisdiction of the Court;

(i) has been substantially diminished in value; or

(j) has been commingled with other property which cannot be divided without difficulty;

it is the intention of the United States, pursuant to Title 18, United States Code, Section 982(b), incorporating Title 21, United States Code, Section 853(p), to seek forfeiture of any other property of the Defendants up to the value of the property described in Paragraph 208 above.

All pursuant to Title 18, United States Code, Section 982(a)(7).

A TRUE BILL

Foreperson of the Grand Jury

SUSAN M. POSWISTILO
K. NATHANIELYEAGER
Assistant United States Attorneys

DISTRICT OF MASSACHUSETTS: December 6, 2016

Returned into the District Court by the Grand Jurors and filed.

Deputy Clerk 12/6/16 @ 2:40pm

EXHIBIT 96

Mallinckrodt Announces Agreement with Xanodyne to Purchase Roxicodone®

August 23, 2012 08:00 AM Eastern Daylight Time

HAZELWOOD, Mo.--(BUSINESS WIRE)--Mallinckrodt, the Pharmaceuticals business of Covidien (NYSE: COV), today announced that it has entered into an agreement with Xanodyne Pharmaceuticals to purchase Roxicodone® (oxycodone hydrochloride tablets USP) in 5, 15 and 30 mg dosage strengths. Roxicodone, currently marketed in the United States, is an immediate release formulation of oxycodone indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate. With this agreement, Mallinckrodt acquires all rights to the Roxicodone New Drug Application (NDA). No financial details were disclosed.

"We are excited about this agreement as it complements our existing portfolio of opioids and leverages our pain management expertise," said Mark Trudeau, President, Pharmaceuticals. "More importantly, we are committed to safe and effective use of all of our products along with ensuring access for all patients in need of pain treatment."

Mallinckrodt is the largest U.S. supplier of opioid pain medications and among the top 10 generic pharmaceuticals manufacturers in the U.S., based on prescriptions. Its branded portfolio includes EXALGO® (hydromorphone HCl) Extended-Release Tablets (CII) and PENNSAID® (diclofenac sodium topical solution) 1.5% w/w. Mallinckrodt is also one of the world's leading producers of bulk acetaminophen.

Covidien announced last December that the Company planned to spin off Mallinckrodt into a stand-alone company, a process that is expected to be completed in mid-2013.

IMPORTANT RISK INFORMATION

About ROXICODONE

Roxicodone tablets are contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment) and patients with acute or severe bronchial asthma or hypercarbia. Oxycodone hydrochloride tablets are contraindicated in any patient who has or is suspected of having paralytic ileus.

Serious adverse reactions that may be associated with Roxicodone tablets therapy include: respiratory depression, respiratory arrest, circulatory depression, cardiac arrest, hypotension, and/or shock. Common adverse events that may be associated with Roxicodone tablets therapy include: nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence.

About EXALGO

INDICATION

EXALGO® (hydromorphone HCl) Extended-Release Tablets (CII) is indicated for the management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time.

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

Abuse Potential

EXALGO contains hydromorphone, an opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing EXALGO. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving EXALGO for signs of misuse, abuse, and addiction during treatment.

Life-threatening Respiratory Depression

Respiratory depression, including fatal cases, may occur with use of EXALGO, even when the drug has been used as recommended and not misused or abused. EXALGO is for use in opioid tolerant patients only. Proper dosing and titration are essential and EXALGO should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of EXALGO or following a dose increase. Crushing, dissolving, or chewing the tablet can cause rapid release and absorption of a potentially fatal dose of hydromorphone.

Accidental Exposure

Accidental ingestion of EXALGO, especially in children, can result in a fatal overdose of hydromorphone.

- EXALGO is contraindicated in:
  - Opioid non-tolerant patients. Fatal respiratory depression could occur in patients who are not opioid tolerant.
  - Patients with significant respiratory depression
  - Patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment

- Patients with known or suspected paralytic ileus
- Patients who have had surgical procedures and/or underlying disease resulting in narrowing of the gastrointestinal tract, or have “blind loops” of the gastrointestinal tract or gastrointestinal obstruction
- Patients with hypersensitivity (e.g., anaphylaxis) to hydromorphone or sulfite-containing medications

- Serious adverse events could also include hypotensive effects, GI effects, cardiac arrest from overdose and precipitation of withdrawal. Most common adverse events (>10%) seen in clinical studies (N=2474) were: constipation (31%), nausea (28%), vomiting, somnolence, headache, asthenia and dizziness.

About PENNSAID

PENNSAID is a nonsteroidal anti-inflammatory drug (“NSAID”) indicated for the treatment of signs and symptoms of osteoarthritis of the knee(s).

WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISK

Cardiovascular Risk

• Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

• PENNSAID is contraindicated in the perioperative setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Risk

• NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

PENNSAID is also contraindicated in patients:

- **With known hypersensitivity to diclofenac sodium or any other component of PENNSAID.**
- **Who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions have been reported in these patients.**

Anaphylactoid reactions may occur in patients without prior exposure to PENNSAID. NSAIDs can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrosis (TEN), which can be fatal.

The most common treatment-related adverse events in patients receiving PENNSAID were application site skin reactions including dry skin (32%), contact dermatitis characterized by skin erythema and induration (9%), contact dermatitis with vesicles (2%) and pruritus (4%). In a long term safety study, contact dermatitis occurred in 13% and contact dermatitis with vesicles in 10% of patients, generally within the first 6 months of exposure, leading to a withdrawal rate for an application site event of 14%. Other common adverse events greater than placebo include: dyspepsia (8%), abdominal pain (6%), flatulence (4%), diarrhea (4%) and nausea (4%).

ABOUT COVIDIEN

Covidien is a leading global healthcare products company that creates innovative medical solutions for better patient outcomes and delivers value through clinical leadership and excellence. Covidien manufactures, distributes and services a diverse range of industry-leading product lines in three segments: Medical Devices, Pharmaceuticals and Medical Supplies. With 2011 revenue of $11.6 billion, Covidien has 43,000 employees worldwide in more than 65 countries, and its products are sold in over 140 countries. Mallinckrodt, the Pharmaceuticals business of Covidien, manufactures active pharmaceutical ingredients, including bulk acetaminophen, opioid pain medications, nuclear and contrast media diagnostic agents. Sales in 2011 were $2.0 billion. Please visit www.covidien.com to learn more about our business.

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EXHIBIT 97

Register for e-Notifications of when site is updated
Contact Us
Tell a Friend About This Site
Glossary of Terms
Site Overview
Search Tips

Welcome...

Make the most of your time on the Internet.

The mission of *Pain Treatment Topics* is to serve as a noncommercial resource for healthcare professionals, providing open access to clinical *news, information, research, and education* for a better understanding of evidence-based pain-management practices.

Visit the Site Overview for an explanation of the various tabs and sections.

See the Feature Box below for important news updates and announcements.

★ = items added during recent updates.

Echoes of Sadness

< About This Artwork>

Affiliates

Addiction Treatment Forum

Addiction Treatment Forum

American College of Hospice Pharmacists

Europad
European Opiate Addiction Treatment Association

Website highlights to see...

This site complies with the HONcode standard for health trustworthy information.

HON @ CODE ACCREDITED 03/2007

Verify here.

★ New Pain-Topics *e-Briefing* Newsletter

Volume 1, Number 2, 2006

-- Methadone safety stressed by FDA > Report from *Pain Treatment Topics* Provides Clinical Guidance
-- Conversion Ratios for Rotation from Methadone to Other Opioids
-- Pain & Addiction: Common Threads
-- Discard "Dependence" > Get Serious About "Addiction"
-- and, more... Download e-Briefing PDF...>

Metha done Safety

★ Current News/Research Updates

November-December 2006, Issue 6

-- Patient Education Avoids Adverse Drug Reactions
-- Suicidal Thoughts in Patients With Chronic Pain
-- Migraine Assessment Tools Improve Patient Care
-- Massage Effective for Osteoarthritis Pain
-- Acupuncture for Knee & Hip Pain
-- Neuropathic Pain Relieved by Duloxetine
-- Pregabalin Extends Relief for Fibromyalgia Sufferers
-- Fish Oil Helps Chronic Neck and Back Pain
-- Recent Drug Approvals and Announcements
-- And more..... See November-December 2006 Updates...>

News

★ Education/CME Locator Updated

20 New CME Courses Added to the Extensive List

Besides offering continuing medical education credits, these courses are of special value because they have high clinical

relevance and incorporate the latest research evidence.
View the List of Courses... >

See the Pain-Topics.org Gallery... "Portraying the Personal Side of Pain"

Artworks in this special gallery depict a broad pallet of pain conditions, created by patients and expressing emotions, thoughts, and perspectives that they often cannot put into words.
Go to Gallery...>

Tab Section Updates Posted...

10 New Resources for Patients added

Go to Patient Resources... >

50 Events added, extending to year 2011

The most extensive listing of events focusing on pain management available anywhere.
Go to Events... >

35 Related Websites added

The most comprehensive listing of noncommercial and credible pain-related websites anywhere on the Internet.
Go to Related Websites... >

New Resource at Pain-Topics.org...

Europad Journal

EUROPAD Journal on Addiction (*Heroin Addiction and Related Clinical Problems*) — full editions of this peer-reviewed international publication from the European Opiate Addiction Treatment Association are now available for free download as PDF documents. Articles discuss medication-assisted treatment for opioid addiction, including the interface of pain and addiction. <Click Here for Details >

Pain-Topics Highlighted by National Pain Foundation

National Pain Foundation

The National Pain Foundation (NPF) is currently featuring the special educational materials on methadone safety from Pain-Topics.org. <Click Here to Access NPF >

Thank you, for visiting, and we hope to see you here often.
Stewart B. Leavitt, MA, PhD; Publisher & Editor-in-Chief

Register for e-Notifications of when site is updated

Please bookmark this site for ongoing reference. And, as we grow Pain-Topics.org rapidly in the months to come, let us keep you posted via e-mail of when this site is updated or there is news of importance - Register for e-Notifications.

If there are problems using this site, contact: Info@Pain-Topics.org
Pain Treatment Topics is produced by Stewart B. Leavitt, PhD, Ltd.; Glenview, Illinois, USA.

This page was last updated 1/3/07

EXHIBIT 98

www.Pain-Topics.org

Oxycodone Safety Handout For Patients

Authors: **Lee A. Kral**, PharmD, BCPS; **Stewart B. Leavitt**, MA, PhD

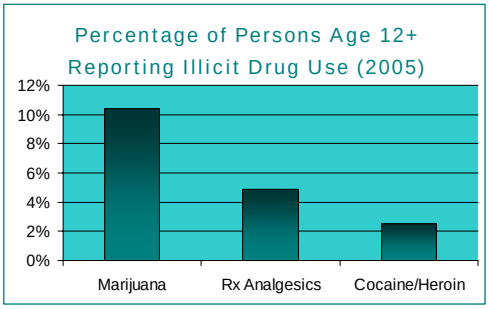
Medical Reviewers: Paul W. Lofholm, PharmD, FACA; Steven Tucker, MD; James D. Toombs, MD

Release Date: June 2007

Patient Education – An Absolute Safety Necessity

Most patients and their families or caregivers find the medication information provided by pharmacies, or product package inserts (if provided), difficult to read and understand. Hence, they are of little help as a safety measure.

Opioid medications must especially be safeguarded by patients. Recent data suggest that teenage pilferage and illicit use of prescription opioids from their parents' medicine cabinets is a continuing and growing problem (CSS 2006). The latest U.S. household survey found that the nonmedical, illicit use of prescription pain relievers was second only to marijuana abuse and exceeded the abuse of any other illicit substance (CESAR 2006a). It was twice that of cocaine and heroin use combined (see ***Graph***). In all, approximately 7.25 million persons age 12 and older used prescription pain relievers for nonmedical purposes in 2005 and the alarming trend was rising.



Furthermore, opioid analgesics are more likely than such agents as cocaine or heroin to be the cause of unintentional drug-poisoning fatalities in the U.S. An analysis of data from 2002, showed that opioid analgesics accounted for more than a third (36.5%) of drug-poisoning deaths (CESAR 2006b).

In the drug-poisoning data, it is not known how many deaths involved *illicit nonmedical opioid use* (eg, recreational) versus those resulting from *medical misuse* (eg, noncompliance with the prescribed dosing regimen or mixing with other medications), or from *misprescribing*. It seems logical that better patient education regarding therapeutic compliance might help prevent unintentional medical misuse of oxycodone, and better safety precautions could help avoid oxycodone from falling into the hands of persons who might use the drug for illicit, nonmedical purposes.

Yet, a recent observational study found that busy healthcare providers often failed to adequately instruct patients and communicate critical information regarding various prescribed medications (Tarn et al. 2006). This might expectedly contribute to misunderstandings by patients leading to noncompliance and/or medication misuse, which could be harmful or fatal in the case of opioids.

About the Patient Oxycodone Instructions Handouts (attached)

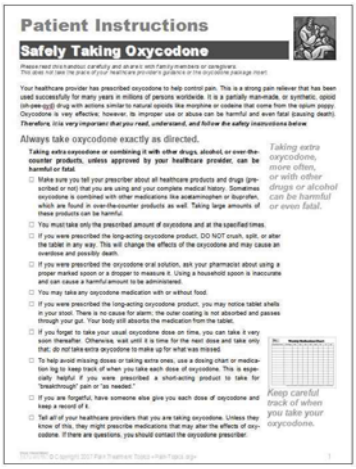
To assist healthcare providers in their vital patient-education responsibilities, *Pain Treatment Topics* developed the special "Patient Instructions" handouts on the pages that follow this introduction. These can be reproduced and given to patients at the time oxycodone analgesia

is prescribed (*see permission to reproduce below*). Ideally, these also would be used as discussion guides for face-to-face education of patients – and their families or caregivers.

The emphasis of the handouts is on ***safety***, to help prevent misuse and avoidable adverse events potentially associated with oxycodone. They do not necessarily include *all* information in oxycodone product package inserts or provided by medical staff, and are not intended to take the place of such guidance. However, unlike traditional communications of this sort, the handouts stress several points that often are overlooked:

The emphasis of the handouts is on safety, to help prevent misuse and avoidable adverse events potentially associated with oxycodone.

- Patients (along with their families or caregivers) must be specifically cautioned that oxycodone can be fatal if it is misused.
- As a strong opioid agent, absolute compliance with the prescribed oxycodone regimen is essential; unauthorized extra doses should never be taken.
- Patients must keep careful track of when they take oxycodone, enlisting the help of others in this if necessary.
- Patients need to understand the importance of reporting all substances that they are using – medications, drugstore products, alcohol, or other drugs – and that unauthorized use of these with oxycodone can be harmful or even fatal.
- Oxycodone must be safeguarded from theft and illicit use by others. It should not be casually stored as many other medications might be.
- Family members or caregivers must know of oxycodone overdose warning signs and be instructed to seek emergency help if any occur.
- Patients' fears of opioid addiction should be dispelled. Along with that, they must be cautioned against reducing oxycodone dosing on their own.


Patient Instructions

Safely Taking Oxycodone

The handouts provide more detail regarding these essential messages and very specific recommendations. It is hoped that healthcare providers will take the extra time necessary for providing such information and instructions that can help promote the effective and safe use of oxycodone analgesia.

References:

CESAR (Center for Substance Abuse Research). Nonmedical use of prescription drugs more prevalent in U.S. than use of most illicit drugs. CESAR Fax. 2006a;15(36). College Park, MD: University of Maryland, Center for Substance Abuse Research. Available at: http://www.cesar.umd.edu/cesar/cesarfax/vol15/15-36.pdf. Access checked 5/9/09.

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Tarn DM, Heritage J, Paterniti DA, et al. Physician communication when prescribing new medications. Arch Intern Med. 2006;166(17):1855-1862.

Further Information for Healthcare Providers

The following document from *Pain Treatment Topics* has vital supplemental information for healthcare providers on how oxycodone works and its safe prescribing. This paper should be reviewed prior to distributing the *Safely Taking Oxycodone* patient instructions handout.

Commonsense Oxycodone Prescribing & Safety

Lee A. Kral, PharmD, BCPS, June 2007.

Get PDF at: http://www.pain-topics.org/pdf/OxycodoneRxSafety.pdf (310 KB; 18 pp).

About the authors of this handout:

Lee A. Kral, PharmD, BCPS is a Faculty Member at The Center for Pain Medicine and Regional Anesthesia at The University of Iowa Hospitals and Clinics in Iowa City, IA, and is a medical advisor to *Pain Treatment Topics.*

Stewart B. Leavitt, MA, PhD, is the Publisher/Editor-in-Chief of *Pain Treatment Topics* and has served as the Editor of *Addiction Treatment Forum* since its founding in 1992.

Medical reviewers:

The qualifications of *Pain Treatment Topics* medical advisors/reviewers for this document may be viewed at: http://www.pain-topics.org/contacts_aboutus/index.php#MedAdvisors.

Disclosures:

This document is sponsored by an unrestricted educational grant from Mallinckrodt Pharmaceuticals, St. Louis, MO, a manufacturer of generic opioid analgesics. The sponsor did not participate in the inception, research, development, or revision of this paper, and the authors and reviewers have no conflicting interests to declare relating to the subject of this paper.

Disclaimer:

Pain Treatment Topics does not endorse any medications or treatments mentioned or discussed in this document. Nor are any representations made concerning efficacy, appropriateness, or suitability of any such medications or treatments. In view of the possibility of human error or advances in medical knowledge, *Pain Treatment Topics* does not warrant the information contained in this document is in every respect accurate or complete, and is not liable for any errors or omissions or for results obtained from the use of this information.

PAIN TREATMENT TOPICS

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Release Date: June 2007

Patient Instructions

Safely Taking Oxycodone

Please read this handout carefully and share it with family members or caregivers.
This does not take the place of your healthcare provider's guidance or the oxycodone package insert.

Your healthcare provider has prescribed oxycodone to help control pain. This is a strong pain reliever that has been used successfully for many years in millions of persons worldwide. It is a partially man-made, or synthetic, opioid (oh-pee-oyd) drug with actions similar to natural opioids like morphine or codeine that come from the opium poppy. Oxycodone is very effective; however, its improper use or abuse can be harmful and even fatal (causing death). ***Therefore, it is very important that you read, understand, and follow the safety instructions below.***

Always take oxycodone exactly as directed.

Taking extra oxycodone, more often, or with other drugs or alcohol can be harmful or even fatal.

Taking extra oxycodone or combining it with other drugs, alcohol, or over-the-counter products, unless approved by your healthcare provider, can be harmful or fatal.

- ☐ Make sure you tell your prescriber about all healthcare products and drugs (prescribed or not) that you are using and your complete medical history. Sometimes oxycodone is combined with other medications like acetaminophen or ibuprofen, which are found in over-the-counter products as well. Taking large amounts of these products can be harmful.
- ☐ You must take only the prescribed amount of oxycodone and at the specified times.
- ☐ If you were prescribed the long-acting oxycodone product, DO NOT crush, split, or alter the tablet in any way. This will change the effects of the oxycodone and may cause an overdose and possibly death.
- ☐ If you were prescribed the oxycodone oral solution, ask your pharmacist about using a proper marked spoon or a dropper to measure it. Using a household spoon is inaccurate and can cause a harmful amount to be administered.
- ☐ You may take any oxycodone medication with or without food.
- ☐ If you were prescribed the long-acting oxycodone product, you may notice tablet shells in your stool. There is no cause for alarm; the outer coating is not absorbed and passes through your gut. Your body still absorbs the medication from the tablet.
- ☐ If you forget to take your usual oxycodone dose on time, you can take it very soon thereafter. Otherwise, wait until it is time for the next dose and take only that; *do not* take extra oxycodone to make up for what was missed.
- ☐ To help avoid missing doses or taking extra ones, use a dosing chart or medication log to keep track of when you take each dose of oxycodone. This is especially helpful if you were prescribed a short-acting product to take for "breakthrough" pain or "as needed."
- ☐ If you are forgetful, have someone else give you each dose of oxycodone and keep a record of it.
- ☐ Tell *all* of your healthcare providers that you are taking oxycodone. Unless they know of this, they might prescribe medications that may alter the effects of oxycodone. If there are questions, you should contact the oxycodone prescriber.

Keep careful track of when you take your oxycodone.

Store oxycodone safely.

Oxycodone absolutely must be kept in a safe place where others – children or adults –cannot gain access to it. A single tablet of oxycodone can be harmful, or even fatal, in an individual who is not used to the medication.

- ☐ Do not keep oxycodone on kitchen counters, in bathroom cabinets, or other obvious places. If necessary, store oxycodone in a locked box or cabinet and in an out of the way location.
- ☐ Remember, persons you may least suspect, such as family members or visitors, might look for drugs like oxycodone to use for illegal purposes.
- ☐ Never share your oxycodone with anyone else, since it could do them great harm.

What are oxycodone side effects to watch for?

Alert your family members or caregivers of important warning signs to watch for that may indicate you are reacting badly to oxycodone and are in distress. If you experience any of the following, they should call for emergency help:

- ■ **Trouble staying awake.** ■ **Difficult or slow breathing.**
- ■ **Loud or unusual snoring at night and difficulty being awakened.**
- ■ **Fast heartbeat, unusual dizziness, or loss of consciousness (fainting).**

- ☐ Oxycodone, like all other opioids, may cause constipation. Your healthcare provider or pharmacist can recommend approaches for preventing or treating this. Reducing the oxycodone dose on your own *will not help*.
- ☐ Certain side effects, if they occur at all, usually become milder or go away with time, such as a lightheaded feeling, nausea, stomach upset, or mild drowsiness. Be careful with other medications that may cause drowsiness, like allergy, cough or cold medicines, sleeping medicine, medicine for anxiety, or other pain medicine. DO NOT drink alcohol while taking oxycodone.
- ☐ Possible other side effects may be more long-lasting, including: itching, dry mouth, flushing, or increased sweating. Allergic reactions to oxycodone – including rash, hives, or swelling – are rare but require prompt medical attention.
- ☐ Uncommon side effects include confusion, mood changes (depression or agitation), shaking, blurred vision, or difficulty urinating. If you experience any of these, tell your healthcare provider.
- ☐ You should refrain from driving and other activities requiring balance or focused concentration until the effects of oxycodone are known, typically a week or longer.

Will you become dependent on or addicted to oxycodone?

- ☐ After awhile, oxycodone causes *physical dependence*. That is, if you suddenly stop the medication you may experience uncomfortable withdrawal symptoms, such as diarrhea, body aches, weakness, restlessness, anxiety, loss of appetite, and other ill feelings. These may take several days to develop.
- ☐ This is not the same as *addiction*, a disease involving craving for the drug, loss of control over taking it or compulsive use, and using it despite harm. Addiction to oxycodone in persons without a recent history of alcohol or drug problems is rare.
- ☐ If you ever want to stop taking oxycodone, do not do so on your own. Gradually reducing the dose as directed by your healthcare provider will help prevent uncomfortable withdrawal reactions.

Do not reduce or stop taking oxycodone on your own.

Instrucciones para el paciente

Cómo tomar oxycodone sin ningún peligro

Sírvase leer este folleto atentamente y compartirlo con su familia o cuidadores.
Esto no sustituye la orientación del proveedor del cuidado de la salud ni el inserto que viene dentro de la caja de oxycodone.

Su proveedor del cuidado de la salud le ha recetado oxycodone para el alivio del dolor. Es un calmante fuerte para el dolor que se ha usado con mucho éxito por muchos años en millones de personas en todo el mundo. Es un fármaco opioide semi-artificial, sintético, con efectos similares a los opioides naturales tales como la morfina o codeína que provienen de la amapola del opio. El oxycodone es muy efectivo; sin embargo el uso inadecuado o el abuso pueden ser dañinos e incluso fatales (puede causar la muerte). ***Por consiguiente, es muy importante que usted lea, entienda y siga las instrucciones de seguridad mencionadas a continuación.***

Siempre tome el oxycodone exactamente como se lo han indicado.

Tomar oxycodone en exceso o combinarlo con otros fármacos, alcohol o productos no recetados, a menos que su proveedor del cuidado de la salud lo apruebe, puede ser dañino o incluso mortal.

Tomar oxycodone, en exceso, muy a menudo, o con otros fármacos o alcohol puede ser dañino o incluso mortal.

- ☐ Asegúrese de informarle a su profesional de la salud acerca de todos los productos para el cuidado de la salud y medicamentos (recetados y no recetados) que está usando y su historial completo de salud. Algunas veces el oxycodone se combina con otros medicamentos tales como el paracetamol (acetaminofén) o el ibuprofeno que se pueden adquirir por venta libre también. El ingerir grandes cantidades de estos productos puede ser perjudicial.
- ☐ Usted debe tomar la cantidad recetada de oxycodone y a las horas indicadas.
- ☐ Si le recetaran el producto oxycodone de efecto prolongado, no triture, parta o altere la tableta de ningún modo. Esto cambiará los efectos del oxycodone y puede causar una sobredosis y posiblemente la muerte.
- ☐ Si le recetaran la solución oral del oxycodone, consulte con su farmacéutico acerca de usar la cucharilla de medición apropiada o gotero de medición de dosis. El uso de una cuchara doméstica no es nada precisa y se puede ingerir una cantidad que sea perjudicial.
- ☐ Usted puede tomar el medicamento oxycodone con o sin alimentos.
- ☐ Si le recetaran el producto de oxycodone de efecto prolongado, usted puede observar las cáscaras del comprimido en las heces. No hay motivo para alarmarse. La capa exterior no se absorbe y recorre los intestinos. Su organismo sigue absorbiendo el medicamento de la tableta.
- ☐ Si se olvida de tomar la dosis habitual de oxycodone a tiempo, usted puede tomarla inmediatamente después. De lo contrario, espere hasta que sea la hora de la próxima dosis y solamente tome esa dosis; no tome oxycodone adicional para compensar la que olvidó tomar.
- ☐ Para evitar que se olvide de la dosis o que tome una dosis de más, utilice un registro o diario de medicamentos para ayudarle a llevar cuenta de cuándo toma cada dosis de oxycodone. Esto es especialmente útil si le recetaran un producto de poca duración para el dolor “impetuoso y repentino” o “cuando lo necesite.”
- ☐ Si usted es olvidadizo(a), pídale a alguien que le dé las dosis de oxycodone y lleve un registro de cada una de ellas.
- ☐ Infórmeles a todos sus proveedores del cuidado de la salud de que usted está tomando oxycodone. A no ser que se les avise, ellos le pueden recetar medicamentos que puedan alterar los efectos del oxycodone. De tener alguna pregunta, usted debe ponerse en contacto con la persona que le recetó el oxycodone.

Lleve un registro minucioso de sus tomas de oxycodone.

Guarde el oxycodone en un lugar seguro.

El oxycodone se debe guardar en un lugar absolutamente seguro donde otras personas, tanto niños como adultos, no puedan tener acceso. Una sola tableta de oxycodone puede ser dañina, inclusive mortal, en una persona que no está acostumbrada al medicamento.

- ☐ No guarde el oxycodone en los armarios de la cocina, del cuarto de baño u otros sitios fácilmente accesibles. De ser necesario, guarde el oxycodone en una caja o armario con llave y en un lugar fuera del alcance.
- ☐ Recuerde que las personas de las que menos sospecha, tales como familiares o visitas, podrían estar en busca de fármacos como el oxycodone para usarlo con fines ilegales.
- ☐ Nunca comparta el oxycodone con nadie más debido a que les podría causar un gran daño.

¿Cuáles son los efectos secundarios del oxycodone a los que se deben estar alertas?

Alerte a sus familiares o cuidadores sobre las señales importantes de peligro a las que deben estar alertas ya que pueden indicar que usted está teniendo una mala reacción al oxycodone y se encuentra en peligro. Si usted experimenta cualquiera de los siguientes síntomas, estas personas deberían pedir ayuda de emergencia:

- **Problemas para mantenerse despierto.**
- **Dificultad para respirar o respiración lenta.**
- **Un ronquido fuerte o extraño en la noche y dificultad para despertarse.**
- **Palpitaciones, mareos no usuales o pérdida del conocimiento (desmayo).**

- ☐ El oxycodone, como todos los demás opioides, puede causar estreñimiento. Su proveedor del cuidado de la salud o farmacéutico le puede recomendar medidas para prevenirlo o darle tratamiento. Reducir la dosis de oxycodone por su cuenta no le ayudará.
- ☐ Algunos efectos secundarios, de ocurrir, generalmente se vuelven más leves o desaparecen con el tiempo, tales como la sensación de mareo, náuseas, malestar estomacal o somnolencia leve. Tenga precaución con otros medicamentos que puedan causarle somnolencia, tales como los antihistamínicos, medicina para la tos o resfriados, medicamento para dormir, medicina para la ansiedad u otros calmantes para el dolor. NO consuma alcohol mientras tome el oxycodone.
- ☐ Otros posibles efectos secundarios pueden ser de larga duración, incluyendo: comezón, sequedad bucal, enrojecimiento o aumento en la sudoración. Las reacciones alérgicas al oxycodone – incluyendo erupción, urticaria o hinchazón – son poco comunes pero requieren de una atención médica rápida.
- ☐ Los efectos secundarios poco corrientes incluyen confusión, cambios de humor (depresión o ansiedad), tembladera, visión borrosa o dificultad al orinar. Si usted experimenta cualquiera de estos síntomas, infórmele a su proveedor del cuidado de la salud.
- ☐ Debe evitar manejar y hacer otras actividades que requieran de equilibrio o mucha concentración hasta que usted sepa cuáles son los efectos del oxycodone, por lo general en una semana o más.

¿Se volverá dependiente o adicto al oxycodone?

No reduzca ni suspenda el oxycodone por su cuenta.

- ☐ Después de un tiempo, el oxycodone causa dependencia física. Esto quiere decir que si usted deja de tomar el medicamento repentinamente, usted puede experimentar síntomas molestos de abstinencia, tales como diarrea, dolores corporales, debilidad, inquietud, ansiedad, pérdida del apetito y otras sensaciones de malestar. Esto puede tomar varios días en aparecer.
- ☐ Esto no es lo mismo que la adicción, una enfermedad que implica un ansia por el fármaco, pérdida del control al tomarlo o el uso compulsivo, y usarlo a pesar del daño que ocasione. La adicción al oxycodone en las personas sin un historial reciente de problemas de alcohol o drogas es poco común.
- ☐ Si alguna vez usted desea dejar de tomar el oxycodone, no lo haga por cuenta propia. La reducción gradual de la dosis tal como se lo indique su proveedor del cuidado de la salud le ayudará a prevenir reacciones molestas de abstinencia.

EXHIBIT 99

Pain Treatment Topics addresses common questions that arise in clinical practice regarding pain management. Answers are based on available evidence in the medical literature (as cited) and are reviewed for consistency with pain-management practices currently accepted at the time of answer development. These FAQs are ***not*** offered as medical advice or treatment recommendations, and professional discretion is advised in their acceptance or application. See also, the Disclaimer below and Site Policies.

FAQ

How can opioid analgesic efficacy be assessed

The assessment of opioid analgesic efficacy should begin when therapy is first considered and continue at each visit. Many clinicians follow the "**4 A's**" developed by Passik and Weinreb (2000), which consider the main domains for evaluating pain treatment outcomes. Current opioid guidelines also recommend routine assessment of the "4 A's" (ASIPP 2006).

Ideally, every interaction with a patient complaining of pain will include a review of the opioid-therapy regimen and the "4 A's," along with documentation of patient responses.

- **Analgesia** – Measure pain relief as reported by the patient. Multiple assessment tools exist and the most commonly used are: a four-category verbal rating scale (VRS-4), an 11-point numeric rating scale (NRS-11), or a 100-mm visual analog scale (VAS). Consistency in using the same instrument to measure pain relief at each visit is more important than the actual choice of scale. In patients with low literacy, the numeric scale has been reported as more reliable than the VAS (Ferraz et al. 1990).
- **ADL's (Activities of Daily Living)** – Assess level of physical and psychosocial functioning, including: bathing, walking, dressing, sexual function, ability to work, mood, sleep, family/social interactions, and recreational or leisure activities (ASIPP 2006, NGC 2005). Consider goals expressed by the patient and how much has been achieved against those goals.
- **Adverse Effects** – Document all adverse effects due to opioid therapy. Consider those that either are not effectively managed or prevent function (e.g., constipation, cognitive impairment), or those that may be minimal (e.g., occasional itching). Determine appropriate strategies to avoid or minimize side effects; for example, reducing opioid dose or frequency, changing the drug formulation, or opioid rotation.
- **Abuse Issues** – Evaluate the patient for any signs suggestive of dependency or drug-seeking behavior. Some suggested criteria to evaluate potential opioid abuse or misuse include: early or frequent prescription refills, inappropriate focus on opioid-medication issues at each visit, escalating opioid use in the absence of an acute or related change in medical condition, multiple telephone calls or visits requesting more opioids, and lost/stolen medications (ASIPP 2006). Also be alert to any signs of potential drug diversion, such as doctor shopping or prescription forgery. However, keep in mind that, rather than an actual addiction/dependency disorder, these behaviors may represent "pseudoaddiction" (which relates to aberrant behaviors associated with a patient's attempts to overcome the undertreatment of pain).

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How is opioid *addiction* different from dependence or tolerance?

Many of the concerns regarding opioid use originate from misconceptions or confusion regarding the terminology describing the risks of addiction, tolerance, and dependence.

Numerous authorities – including the American Academy of Pain Medicine, American Pain Society, and the American Society of Addiction Medicine – have addressed these concerns. An appreciation of more concise definitions can help dispel misunderstandings, which otherwise might lead to inadequate pain management therapy.

Addiction (Substance Dependence) – is a disorder in which patients exhibit compulsive use of the drug, cravings, and loss of control (use of the drug continues despite harm to themselves or to others). Addiction is not a pharmacological side effect but rather a cluster of behavioral symptoms. While patients with a history of substance abuse may be at higher risk for developing addiction to opioids, the risk for most patients is very small.

A commonly used reference from the American Psychiatric Association (APA 2000) – the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)* – does not use the term addiction at all; rather, it uses "substance dependence." And, to be more precise, the particular drug involved is specified: for example, heroin dependence or alcohol dependence. However, for the general public, the term "addiction" is generally synonymous with "substance dependence."

The>DSM defines dependence (addiction) as a maladaptive pattern of substance use leading to significant impairment or distress in 3 or more of the following 7 areas during a 12-month period:

- Tolerance – defined by either: a) a need for increased amounts of substance to achieve intoxication or desired effects, b) diminished effect with continued use of the same amount of substance.
- Withdrawal – evident by either: a) characteristic, uncomfortable abstinence signs/symptoms for the particular substance, b) the same (or closely related) substance is taken to relieve or avoid the withdrawal syndrome.
- The substance is used in greater quantities or for longer periods than intended.
- There is a persistent desire or unsuccessful efforts to cut down or control substance use.
- Considerable time and effort are spent in obtaining or using the substance or in recovering from its effects.
- Important social, employment, and/or recreational activities are given up or reduced because of an intense preoccupation with substance acquisition and use.
- Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely caused or exacerbated by the misuse of the substance.

Addiction may occur with or without tolerance and withdrawal. A key issue in addiction is the patient's complete failure or inability to abstain from using a substance that serves no bona fide medical purpose — that is, loss of control.

In many cases, excessive (compulsive) use, loss of control, and neglect of activities/obligations are best confirmed by those close to the patient. Furthermore, no single event or criteria is diagnostic of an addiction disorder; rather, addiction becomes evident via a *pattern* of behavior that takes place over time. In that regard, opioid addiction is not *solely* associated with opioid-induced euphoria (feelings of well-being), craving, or physical withdrawal (hyperexcitability, tremors, seizures, etc.). Nor are persons who merely use opioids too often and/or in larger quantities than prescribed necessarily addicted, at least not according to commonly accepted definitions.

Physical/Physiological dependence – occurs when withdrawal symptoms are precipitated upon abrupt withdrawal of the opioid, rapid dose reduction, and/or administration of an antagonist. Physical dependence is not necessarily indicative of addiction; rather, it is an *expected consequence* of long-term therapy with opioids, just as it is with some antihypertensive medications or with corticosteroid therapy. In these scenarios, the patient will experience withdrawal symptoms if therapy is abruptly discontinued rather than gradually tapered. Symptoms commonly associated with opioid withdrawal include tremor, anxiety, abdominal pain, increase in blood pressure, and sweating (diaphoresis).

Tolerance – is the most common response to repetitive use of the same drug. It can be defined as a state of adaptation where a higher dose is required to produce the same effect previously obtained at a lower dose. Tolerance to some drug effects develops more rapidly than to others. With opioids, for example, tolerance to sedation, euphoria, and depressed respiration develops faster than tolerance to analgesia or to the constipating side effects of these drugs.

Pseudoaddiction – has been used to describe aberrant patient behaviors that may occur when pain is undertreated (AAPM 2001). Although this diagnosis is not supported by rigorous investigation, it has been widely observed that patients with unrelieved pain may become very focused on obtaining opioid medications, and may be erroneously perceived as "drug seeking." Pseudoaddiction can be distinguished from true addiction in that the behaviors resolve when the pain is effectively treated. Along with this, two related phenomena have been described in the literature (Alford et al. 2006):

Therapeutic dependence – sometimes patients exhibit what is considered drug-seeking because they fear the reemergence of pain and/or withdrawal symptoms from lack of adequate medication; their ongoing quest for more analgesics is in the hopes of insuring a tolerable level of comfort.

Pseudo-opioid-resistance – other patients, with adequate pain control, may continue to report pain or exaggerate its presence, as if their opioid analgesics are not working, to prevent reductions in their currently effective doses of medication.

Patient anxieties about receiving inadequate pain control can be profound, resulting in demanding or aggressive behaviors that are misunderstood by healthcare practitioners and ultimately detract from the provision of adequate pain relief.

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What evidence supports neurobiological dysfunction in addiction?

Through the years, some commentators have asserted that drug addiction is not a neurobiological disease process; rather, detractors say, it relates solely to poor choices people make based on a distorted value system. This is an old and outdated argument viewing persons who develop addictions as being weak-willed, morally corrupt, and irresponsible.

Such perspectives ignore the evidence-based findings of modern neuroscience. That is, although that initial abuse of an addictive substance may be voluntary, it can result in neurobiological dysfunctions that are beyond individual control.

Using advanced brain-imaging techniques, researchers have been able to conclusively demonstrate that there are chemical, anatomical, and functional changes in the brains of substance-addicted persons, similar to the changes in other neurobiological disease processes. For example, the colorful **images** here depict SPECT scans (from Amen 2001) demonstrating that addictions (to heroin or alcohol, in this case), as well as mental disorders, affect brain function similarly to a neurological impairment such as stroke. Single-photon emission computed tomography (SPECT) uses small doses of radioisotope tracers to study regional cerebral blood flow and thus, indirectly, brain function during health and disease states.

The images graphically show the cerebral regions of different patients. As can be seen, compared with a normal subject, there are multiple disruptions in the brains of these patients — the Swiss cheese appearance indicates defects in blood circulation and, hence, abnormal cerebral activity. Portions of the cerebral cortex are responsible for executive functions of cognition, judgement, and impulse control, which become critically dysfunctional in many mental and addictive disorders.

Other types of imaging studies (e.g., PET, fMRI) have demonstrated that deeper structures in the brain also may be adversely affected during addiction. And, substances of abuse also selectively alter neurochemical and receptor systems (such as the mesolimbic dopamine "reward" pathways).

Thus, substance addiction may best be understood to a great extent as a neurobiological disease process. With effective medical and psychosocial treatments, patients may benefit from at least partial "normalization" of brain activity in the affected regions.

Whether or not the long-term use of opioid analgesics – many of which have abuse potential – might adversely affect neurobiological function has not been adequately investigated. Available evidence suggests that appropriate use of these agents, as properly prescribed, does not incur permanent dysfunction during short- or long-term application. For example, a favorable safety profile, including unaffected mental functioning, has been demonstrated in patients receiving long-term methadone therapy; some of whom have been maintained on the drug for 20 years or more.

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Is there a rationale for concurrently prescribing multiple long-acting opioid analgesics?

Presently, evidence does not support the concurrent and continued use of more than one *long-acting* opioid analgesic. And, depending on the half-lives and dosing intervals of multiple long-acting opoids, there is a potential for harmful drug accumulation and additive adverse effects over time.

In certain cases, a patient might receive two long-acting opioids concurrently for a brief time when the intent is to wean the patient off one agent and onto the other. The dose of one is appropriately tapered while the other agent is titrated upward.

In clinical practice, it is more common to use a long-acting analgesic dosed appropriately to control baseline chronic pain, and to add a short-acting analgesic as a rescue medication taken for episodes of breakthrough pain

Guideline recommendations include the following points:

- Rational polypharmacy could include the use of two or more drugs with complementary mechanisms of action, and this may provide greater pain relief at lower doses of each drug and with less toxicity. However, prescribing two drugs in the same class at the same time for an extended period is generally not advised.
- Be alert for possible interactions with other medications the patient is taking and for additive side effects.
- Titrate doses to achieve optimal balance between analgesic benefit, side effects, and functional improvement.
- Optimize administration of analgesics. Generally better pain control is obtained with regularly scheduled doses and supplemented with as needed (PRN) doses, up to prespecified limits, for breakthrough pain.

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Are patient agreements helpful when initiating long-term opioid therapy?

A patient opioid-medication contract, sometimes called a controlled-substances agreement, is not required by federal regulations; yet, many pain management practitioners employ them for some or all patients receiving long-term opioid therapy. In a nationwide survey of more than 2,500 board-certified pain specialists, 85% reported using an opioid agreement (Breuer et al. 2006).

Although the evidence favoring the efficacy of these agreements in curbing drug abuse is limited, proponents of patient agreements believe they can serve as a communication tool between physician and patient by clarifying the patient's (and healthcare provider's) responsibilities. Agreements seem to be most helpful in patients with a history of substance abuse, or if the healthcare provider determines that a patient is at high risk for medication abuse.

Carefully worded patient agreements may help with the following:

- explaining the goals of therapy;
- educating patients and caregivers about benefits, side effects, and concerns related to opioid therapy;
- outlining consequences of not adhering to the agreement, such as drug discontinuation; and
- addressing potential behavioral concerns, for example, when patients repeatedly "lose" medication, are unable or unwilling to store the medication in a safe place, repeatedly run short and ask for early refills, or obtain medication from more than one physician or pharmacy.

Those critical of patient agreements cite the following reasons:

- there is limited evidence that such agreements significantly reduce opioid abuse;
- there are ethical concerns about their equitable implementation and enforcement; and
- the objectives can be overly complex and ill-defined.

Although patient agreements seem to vary substantially in their content, the American Academy of Pain Medicine (AAPM 2001) has samples available online for clinicians to download and use (see below). Aside from some dissenters citing a lack of clear evidence and the need for further research, there can be advantages for healthcare providers and patients, and the use of opioid-management agreements in certain patients, such as those with substance-abuse potential, may be helpful as a preventive measure.

Resources:

AAPM: American Academy of Pain Medicine. Long-term Controlled Substances Therapy for Chronic Pain - Sample Agreement. 2001. Available on line at: http://www.painmed.org/productpub/statements/pdfs/controlled_substances_sample_agrmt.pdf. Access checked 6/5/06.

Breuer B, Pappagallo M, et al. A national survey on pain management practices in the United States. 2006 Annual Meeting of the American Pain Society. Poster abstract available online at: http://www.ampainsoc.org/db2/abstract/view?poster_id=3007#100. Access checked 6/6/06.

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ICSI. Assessment and management of chronic pain. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2005. Available online at: http://www.icsi.org/knowledge/detail.asp?catID=29&itemID=2335. Access checked 5/31/06.

Researcher/Writers: Stewart B. Leavitt, MA, PhD; Sandra E. Checri, RPh. Medical Reviewers: Lee A. Kral, PharmD, BCPS; Paul W. Lofholm, PharmD, FACA; James D. Toombs, MD; Steven J. Tucker, MD. – Posted June 2006.

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How can sleep disturbances in patients with pain be managed?

The National Institutes of Health (NIH) has defined insomnia as complaints of disturbed sleep in the presence of adequate opportunity and circumstance for sleep. The disturbances may including one or more of the following: 1) difficulty initiating sleep; 2) difficulty maintaining sleep; or 3) waking up too early. Lack of restorative, REM sleep also is frequently associated with insomnia (NIH 2005).

Patients with unresolved pain frequently have disturbed sleep, including nighttime awakenings, difficulty falling back to sleep after awakenings, and less time spent in restorative rapid eye movement (REM) sleep. Research has shown that losing as little as 4 hours of sleep in one night may result in a significant lowering of the pain threshold (Roehrs et al. 2006).

In the patient with chronic pain, treating insomnia can present some challenges: 1) comorbid physical and psychiatric conditions may also be present (e.g., depression, anxiety), either as a cause of insomnia or a contributory factor; 2) opioid analgesics are known to be REM suppressants and lack of restorative sleep, as noted earlier, may contribute to

hyperalgesia; 3) pharmacologic therapies may be limited for insomnia in patients receiving long-term opioids or adjunctive medications due to potential drug interactions, side effects, or additive effects (e.g., respiratory depression).

Depending on the patient's particular situation, several strategies might be considered (NIH 2006; Moldofsky 2004):

Problem Assessment:

- **Evaluate current therapy** – If medication interactions are present and they are causing the insomnia, a change may be warranted. Conversely, current analgesic therapy may not adequately provide pain relief through the night. In either case, consultation with a clinical pharmacist may be helpful.
- **Ask the Patient** – Patients may fail to report sleep disturbances. Although there are a number of insomnia questionnaires (e.g., Insomnia Severity Index), the best approach is to ask the patient if he/she is having problems with falling or staying asleep, or with staying awake during the day.

Non-pharmacologic Strategies:

- **Sleep hygiene** – Patients should be advised about practicing good "sleep hygiene," such as: using the bed only for sleeping; relaxing before bedtime; avoiding caffeine, nicotine, and alcohol; daily exercise to the extent possible; controlling noise and light in the bedroom; and, setting a regular schedule for sleeping and waking.
- **Stress reduction or biofeedback** may help in the long-term management of insomnia, and in stressed or depressed patients.
- **Alternative activities** like tai chi, yoga, acupuncture, and light therapy might be useful in the treatment of insomnia; however, these have not been adequately evaluated at this time.

Pharmacologic Approaches:

In general, lower doses of sleep medications may be necessary in patients taking opioid analgesics due to potentially additive CNS-depressant effects — clinical discretion is advised. Also consider that the elderly are usually more sensitive to the effects of these agents.

- **Over-the-Counter (OTC)** products include medications such as Nytol®, Sleep-Eze®, Sominex®, and others. Most of these products contain antihistamines, such as diphenhydramine that act as a sedative and provide the relaxation needed for falling asleep. However, patients should be cautioned against their routine use.
- **Benzodiazepines** like flurazepam (Dalmane®), quazepam (Doral®), triazolam (Halcion®), and temazepam (Restoril®) are useful in treating co-existing anxiety conditions or sleep disorders. Consider their half-lives; those with longer half-lives can cause daytime sleepiness and impair waking cognitive and motor function, while those with shorter half-lives may wear off before desired or scheduled wake-up times. Some benzodiazepines may disturb sleep architecture, and there can be uncomfortable withdrawal following cessation after long-term use.
- **Non-benzodiazepine hypnotics** like zolpidem (Ambien®), zaleplon (Sonata®), and others seem to have better side-effect profiles than the benzodiazepines. They help patients fall asleep, but may not be as helpful in those frequently waking after falling asleep.
- **Antidepressants** can have sedative side effects and two commonly used for this purpose include trazodone (Desyrel®) and doxepin (Sinequan®).These medications can be associated with more troubling adverse effects (e.g., anticholinergic side effects) than prescription sedative-hypnotic medications; however, clinicians may find them useful when insomnia occurs in the context of depression. **Note**: These antidepressants are currently not FDA approved for insomnia and their value in the treatment of insomnia has been questioned.
- **Herbal remedies** may have been considered or used by some patients before talking to their physicians. Melatonin, the most commonly used, seems to help some patients fall asleep but not all patients stay asleep. Others promoted for insomnia include valerian, chamomile, and L-tryptophan. The effectiveness and safety of these products for this application have not been established.

References:

Moldofsky H. Pain and Insomnia: What Every Clinician Should Know. Medscape Neurology & Neurosurgery 6(2), 2004. Available online: http://www.medscape.com/viewarticle/494872. Access checked 5/31/06.

NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults. June 13–15, 2005. Available online: http://consensus.nih.gov/2005/2005InsomniaSOS026html.htm. Access checked 5/31/06.

Roehrs T, Hyde M, Blaisdell B, et al. Sleep loss and REM sleep loss are hyperalgesic. Sleep. 2006 Feb 1:29(2):145-151.

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Is shockwave therapy a valid alternative for treating plantar fasciitis?

Extracorporeal shockwave treatment (ESWT) may be an alternative therapy for plantar fasciitis that is unresponsive to other measures. Plantar fasciitis is a painful condition that can lead to functional limitations, and it sometimes responds poorly to treatments like rest, physical therapy, orthotics, NSAIDs, and/or corticosteroid injections.

Wang et al. (2006) reported positive long-term results using ESWT in a prospective randomized clinical trial evaluating 149 patients with a diagnosis of chronic plantar fasciitis. After the treatment intervention, patients were evaluated at 60-72 months for the study group (ESWT), and at 34-64 months for the control group. Clinical outcomes assessed were improvements in pain and function rated as excellent, good, fair, or poor. Patients in the study group (n=79) received one shockwave therapy session; 69.1% of them reported excellent results and 13.6% reported good results. Control group patients (n=70) received standard conservative treatment; 0% reported excellent results and 55% good results.

A more cautious viewpoint has been expressed by the Technology Evaluation Center (TEC) of the Blue Cross Blue Shield Association. Published in March 2005, the TEC assessment looked at 8 double-blind randomized clinical trials to determine if ESWT for plantar fascitis improved health outcomes (pain and functional limitations). The TEC review concluded that ESWT improved morning pain as measured on a 0-10 point score Visual Analog Scale; however, it was uncertain from the available evidence whether the treatment effect was clinically significant. Overall, the evidence was not sufficient to permit definitive conclusions on the health outcome benefits of ESWT for plantar fasciitis.

Therefore, ESWT studies published to date appear to offer mixed results. Until more studies are published, currently available evidence suggests that extracorporeal shock wave treatment (ESWT) may improve pain scores and functionality in some, but not all, patients.

References:

Wang CJ, Wang FS, Yang KD, et al. Long-term results of extracorporeal shockwave treatment for plantar fasciitis. Am J Sports Med. 2006;34(4):592-596.

Extracorporeal Shock Wave Treatment for Chronic Plantar Fasciitis. Blue Cross Blue Shield Association TEC (Technology Assessment Center). Assessment Program, Volume 19, No. 18, March 2005. Overview available at: http://www.bcbs.com/tec/vol19/19_18.html. Full report (40-page PDF) available at: http://www.bcbs.com/tec/Vol19/19_18.pdf. Access checked 5/31/2006.

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Are epidural steroid injections helpful for chronic low back pain?

Although significant questions remain in the management of chronic low back pain, clinical data suggest that patients with unresolved low back pain lasting more than 3 months may be candidates for epidural steroid injections. The pain should be severe enough that it significantly limits function and quality of life, and has not responded to oral analgesic medications and/or conservative care measures.

For pain control, epidural steroid injections might be considered as an adjunct to conservative treatment and/or as an alternative to surgery in conditions causing chronic low back and/or leg pain, such as:

— degenerative disc disease,
— lumbar disc herniation,
— lumbar spinal stenosis, and/or
— recurrence of pain post-laminectomy.

Contraindications include:

— history of allergic reactions to any of the injected solutions (e.g., local anesthetic, steroids),
— systemic or local infection in the area where the injection is planned,
— bleeding disorders, and/or,
— anticoagulant therapy.

In terms of efficacy, review articles present variable results and published data show an even mix of positive and negative outcomes. Some authors have noted methodological and/or research-design limitations as the reasons for this variability. At this time, research results fail to demonstrate conclusively that epidural injection therapy is either effective or ineffective. Patient response and overall effectiveness often depend on the etiology and duration of the nerve root irritation, with a better response in conditions lasting less than one year. Furthermore, injected steroids could be relatively contraindicated in diabetes, since they may increase blood sugars for up to a few weeks.

Although the evidence is ambivalent, epidural steroid injections seem beneficial in some patients for at least decreasing pain on a short-term basis (e.g., for up to 3 weeks post-injection), and possibly much longer. Additional strategies include an overall multidisciplinary rehabilitation program to help reduce pain and improve function. Patient education and participation in the overall treatment plan are important as well.

Resources:

Adult low back pain. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2005 Sep. Available online at: http://icsi.org/knowledge/detail.asp?catID=29&itemID=149. Access checked 5/31/06.

Koes BW, Scholten RJPM, Mens JMA, et al. Efficacy of epidural steroid injections for low-back pain and sciatica: a systematic review of randomized clinical trials. Pain. 63 (1995) 279-288.

Samanta A, Kendall J. Is epidural injection of steroids effective for low back pain? Editorial. BMJ. 2004;328:1509-1510. Available online at: http://bmj.bmjjournals.com/cgi/content/extract/328/7455/1509. Access checked 5/31/06.

Patient Resource Available at Pain-Topics.org:

Handout on Health: Back Pain (Booklet by the U.S. Department of Health and Human Services National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases). See: http://www.pain-topics.org/patient_resources/index2.php#handoutback. Access checked 5/31/06.

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EXHIBIT 100

PAIN TREATMENT TOPICS www.Pain-Topics.org

Commonsense Oxycodone Prescribing & Safety

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Key Practice Pointers for Oxycodone IR and CR

Oxycodone Overall

- Oxycodone is approved for treating acute or chronic pain that is moderate to severe.
- Oxycodone is approximately 1.5 times more potent than morphine (20 mg oxycodone = 30 mg morphine).
- At equianalgesic doses, oxycodone IR or CR are equivalent in effectiveness to morphine IR or CR.
- When switching opioids, there is incomplete cross-tolerance, so the dose of the second agent is typically reduced by 33% to 50% to prevent toxicity.
- When opioids are used with adjuvant agents, there is enhanced analgesia; however, doses of combination products are limited by their nonopioid ingredients.
- When used in combination with other CNS depressants, oxycodone should be started at 30% to 50% of the usual daily dose.
- "Plain" oxycodone, rather than combination products, may be more beneficial for patients who have liver disease or risk factors for liver disease.
- In severe hepatic impairment, oxycodone should be initiated at 30% to 50% of the usual dose and titrated cautiously to avoid respiratory depression.
- Use oxycodone cautiously in renal dysfunction, and avoid using it with hemodialysis.
- No oxycodone dosing adjustments are required in patients older than age 65.
- Suggested upward adjustments of oxycodone are 25% to 50% of the current daily dose every 1-2 days.
- If a dose increase does not produce increased analgesia, maintain previously effective oxycodone dose and investigate other analgesic options. Raising the dose without notable analgesic benefit only furthers the risk of adverse effects**.**
- During chronic use, opioids have not been shown to specifically affect driving ability. However patients should be cautious about operating any vehicle until they feel that they will not be too sedated to drive. This is particularly important following initiation of therapy or a dose increase.

Oxycodone IR

- Oxycodone IR is similar to morphine with an onset of about 15 minutes, peak blood levels after about 1 hour, and a 4 hour duration of action.
- Oxycodone IR formulations do not show any particular advantage or disadvantage compared with other short-acting opioids.

Oxycodone CR

- At equivalent doses, there is no difference in analgesic effect between CR and IR oxycodone: eg, oxycodone CR 10 mg bid = oxycodone IR 5 mg QID.
- Oxycodone CR tablets must be swallowed whole; any tampering may be harmful.

Abbreviations used in this document: bid = twice daily; CR, ER, SR = long-acting formulations (Controlled-Release, Extended-Release, Sustained-Release); IR = short-acting formulation (immediate-release); prn = as needed; qid = four times daily; qd = once daily; tid = three times daily.

Introduction

Oxycodone is FDA-approved for treating moderate to severe pain that is either acute or chronic in nature. It has been widely used in pain management practice for decades but has recently been receiving much negative attention due to abuse, overdose, and deaths associated with the controlled-release formulation. So, in the overall approach to pain management, what is the appropriate role of oxycodone?

Oxycodone is approved for moderate to severe pain that is either acute or chronic.

A number of questions must be considered when choosing therapy. For example, how does oxycodone compare with other opioids? When should immediate-release oxycodone be used rather than the controlled-release product? Is oxycodone in combination with acetaminophen or an NSAID better than "plain" oxycodone? Are the risks of using oxycodone greater than the benefits? How can risks of misuse or abuse be minimized when prescribing oxycodone?

Those and other commonsense questions concerning oxycodone prescribing, safety, and risk management are addressed in this paper.

A range of oxycodone products is available in the United States as single-agent immediate-release (**IR**) formulations – including tablets, capsules, and oral solution – and in combination with acetaminophen, aspirin, or ibuprofen (see ***Table***). Oral oxycodone solutions must be used cautiously so the 2 different strengths – 1 mg/mL vs 20 mg/mL – are not confused. Many of the IR oxycodone products are more economically available as generics.

A controlled-release (**CR**) oxycodone product, sometimes referred to as long-acting or long-duration, is available (OxyContin®, Purdue Pharma LP), and generic versions of oxycodone CR have been marketed in recent years. Outside the US, oxycodone also is available as an injection (United Kingdom) and a rectal suppository (United Kingdom, Canada, and Australia). An intranasal formulation has been tested, although with variable results [Takala et al. 1997].

Oxycodone Formulations

Oxycodone HCl	5 mg capsule; 5 mg, 15 mg, 30 mg tablet
Oxycodone (mg) / Acetaminophen (mg)	5/325, 7.5/325, 10/325; 5/500, 7.5/500; 10/650
Oxycodone (mg) / Aspirin (mg)	2.5/325, 5/325
Oxycodone (mg) / Ibuprofen (mg)	5/400
Oxycodone (mg) / Acetaminophen (mg) / Caffeine (mg)	4.5/325/0.38
Oxycodone HCl Oral Solution	1 mg/mL
Oxycodone HCl Concentrate	20 mg/mL
Oxycodone CR (generic)	20 mg, 40 mg
OxyContin® (oxycodone CR brand)	10 mg, 20 mg, 40 mg, 80mg, 160mg

Source: Red Book 2005, 2007

Oxycodone Pharmacology

Oxycodone is a DEA Schedule II semisynthetic opioid analgesic derived from thebaine, an alkaloid in opium. Originally developed in 1916 and introduced into clinical practice in Germany in 1917 [Kalso 2005], it is a mu- and kappa-opioid receptor agonist structurally related to codeine, but it behaves pharmacodynamically like morphine. In addition to analgesia, oxycodone can produce anxiolysis, euphoria, feelings of relaxation, and cough suppression, as well as respiratory depression, constipation, miosis, sweating, and somnolence.

Oxycodone potency is approximately 1.5 times greater than morphine (eg, 20mg of oxycodone = 30mg morphine)

While its potency is approximately 1.5 times greater than morphine [Benziger et al. 1997], oxycodone has a similar onset, duration of action, and effectiveness in equianalgesic dosing (20mg of oxycodone = 30mg morphine; see ***Table***). The minimum effective plasma concentration varies between patients, which occurs with all opioids. Also consistent with other pure opioids (as compared with mixed agonist/antagonist agents), oxycodone usually does not have a "ceiling effect" (a point where increasing the dose does not increase analgesia).

Absorption and Bioavailability

The oral bioavailability of oxycodone is 2-3 times greater than for morphine [Leow et al. 1992; Poyhia et al. 1992; Sawe et al. 1981] (see ***Table***). Despite differences in bioavailability, the pharmacodynamic behavior of immediate-release oxycodone is similar to morphine with an onset of action within about 15 minutes and peak blood levels after about 1 hour [Poyhia et al. 1992].

In contrast, controlled-release oxycodone exhibits biphasic absorption, with an immediate-release component having an absorption half-life of 37 minutes, accounting for 38% of the total dose. The second phase is a slow release component with an average absorption half-life of 6.2 hours [Mandema et al.

Pharmacokinetics Immediate-Release Oxycodone vs Morphine

	Oxy IR	Morph IR
Bioavailability	60% - 87%	30%
Onset of Action	15 min	15 min
Time to Peak Level	1.4 hr	1.5 – 2hr
Duration of Action	4 hr	4 hr
Half-Life	3.2 hr	1.4 - 4.5 hr

Pharmacokinetics Controlled-Release Oxycodone

Peak Pain Relief	1 hr
Time to Peak Blood Level	2-3 hr
Half-Life	4.5 - 8 hr
Time to Steady State	24 - 36 hr

1996]. Peak pain relief occurs in approximately 1 hour, but peak blood levels are not reached for 2-3 hours [Mandema et al. 1996; Poyhia et al. 1992; Reder et al. 1996]. This complex release mechanism requires that the tablets be swallowed whole — crushing, splitting, or other tampering alters the release mechanism and may lead to drug overdose.

Absorption rate and extent have been found comparable between one 20 mg and two 10 mg oxycodone CR tablets [Benziger et al. 1997]. And, while absorption is generally not affected by food, a high-fat meal increases the extent of absorption and overall drug concentration (the AUC) while decreasing peak blood level [Benziger et al. 1996]. If doses are consistently taken at the same times during the day (preferably apart from meals), the clinical effects should not be altered significantly by food.

Metabolism, Excretion

Oxycodone has two metabolic pathways including N-demethylation, accounting for 45% of a dose, and O-demethylation, which accounts for 10% of a dose. The principal active metabolite via the first pathway is *noroxycodone,* which has only weak affinity for the mu-opioid receptor [Lalovic et al. 2006]. A minor active metabolite is *oxymorphone,* which is 30 times more potent than oral morphine [APS 2003]; however, it has little clinical activity because it is produced in such small amounts.

Compared with its metabolites, the parent oxycodone compound contributes the greatest portion of pharmacodynamic and analgesic activity.

The second metabolic pathway uses CYP450 2D6 enzymes. This may be genetically influenced, with some patients having multiple copies of the 2D6 gene, leading to rapid metabolism, or no gene at all, engendering slow or absent metabolism. Several other medications are metabolized via this pathway. However, research has shown very little clinical effect on oxycodone when this pathway is inhibited. Compared with its metabolites, the parent oxycodone compound contributes the major portion of pharmacodynamic (and analgesic) activity [Heiskanen et al. 1998; Kaiko et al. 1996; Lalovic et al. 2006].

Renal excretion of free oxycodone is estimated to be from 8% to 19%. Metabolites are excreted in the urine as conjugated oxycodone and oxymorphone, and as both free and conjugated noroxycodone [Poyhia et al. 1992]. Excretion and clearance of oxycodone are affected by renal or hepatic disease, influencing the need for dosing adjustments (discussed below).

Oxycodone Dosing

Patients who have not been taking opioids should be started on the lowest recommended oxycodone dose, with escalation as needed for pain control. Recommended starting doses of oxycodone IR are *5 mg to 15 mg every 4 hours*. The typical adult dose ends up being *10 mg to 30 mg every 4 hours*, reflecting the degree of pain the patient is experiencing [Oxycodone PI 2005].

Author's Note: In an opioid-naïve patient, I would recommend starting with an immediate-release product and titrate upward to adequate pain relief, followed by conversion to a long-acting product to improve compliance and avoid erratic blood levels.

The starting dose of oxycodone CR in opioid-naïve patients is *10 mg every 12 hours*. The dose may be increased every 1-2 days, as it takes 24 to 36 hours to reach steady state after a change in dose [OxyContin PI 2007].

Suggested upward adjustments are 25%-50% of the current daily dose (eg, an increase of 10-20 mg in a patient taking 20 mg twice daily) [Kaplan et al. 1998]. For patients switching between IR and CR tablets, the total daily dose of oxycodone should remain about the same (eg, oxycodone IR 5 mg q 6 hr = 10 mg q 12 hr oxycodone CR) [Kaplan et al. 1998; Stambaugh et al. 2001].

Equianalgesic Conversions

There is significant inter-patient variability in response to opioids. Kalso et al [2004] reviewed several opioid studies in the noncancer pain population and found a 30% mean decrease in pain (80% with at least one adverse effect). Watson and colleagues [2004] surveyed noncancer patients and found that one-third of patients reported a reduction from severe to moderate pain. Individual response depends on a number of factors: comorbid medical conditions may predispose patients to opioid toxicity, pain pathophysiology may be unresponsive to opioids, and pharmacogenetic variations in mu-receptor conformation may alter sensitivity to opioids. One strategy to improve responsiveness is to rotate opioids, involving an imprecise process of calculating a new regimen based on equianalgesic doses [Anderson et al. 2001].

Opioids have incomplete cross-tolerance, so the dose of the second agent is typically reduced by 33%-50% to prevent toxicity. However in cancer patients, if the disease process is expected to progress, the pain would be expected to escalate as well, and dose reduction may be detrimental to optimizing pain control.

Equianalgesic Conversions

	IM/IV	PO
Morphine	10 mg	30 mg
Oxycodone	–	20 mg
Hydrocodone	–	20 mg
Hydromorphone	1.5 mg	7.5 mg

Partial list adapted from APS 2003

Published oral morphine-to-oxycodone equianalgesic dose ratios range from 1-to-1 to 2.3-to-1, reflecting the differences in bioavailability and incomplete cross-tolerance. Practitioners should always take the patient's clinical status into account when determining whether a more conservative or more aggressive conversion is needed. Conversion factors published by the America Pain Society [2003] are a dependable resource (see excerpt in ***Table***). With long-duration opioids, some practitioners employ a more conservative conversion and use an immediate-release opioid for initial titration to optimal analgesia.

EXAMPLE OF DOSING CONVERSION

A patient has been taking controlled release (CR) morphine, 90 mg bid, for pain related to degenerative joint disease in his spine. He reports that he can no longer tolerate the nausea, despite using an antiemetic, so he will be switched to oxycodone. What would be the appropriate starting dose?

> Total daily dose of morphine = 180 mg.

> Conversion: 30 mg oral morphine = 20 mg oral oxycodone.

> # mg/day oxycodone / 180 mg/day morphine = 20 mg oxycodone / 30 mg morphine

> # mg/day oxycodone = 2/3 x 180 mg/day = 120 mg/day oxycodone

> Reduce by 1/3 due to incomplete cross-tolerance between opioids = 80 mg/day oxycodone

Since oxycodone is available in both long-acting and short-acting formulations, either of the following might be appropriate…

- oxycodone CR 40 mg PO bid, or…
- oxycodone CR 20 mg PO tid plus a short-acting oxycodone (or oxycodone/acetaminophen) product 5-10 mg q6h as needed

Note: *If the calculation results in a dose between 2 available dosage forms (eg, 30 mg, and either 20 mg or 40 mg tabs are available), choose the lower strength product and allow titration upward if the patient requires it. Many times, dosing titration is done with a short-acting agent for more precise adjustments.*

Special Considerations

Oxycodone Rx Special Considerations	
Kidney Disease	Start at 50% of the usual dose. Titrate cautiously. Avoid products containing ibuprofen. Avoid during hemodialysis.
Liver Disease	Start at 30%-50% of the usual dose. Titrate cautiously to avoid respiratory depression. Avoid products with acetaminophen.
Elderly Patients	Dosing adjustments not necessary unless the patient is debilitated.
Patients Taking CNS Depressants (eg, benzodiazepines)	Start with 30%-50% of the usual dose.

Renal Disease

Excretion of oxycodone is impaired with renal compromise [Poyhia et al. 1992]. In the presence of renal failure, the half-life is significantly prolonged for both the parent compound and metabolites (by more than 20 hours in one patient [Kirvela et al. 1996]). Some authors have recommended that oxycodone be used with caution in patients with renal dysfunction and avoided in those undergoing hemodialysis, as there is no data to support its safety in this situation [Dean, 2004]. A recent case report describes significant respiratory depression in a hemodialysis patient who received several doses of oxycodone-acetaminophen over several days [Foral et al. 2007] (see ***Table***).

Editor's Note: For a more complete discussion of opioid safety in patients with renal or hepatic dysfunction, see Johnson 2007 [listed in references with URL link].

Hepatic Disease

Clearance of oxycodone is impaired in the presence of liver disease, requiring a dose reduction. Patients with mild or moderate hepatic dysfunction exhibit accumulation of oxycodone: a 50% increase in peak blood levels and a 95% increase in overall blood concentrations (AUC). For the oxymorphone metabolite, liver disease results in a 30% lower peak blood level and 40% lower AUC (which is expected because metabolites are not being produced as efficiently) [OxyContin PI 2007].

Patients with cirrhosis exhibit a significant reduction in clearance of oxycodone, with a half-life of about 14 hours [Tallgren et al. 1997], which correlates with an increase in respiratory depression. Patients with severe hepatic impairment should be initiated at 30% to 50% of the usual dose and should be titrated cautiously to avoid respiratory depression [Lugo and Kern 2004] (see ***Table***).

Elderly Patients

No dosing adjustments are required in patients older than 65 years of age. The plasma concentration in these patients is about 15% greater than in younger patients, but no adverse clinical consequences have been noted [Coluzzi and Mattia, 2005]. However, debilitated elderly patients may require a dosage reduction (see ***Table***).

Drug Interactions

Start at 30% - 50% of the usual daily dose when used in combination with other CNS depressants

The most significant drug-drug interactions with oxycodone are the same as with most other opioids. The greatest of these is concurrent administration of other CNS depressants, such as alcohol, benzodiazepines, barbiturates, or other opioids, which increases the risk of respiratory depression. It is suggested that oxycodone should be started at 30% to 50% of the usual daily dose when used in combination with other CNS depressants [OxyContin PI, 2007] (see ***Table***).

The potential for hepatic enzymes to variably influence metabolism of oxycodone was discussed above and is unlikely to significantly affect oxycodone, even when using a strong 2D6 inhibitor like quinidine [Heiskanen et al. 1998]. There have been case reports of fluoxetine inhibiting the 2D6 enzymes [Otton et al. 1993], and patients taking cyclosporine also have been reported to be at risk for a drug interaction with oxycodone [Rosebraugh

et al. 2001], but neither of these has been reported widely in clinical practice. Serotonin syndrome during concurrent use of serotonergic agents and oxycodone has been reported [Karunatilake and Buckley 2006; Rosebraugh et al. 2001], possibly because opioids increase serotonin concentrations in the CNS, but this is not frequently observed in clinical practice.

Adverse Effects & Safety

The greatest risks when prescribing any opioids are overdose and, potentially, death. Prescribers take great care to avoid this; however, a recent report showed that the number of unintentional opioid-associated deaths in the US is growing. Mortality due to drug poisoning overall increased by roughly 68% between 1999 and 2004 [CDC 2007], and this trend has been linked to increasing numbers of deaths associated with prescription opioid analgesics [Paulozzi et al. 2006]. Despite this, there is a need to treat pain effectively with adequate doses of potent analgesics, including oxycodone.

Even when opioids are used appropriately for pain management by educated healthcare providers, there are inevitable adverse effects in a proportion of patients. Respiratory depression is obviously a concern, but is less likely to occur than some of the other common adverse effects; furthermore, its likelihood diminishes with continued use due to tolerance, as long as doses are not increased excessively or other CNS depressants added.

Oxycodone may cause constipation, nausea, and sedation, like all opioids; although some authors report that it is less likely to cause hallucinations, nausea, or itching than morphine [Kalso and Vainio 1990; Mucci-LoRusso et al. 1998]. Opioids also are associated with histamine-related side effects like itching, flushing, and rash; however, oxycodone's semisynthetic chemistry incurs less histamine release (compared with natural opioids like morphine and codeine) and is usually better tolerated. The ***Table*** lists common adverse effects with oxycodone.

Common Oxycodone Adverse Effects
(% of Patients Affected)

Constipation	26%
Nausea	27%
Somnolence	24%
Dizziness	16%
Vomiting	14%
Pruritus	12%
Headache	8%
Dry mouth	7%
Asthenia	7%
Sweating	6%

Source: OxyContin PI 2007

Oxycodone's adverse effects are associated with blood levels of the drug; therefore, *a dose reduction may alleviate or reduce the severity of CNS effects such as sedation, dizziness, and respiratory depression.* If a reduction is not feasible due to a patient's escalating pain (eg, a patient with cancer), an opioid rotation may be a reasonable option.

For some of the common adverse effects, such as sedation and nausea, patients develop tolerance with continued use. For adverse effects that do not subside with continued use, concurrent pharmacotherapy may be given to reduce severity or prevent symptoms, such as a bowel regimen for constipation [see Goodheart and Leavitt 2006]. Other effects, such as sweating, are not predictable, preventable, or treatable. If these symptoms become intolerable, an opioid rotation may be necessary.

One of the concerns with opioids shared by patients, healthcare providers, and employers is the extent of cognitive impairment caused by these agents. Patients may ask if they should refrain from driving while taking oxycodone. Several investigators have evaluated the effect of opioids on cognitive and psychomotor function with inconclusive results. Hanks et al [1995] found that single doses of immediate-release morphine caused some difficulty with memory retrieval, but was not as significant as that seen with lorazepam. Drowsiness and cognitive dysfunction may be predicted early in therapy or with dose increases, but with chronic use of opioids, tolerance to these effects develops and they theoretically would not cause impairment. Caution should always

Author's Comment: To date, opioids have not been shown to specifically affect driving ability with chronic use. However, patients should be very cautious about operating any motor vehicle until they feel that they will not be too sedated to drive. This is particularly important following initiation of therapy or a dose increase, when blood levels are not at steady state.

be exercised when using opioids and patients should not attempt to drive or operate heavy machinery until they know how they respond to the medication.

Another risk of long-term opioid therapy is the suppression of gonadotropin hormones, including testosterone, leuteinizing hormone, estradiol, and progesterone. This may lead to sexual dysfunction, osteopenia, and osteoporosis [Abs et al 2000; Daniell 2002]. This has been reported with several opioids, although no studies have specifically examined oxycodone. The adverse sequelae are related to degree and duration of gonadotropin suppression. Treatment usually includes hormone replacement therapy and osteoporosis medications where appropriate.

Opioid-induced hyperalgesia is another phenomenon that is a concern with opioid use [Chang et al. 2007]. This presents clinically as an increase in pain with opioid administration or dose increase. Sometimes it is difficult to determine whether a patient is exhibiting opioid tolerance or hyperalgesia. If tolerance is occurring, an opioid dose increase should produce an increase in analgesia. If this does not occur, or if pain increases, hyperalgesia may be a factor.

If tolerance is occurring, an opioid dose increase should produce an increase in analgesia. If this does not occur, or if pain increases, hyperalgesia may be a factor.

Physiologic tolerance and dependence (*not* addiction) are expected consequences with long-term use of oxycodone, or any opioid. These should be managed on an individualized basis and handled with either slow titration for dose increases or gradual dose reductions during tapering to prevent withdrawal symptoms.

Psychological dependence, or addiction, cannot always be predicted. Very few patients taking opioids continuously for pain will exhibit addictive behavior; however, patients with a history of substance addiction or active addiction to other drugs or alcohol are at risk for addiction with oxycodone as well. (See Joint Statement… [1996] for definitions of tolerance, dependence, addiction, and pseudoaddiction.)

It must be recognized that there is an overlap of patients who have opioid addiction and those who have legitimate pain. Such patients may require aggressive pain relief measures, but opioid therapy must be handled judiciously, ideally involving experts in pain management and in addiction medicine.

Oxycodone Prescribing Decisions: FAQs

In deciding on an appropriate opioid analgesic for patients with acute or chronic pain, a number of questions arise. To the extent possible, decisions should be based on available evidence, as noted in the following FAQs (Frequently Asked Questions… and answers).

Is oxycodone as effective as other opioids?

Pain management usually must be individualized to patient needs, especially when using opioids. Different factors determine a patient's response to a particular agent, including genetics, opioid receptor sensitivity in the central nervous system, and tolerability of a particular agent. Semisynthetic opioids, like oxycodone, tend to be tolerated better than the natural opioids, like morphine and codeine. The semisynthetics cause less histamine release than the natural opioids, and, therefore, produce less vasodilation, flushing, itching, and/or rash. Many times patients who report an opioid allergy actually are experiencing symptoms occurring due to histamine release.

Patients who do not tolerate natural opioids, like morphine or codeine, may do well with oxycodone.

Semisynthetic opioids like oxycodone also tend to be less constipating, although this is highly dependent on the patient. Therefore, patients who do not tolerate natural opioids may do very well with oxycodone.

In terms of analgesic effectiveness, several investigators have found that oxycodone CR is equivalent to morphine CR [Rischitelli and Karbowicz 2002]. This has been noted in several studies in the cancer population [Bruera et al. 1998; Heiskanen et al. 2000; Mucci-LoRusso et al. 1998]. However, one study showed that patients consumed significantly more rescue doses and average pain intensities were significantly greater with oxycodone CR [Heiskanen and Kalso 1997]. At the same time, more patients had vomiting with morphine and more patients experienced constipation with oxycodone.

Heiskanen et al [2000] and Mucci-LoRusso et al [1998] found less fluctuation in blood levels when using oxycodone CR, compared with morphine CR. However, Nicholson et al [2006] concluded that oxycodone CR may need to be administered 3 or 4 times daily, which could be a disadvantage.

In noncancer pain, morphine CR was found to be equivalent to oxycodone CR in terms of pain reduction, sleep quality, and most other quality of life scores. However, only the morphine product achieved a clinically meaningful reduction in pain (difference of 2 or more points on a 0 to 10 Likert scale) at 8 and at 24 weeks [Nicholson et al 2006].

Author's Note – because of its safety issues, expense, and need for multiple daily doses in some patients, oxycodone CR is considered a 3rd line agent for chronic pain.

Morphine CR is generally chosen as the first-line long-duration opioid because of its familiarity and safety, compared with methadone, and due to its lower cost and lower risk of diversion and abuse, compared with oxycodone CR. If patients do not tolerate morphine and prescribers are not comfortable prescribing methadone, oxycodone CR is a reasonable third-choice option [VA Criteria 2003].

As for immediate-release oxycodone products, they are comparable to their hydrocodone counterparts for acute pain management [Marco et al. 2005]. Oxycodone IR formulations do not show any particular advantage or disadvantage compared with other short-acting opioids. Therefore choosing an agent is based on nonpharmacologic factors, such as cost, insurance coverage, and nonopioid components, if applicable. Use of a particular short-acting agent also is generally influenced by prescriber preference and patient response.

When should an immediate-release (IR) oxycodone be used?

Oxycodone IR is very effective for use in acute pain and for titration in chronic therapy.

Oxycodone IR is very effective for use in acute pain and for titration in chronic therapy. It is commonly given for acute pain in the post-operative setting [Fricke et al. 2002; Gammaitoni et al. 2003]. Short-acting oxycodone products also are used in the emergency department and the outpatient clinic after an acute injury such as back pain [Palangio et al. 2002] or bone fracture [Marco et al. 2005].

In cancer pain, it is common to use short-acting agents for "breakthrough" pain, in addition to a long-duration agent for "baseline" analgesia. Short-acting agents also help patients titrate gradually to the next higher strength of a long-duration agent. Particularly in the setting of hospice care, there is a need to provide analgesia with a fast onset of pain relief, and oxycodone provides pain relief onset within 15 minutes.

For chronic noncancer pain the use of short-acting opioids is a bit more controversial. Some practitioners believe only long-duration opioids should be used for chronic pain so that the patient is not focused on the clock in anticipation of the next dose. Others believe that short-acting opioids can and should be used, either as a scheduled regimen (eg, 1 dose 4 times daily) or on an "as needed" (prn) basis (eg, 1 dose every 4-6 hours prn) for acute flares in chronic pain. Since there is no difference in analgesic effect between short-acting and long-acting oxycodone [Kaplan et al. 1998], providers must weigh the risks and benefits for each patient and situation and decide what is in the patient's best interest.

There are certainly situations when a short-acting opioid is advantageous. An example of this would be an elderly patient with osteoarthritis who has reached the point of needing an opioid to maintain daily activities. The short half-life of IR agents may prevent cognitive difficulties potentially experienced when serum levels remain elevated with long-duration agents.

Short-acting opioids may cause fewer cognitive difficulties in elderly patients than long-acting agents.

Is a combination product or "plain" oxycodone preferred?

There is an enhanced analgesic effect when opioids are used in conjunction with an NSAID or acetaminophen. Therefore, using combination products may confer better pain relief along with patient convenience and increased compliance; that is, patients may take one combination tablet instead of 2 separate medications.

For the patient with osteoarthritis mentioned above, the combination product may be a good choice. Acetaminophen is regarded as first line therapy for osteoarthritis, so it is convenient to use a combination product that allows the nonopioid to be given with each dose of oxycodone. The doses still must be taken frequently throughout the day (usually every 6 hours on either a scheduled or prn basis); however, in elderly patients, this may be an advantage, as mentioned above.

Combination products must be used with caution, and doses of these products are limited by their nonopioid ingredients.

The combination products must be used with caution, and their dosing is limited by the nonopioid ingredients. Opioids and NSAIDs are used in combination frequently, as NSAIDs are also considered first-line therapy for both rheumatoid arthritis and osteoarthritis, as well as any type of inflammatory pain. While this is a very effective combination, one must also take into consideration the risks associated with either short-term or long-term NSAID therapy, specifically the risks of GI bleeding, platelet dysfunction, acute renal failure, and possibly respiratory or cardiovascular events [FDA NSAIDs 2007]. Risks of GI bleeding and platelet dysfunction have historically limited the use of aspirin-containing products.

With the introduction of the acetaminophen/oxycodone combinations and the recommendations of acetaminophen as a first-line therapy for osteoarthritis, aspirin for analgesic use has fallen out of favor. However, the recommended maximum daily dose of acetaminophen is 4000 mg or less to avoid liver toxicity. For example, a patient may take up to 12 tablets daily of a product that contains 325 mg of acetaminophen, but only 8 tablets of a product that contains 500 mg. The combination oxycodone/ibuprofen product is restricted to use in the acute pain setting and has a maximum recommended dose of 4 tablets daily for a 7 day course of therapy [Combunox® PI 2004].

When using an oxycodone-acetaminophen combination product, monitor the total daily dose of acetaminophen. Daily doses greater than 4000 mg can be hepatotoxic.

Use of "plain," single-agent, oxycodone may be beneficial for patients who have liver disease or have risk factors for liver disease (such as avoiding acetaminophen in patients who drink alcohol). It also may be beneficial in patients who have significant comorbidities, such as diabetes, renal insufficiency, coronary artery disease, or congestive heart failure (to avoid ibuprofen). Single-agent oxycodone may also be more beneficial than the combination products if a patient requires frequent changes in therapy. Giving the oxycodone and the nonopioid agent separately allows more freedom to individualize therapy, such as exchanging acetaminophen for an NSAID (or conversely) without altering the opioid component.

When should the CR (long-duration) oxycodone be used?

Oxycodone CR is intended for use in patients with moderate to severe pain who require around-the-clock pain control on a long-term basis. It is not intended for intermittent administration, nor is it indicated for the acute postoperative setting unless the patient has been taking it preoperatively. In equivalent daily dosing, oxycodone CR is considered to be bioequivalent to the immediate-release formulation [Mandema et al. 1996; Reder et al. 1996; Stambaugh et al. 2001].

Oxycodone IR and CR are bioequivalent in effectiveness: 5 mg IR qid = 10 mg CR bid.

During long-term use, as with all long-acting analgesics, oxycodone CR offers increased compliance, as the patient is required to take fewer doses throughout the day. The CR formulation also removes the need for "clock watching" and the anxiety about taking doses at the right time to prevent an increase in pain.

Oxycodone CR has been demonstrated as effective in chronic painful conditions, such as painful diabetic neuropathy [Watson et al. 2003], chronic back pain [Hale et al. 1999], osteoarthritis [Caldwell et al. 1999; Roth et al. 2000], and cancer pain [Kaplan et al. 1998]. Recommended dosing for oxycodone CR is 1 dose every 12 hours; however, in research studies [Nicholson et al. 2006], as well as in clinical practice, it is not uncommon for patients to require administration 3 to 4 times per day, which decreases the compliance advantage of a long-duration formulation.

An important caution about the use of oxycodone CR products is that the tablets must be swallowed whole. If they are crushed, split, or otherwise altered, the medication-release mechanism is destroyed and may cause a large bolus dose to be delivered, possibly causing overdose and death. Hence, patients who might misuse the drug or have difficulty swallowing tablets are not good candidates for this product.

Oxycodone CR tablets must be swallowed whole. Any alteration of the tablet may be hazardous.

Altering the dosage form has caused oxycodone CR to become a widespread drug of abuse. Because of cost and concerns about diversion and abuse, several government agencies (eg, public-aid programs) have removed oxycodone CR from their "preferred" lists of medications [eg, Preferred Drug List… 2007]. In this regard, the US Veterans Administration has published a guidance paper outlining criteria for the safe use of oxycodone CR [VA Criteria 2003]. This document contains evidence-based information about the drug, as well as cost comparison and equianalgesic dosing tables.

Is oxycodone CR a better choice than oxycodone IR?

Several authors have compared the analgesic effectiveness of long-acting with short-acting oxycodone agents and found that they are equally effective [Caldwell et al. 1999; Hale et al. 1999; Kaplan et al. 1998; Parris et al. 1998]. Rischitelli and Karbowicz [2002] did an extensive literature review and also concluded that the immediate-release and controlled-release products were analgesically equivalent.

Long-acting and short-acting oxycodone are equivalent in terms of analgesic effectiveness.

Furthermore, the two formulations also were comparable in adverse effects, although some studies have reported fewer adverse effects with the controlled-release formulation [Kaplan et al. 1998; Caldwell et al. 1999]. There is a potential advantage with the controlled-release agent if it can be dosed only twice daily; however, if it must be taken 3 to 4 times daily, the immediate-release product is a more cost-effective choice, with or without a nonopioid component in combination.

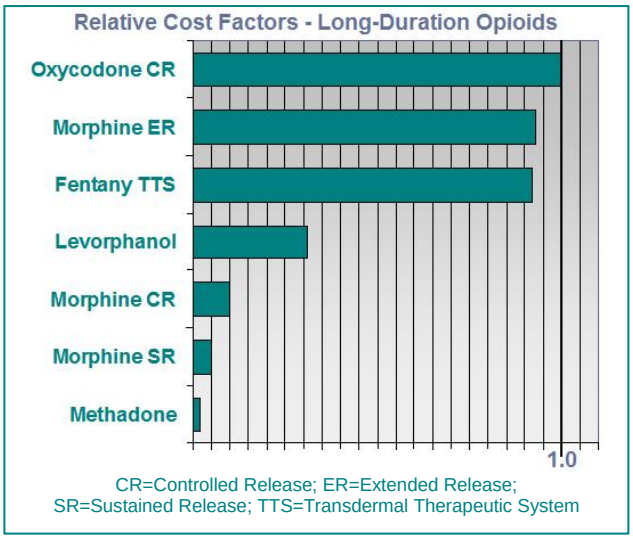
Can oxycodone products be used safely in children?

Oxycodone has not been studied in patients under age 18, and the FDA has not approved it for pediatric use. Although some sources offer dosing suggestions in pediatric patients [Bonica 2001], the use of oxycodone is not currently considered a standard therapy for analgesia in chil-

dren. Furthermore, young children present a challenge in that they may be unwilling or unable to swallow oral tablets.

How does oxycodone CR compare in cost with other long-duration opioids?

Cost is frequently a factor when choosing analgesic therapy, and monthly costs of long-duration opioids can vary considerably, depending on how calculations are done. Using actual doses of different opioids required for achieving comparably adequate analgesia would be best in determining cost differentials.



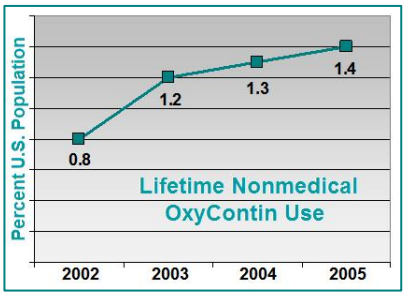
The ***Table*** depicts relative costs of long-duration opioids compared with oxycodone CR (baseline factor of 1.0) calculated by the US Veterans Administration [VA 2003], using manufacturer-recommended initial dosing and equianalgesic dose conversion ratios recommended by the American Pain Society [APS 2003]. Drug prices were based on lowest available costs of products in the VA formulary as of June 2003; however, current product availability (including generics) and pricing for individual purchasing organizations may vary.

According to the VA analysis, oxycodone CR was a relatively premium-priced choice for long-duration opioid analgesia, more expensive than morphine CR by a factor of about 10. The least expensive agent was methadone. The VA and others [Rischitelli and Karbowicz 2002] concluded that, due to similar efficacy, comparable adverse effects, and substantial cost savings, morphine CR or SR might be a preferred choice, and methadone secondarily. Oxycodone CR would be reserved for patients having intolerable adverse effects from morphine or methadone that prevent adequate titration for desired analgesia.

Oxycodone Risk Management: FAQs

How extensive is the problem of oxycodone abuse?

Abuse and misuse of prescription opioid analgesics is not new. It is hardly surprising that, with the dawn of the "Decade of Pain Control and Research" in 2001, there would be greater use of opioid analgesics and, consequently, greater abuse of this therapy as well. Abuse of oxycodone was noted as early as the 1960's when it was placed on the DEA's Schedule II drug list, and reports of abuse increased substantially when the long-acting formulation (OxyContin) was introduced in 1996.



More recently, the FDA strengthened warnings of potential OxyContin diversion and abuse [FDA 2006], and trends in US national survey data portray the scope of the problem. Lifetime nonmedical use of OxyContin has been steadily increasing (see ***Graph***), reaching more than 3 million persons in the US age 12 and older in 2005, according to the government's National Survey on Drug Use and Health (NSDUH) [SAMHSA 2006].

The Drug Abuse Warning Network [SAMHSA 2007] reported that in 2005 (the most recent data available), drug abuse-related emergency department visits involving opioid analgesics rose 21% from 2004 to 2005. This is significant because the number of visits related to abuse of illicit drugs or alcohol was stable during this time. In 2005 alone, there were nearly 43,000

emergency department visits related to the nonmedical use of oxycodone products, exceeded only by incidents involving the misuse of hydrocodone products.

Why has OxyContin® been so widely abused?

Oxycodone CR products offer a relatively large dose of opioid, providing greater euphoria or other desired reinforcing effects.

Oxycodone CR products offer a relatively large dose of drug per tablet, providing greater euphoria or other desired reinforcing effects. Whereas, a typical immediate-release oxycodone product may have only 5 mg to 10 mg of oxycodone per tablet, a long-acting formulation contains up to 160 mg in each tablet, and altering the dosage form leads to rapid release of the total dose. Those who abuse the drug usually do so by crushing the tablet and snorting or chewing it, or dissolving it in water for intravenous injection [SAMHSA 2006]. Unfortunately, some of those people have low opioid tolerance and/or may mix the drug with alcohol or other drugs, like benzodiazepines, resulting in overdose and/or death.

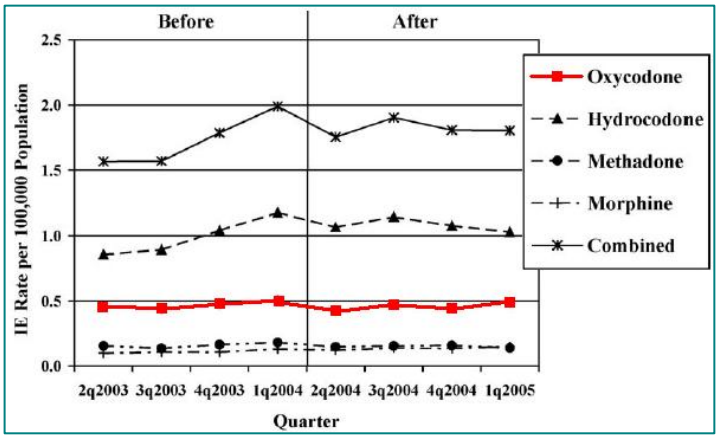
One reason the OxyContin brand product, in particular, has been so widely diverted for abuse is that selling it "on the street" is profitable. According to government estimates, the drug can garner upwards of $1-per-milligram via illicit trafficking [SAMHSA 2006].

It also came to light that the manufacturer of OxyContin had falsely and aggressively promoted the product as producing less euphoria and being less addictive than other opioids, and as capable of abrupt discontinuation without patients suffering withdrawal symptoms. In May 2007, the manufacturer agreed to pay more than $600 million in fines to resolve criminal charges and civil liabilities in connection with those deceptive practices [FDA News 2007].

Meanwhile, since OxyContin had been erroneously portrayed and perceived as a safer opioid alternative, it may have been over-prescribed as a first-line choice by well-meaning healthcare providers, rather than a third-line option as recommended by guidelines [eg, VA 2003]. And, it might have been inadvertently prescribed for patients most at risk for abusing an opioid medication. With greatly increasing amounts of OxyContin in circulation, often in the "wrong" hands, there was likely to be more abuse and associated overdoses or deaths. Expectedly, more prudent prescribing practices, and appropriate efforts to better manage the risks (discussed below), will significantly curtail the trend of oxycodone abuses and overdoses.

Does *generic* oxycodone CR have the same risks of abuse and diversion?

When a generic oxycodone CR was approved by the FDA in 2004, there was concern that a less expensive version of OxyContin would spark a significant increase in prescribing and subsequent abuse and misuse of this drug. Bailey et al [2006] found no increase in rates of oxycodone CR abuse (IE rate, see ***Graph***) in the year following release of the generic product, compared with the quarter prior to its release. There was no way to distinguish if the branded or generic oxycodone was involved in specific cases recorded; however, overall, there was *no increase* in rates of oxycodone abuse. Interestingly, the same trend was found for the other opioids investigated: hydrocodone, methadone, and morphine.



Author's Note: Anecdotally, it has been observed that generic versions of popularly abused opioids usually are less appealing; persons buying drugs for illicit purposes prefer brand names

because they are more recognizable and the generics have a lower value "on the street," which also makes them less alluring for drug dealers.

How can healthcare providers minimize oxycodone misuse/abuse?

There is no evidence that oxycodone, compared with other opioid analgesics, is any more or any less prone to causing addiction – *IF* it is properly prescribed – and most people who take oxycodone for pain relief do not become addicted to it. However, like all opioids, it can produce physiologic dependence, whether used for pain or illicit purposes.

Most people who take oxycodone do not become addicted to the medication.

In general, a key to any risk management strategy is determining the individual risks of using an opioid as compared with the benefits. The first step is to evaluate the patient, which includes a thorough history-taking and physical examination as well as reviewing the patient's previously recorded medical history and any prior medical assessments. Treatment plans should be developed with the patient's (and any caregiver's) input and commitment, so that all involved persons understand the recommended therapies and expectations.

If an opioid trial is initiated, periodic reassessment must be done, documenting efficacy and any adverse effects. After each assessment, a decision must be made to either continue the same course of therapy or alter that course. Again expectations must be explained to all parties involved, reassessed, and adjusted if necessary.

Principles of Good Medical Practice

- Evaluate the patient.
- Develop and follow a comprehensive treatment plan.
- Consult specialists as needed.
- Review efficacy of treatment periodically.
- Document therapeutic response.

Source: Joint Statement… 1996.

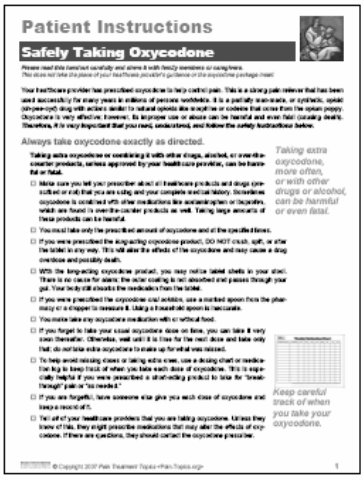
It is essential to document all of the above as part of the ongoing treatment plan. The American Academy of Pain Medicine and the American Pain Society published a brief list summarizing principles of good medical practice that can be applied to all aspects of medical care, including opioids in pain management (see ***Table***).

More specific guidance for assessing, anticipating, and managing individual patient risks for oxycodone misuse or abuse is an important and complex subject, beyond the scope of this paper. A number of excellent resources for healthcare providers in this regard are available for free access at the *Pain Treatment Topics* website, in the "Opioid Rx" tab section.

To view the resources, go to...

http://www.pain-topics.org/opioid_rx/risk.php

The other essential element in managing risk hinges on patients (and their caregivers) accepting responsibility for following the agreed upon treatment plan and complying with using oxycodone safely. To facilitate that, and to help prevent misuse and avoidable adverse events potentially associated with oxycodone, patients and their caregivers need proper instructions. A 2-page patient instructions handout – *Safely Taking Oxycodone* – is available in English and Spanish from *Pain Treatment Topics* and may be freely duplicated for distribution.


Patient Instructions

Safely Taking Oxycodone

Always take oxycodone exactly as directed.

The handouts can be downloaded at…

http://www.pain-topics.org/pdf/OxycodoneHandout.pdf

Summary

Oxycodone is a versatile oral opioid that is effective in treating many types of cancer and noncancer pain. Dosage forms are flexible and easily interchangeable. It is not subject to significant alterations in pharmacokinetics, but dosing must be adjusted for hepatic and renal dysfunction, and it should be avoided in patients receiving hemodialysis. There are very few pharmacokinetic oxycodone-drug interactions, although caution regarding additive effects should be used when administering any other CNS depressants. Side effects reported with oxycodone are predictable and similar to other opioids, although oxycodone may be better tolerated than morphine in some patients. Its ultimate role depends on patient response, prescriber comfort in using the agent, and relative cost considerations. Concerns about diversion, misuse, and abuse of oxycodone are justified, but with appropriate risk management and patient education, it remains a useful analgesic option in the practice of pain management.

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All URL links listed below were valid at the time of posting; however, the Internet is constantly changing and some linked documents may be moved or inactivated with time.

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EXHIBIT 101

The Intercept_

DONALD TRUMP'S PICK TO OVERSEE BIG PHARMA IS ADDICTED TO OPIOID-INDUSTRY CASH

Lee Fang

April 4 2017, 2:15 p.m.

Photo: John Moore/Getty Images

Newly-released financial disclosure documents show that Dr. Scott Gottlieb, President Trump's nominee to lead the Food and Drug Administration, has received significant payments from the opioid industry — while attacking attempts to deter the explosion of opioid pill mills.

The FDA has some of the most significant authority in the federal government to oversee manufacturers of prescription painkillers. Gottlieb is set to appear for his confirmation hearing before the Senate Health, Education, Labor, and Pensions Committee at 10 a.m. tomorrow.

Gottlieb's disclosure statements, required under federal law, show that since the beginning of 2016 he has received almost $45,000 in speaking fees from firms involved in the manufacture and distribution of opioids.

"Our country is in desperate need of an FDA commissioner who will take on the opioid lobby, not one who has a track record of working for it," said Dr. Andrew Kolodny, the co-director of Opioid Policy Research at Brandeis University, reacting to this information.

Mallinckrodt Pharmaceuticals, the maker of a highly addictive generic oxycodone pill, paid Gottlieb $22,500 for a speech in London last November shortly after the U.S. presidential election. Prosecutors have charged that the firm ignored red flags and supplied as many as 500 million suspicious orders in Florida for its oxycodone product

between 2008 and 2012. Mallinckrodt reached a tentative settlement this week, agreeing to pay $35 million while admitting no wrongdoing.

The Healthcare Distributors Alliance, a trade group for the largest opioid wholesale distributors in America, also retained Gottlieb as a speaker last September.

Dr. Scott Gottlieb, left, on Capitol Hill in 2009. Photo: Harry Hamburg/AP

Among the distributors represented on the HDA executive committee are AmerisourceBergen Drug Corp., McKesson Corporation and Cardinal Health. Cardinal's CEO, Jon Giacomin, is chairman of HDA.

A 2016 investigation by the Charleston Gazette-Mail found that these three companies supplied unusually large shipments of prescription painkillers in West Virginia, and provided the bulk of 780 million prescription pills sent to pharmacies in the state, a key factor in the fatal overdose epidemic.
Cardinal Health also temporarily lost its license to distribute opioids from its Florida warehouse in 2012 after the Drug Enforcement Administration found that the firm supplied several pharmacies known to act as so-called pill mills that routinely filled inappropriate prescriptions for oxycodone.

Gottlieb swiftly condemned the DEA's action at the time, writing in the Wall Street Journal that the agency had overstepped its bounds, and that it should lose its authority to police the opioid market.

Gottlieb argued that the DEA should not treat corporate pharmaceutical firms like street drug dealers. "So Cardinal isn't a Colombian drug ring. Its CEO isn't Pablo Escobar. Like other large distributors, Cardinal has invested heavily in systems to track unusual narcotics-sales patterns," said Gottlieb.

Gottlieb was also paid as a speaker by Johnson & Johnson, which owns a subsidiary that produces the opioid painkiller Nucynta, in January of last year. The federal drug payment disclosure database shows that Gottlieb received payments from Pfizer, the manufacturer of several opioid products, in 2015.

On a call with reporters on Tuesday, Sens. Ed. Markey, D-Mass., and Sherrod Brown, D-Ohio, announced their opposition to Gottlieb's nomination, citing his opioid industry ties.

"People die because of the opioid epidemic," said Brown. "We need all hands on deck to fight this crisis, including and especially the FDA. Unfortunately Dr. Gottlieb's record indicates that as commissioner he wouldn't take the epidemic and the FDA's authority to rein in prescription painkillers and other drugs seriously enough."

Markey, who opposed President Barack Obama's last FDA commissioner, Dr. Robert Califf, on grounds that the agency was moving too fast to approve dangerous new prescription painkillers, voiced similar concerns over Trump's nominee.

"Dr. Gottlieb has also said he wants the FDA approval process to move faster, and that FDA has too high of a standard for safety. I strongly disagree with that," said Markey during the call.

The opioid crisis claims more than 16,000 lives from overdose deaths every year. The crisis stems in large part to the over-prescribing phenomenon, which has been fueled by deceptive marketing practices and efforts by industry to court doctors. As we've reported, Americans consume about 81 percent of the global supply of oxycodone products (the active ingredient in OxyContin) and almost 100 percent of hydrocodone (the active ingredient used in brands such as Vicodin).

The painkiller crisis is closely linked to heroin addiction, with many heroin users embracing the drug after first using opioids that were prescribed to them.

Gottlieb's financial disclosure form further shows that he made more than $3 million throughout 2016 and the first three months of this year, through a combination of speaking fees, consulting arrangements with drug companies in general, board memberships, and his work at several healthcare-focused investment firms. Gottlieb is well-known as a critic of the FDA approval process and regulations, and has called for revamping agency rules to bring new drugs to market. In sharp contrast to Trump's rhetoric on the campaign trail, Gottlieb has also criticized a range of proposals to bring down drug costs through government intervention in the market.

Top photo: Oxycodone pain pills prescribed for a patient with chronic pain lie on display on March 23, 2016, in Norwich, Conn.

RELATED

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Makers of OxyContin Bankroll Efforts to Undermine Prescription Painkiller Reform

EXHIBIT 102

The Washington Post

The government's struggle to hold opioid manufacturers accountable

Sixty-six percent of all oxycodone sold in Florida came from this company. But the DEA's case against it faltered.

Mallinckrodt's blue 30-milligram oxycodone tablets became so popular among drug users and dealers that they acquired a street name — "M's," for the company's distinctive block-letter logo. (Illustration by Peter and Maria Hoey for The Washington Post)

By Lenny Bernstein and Scott Higham
April 2, 2017

To combat an escalating opioid epidemic, the Drug Enforcement Administration trained its sights in 2011 on Mallinckrodt Pharmaceuticals, one of the nation's largest

manufacturers of the highly addictive generic painkiller oxycodone.

It was the first time the DEA had targeted a manufacturer of opioids for alleged violations of laws designed to prevent diversion of legal narcotics to the black market. And it would become the largest prescription-drug case the agency has pursued.

Ultimately, the DEA and federal prosecutors would contend that the company ignored its responsibility to report suspicious orders as 500 million of its pills ended up in Florida between 2008 and 2012 — 66 percent of all oxycodone sold in the state. Government investigators alleged in internal documents that the company's lack of due diligence could have resulted in nearly 44,000 federal violations and exposed it to $2.3 billion in fines, according to confidential government records and emails obtained by The Washington Post.

But six years later, after four investigations that spanned five states, the government has taken no legal action against Mallinckrodt. Instead, the company has reached a tentative settlement with federal prosecutors, according to sources familiar with the discussions. Under the proposal, which remains confidential, Mallinckrodt would agree to pay a $35 million fine and admit no wrongdoing.

"Mallinckrodt's response was that 'everyone knew what was going on in Florida but they had no duty to report it,' " according to an internal summary of the case prepared by federal prosecutors and obtained by The Post.

The case shows how difficult it is for the government to hold a drug manufacturer responsible for the damage done by its product. DEA investigators appalled by rising overdose deaths said they worked for years to build the biggest case of their careers only to watch it falter on uncertain legal territory and in the face of stiff resistance from the company.

"They just weren't taking this seriously, and people were dying," said a former law enforcement official who spoke on the condition of anonymity because the case is pending. "People were dying all over the place. It wasn't their kids, their wives, their husbands, their brothers. It was some hillbilly in Central Florida, so who cares?"

In a statement, a Mallinckrodt spokesman said the company has worked hard to fight drug diversion.

"Mallinckrodt has long been a recognized leader in developing and sharing best practices related to the prevention of opioid diversion and misuse, and has continuously invested significant resources to address this serious drug epidemic," the statement said. "We are proud of the programs and initiatives we've developed to ensure

appropriate use of pain medication and, most importantly, to deter such medications from ending up in the wrong hands."

Officials at the DEA declined to comment for this article. The U.S. attorney's office in Detroit, which is handling the case, issued a statement. "Our office works diligently to use all the legal tools available to us to hold corporations responsible for their actions," acting U.S. attorney Daniel Lemisch said. "This is particularly true in a highly regulated industry such as the manufacture of opioids. As this case is still in settlement negotiations, we cannot comment on the specifics of the matter."

THE PATH OF A PAIN PILL

Manufacturers

The oxycodone pill's journey begins at Mallinckrodt Pharmaceuticals. The tablet is created and packaged in a facility in Hobart, N.Y.

Distributors

Mallinckrodt sends the pills to a network of distributors like Sunrise Wholesale and KeySource Medical. The distributors then supply the drugs to retailers.

Retailers

Pharmacies and hospitals dispense oxycodone to patients with a prescription from a doctor. Some retailers have been accused of illegally diverting these drugs.

Patient

When patients pay in cash or receive an unusually high volume of oxycodone, that

can be an indication of abuse or diversion of the pills to the black market.

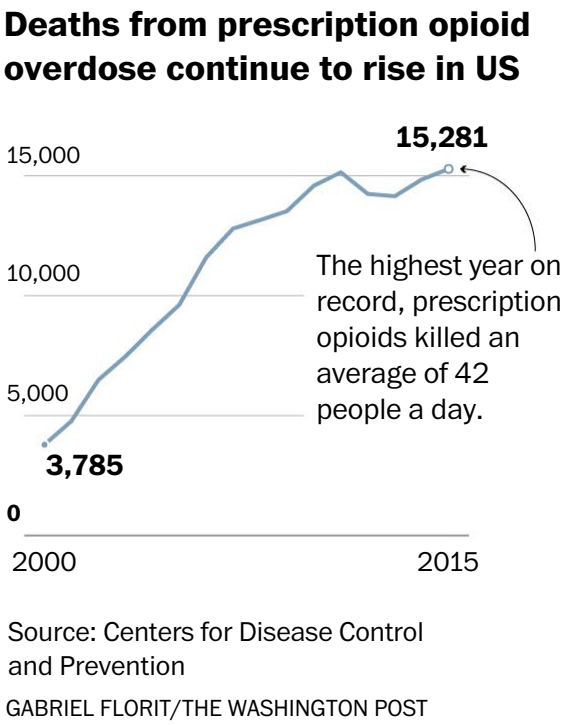
Sources: Centers for Disease Control and Prevention | Drug Enforcement Administration
ILLUSTRATIONS BY PETER AND MARIA HOEY FOR THE WASHINGTON POST

Under federal law and DEA policy, pharmaceutical companies such as Mallinckrodt are required to "know their customers" and monitor the pattern, frequency and amounts of drug orders. When suspicious orders occur, companies must immediately notify the agency or risk losing their DEA licenses to sell or manufacture controlled substances, as well as face civil and criminal penalties.

According to the documents and sources familiar with the settlement talks, Mallinckrodt was willing to acknowledge its responsibility to report suspiciously large orders placed by its customers, a network of wholesale distributors. But the company said that it should not be held responsible for what happens to its drugs once the distributors send them to their customers, such as doctors and pharmacies. Mallinckrodt contended that the DEA has never required manufacturers to know their customers' customers and that the agency provided the company with conflicting advice about its responsibilities under the law.

"Mallinckrodt took unprecedented steps beyond the legal obligations of a manufacturer. Mallinckrodt began monitoring downstream sales between wholesalers and pharmacies, and proactively informed both its customers and the DEA of its findings," said Brien T. O'Connor, a lawyer for the company. "The company continues to enhance its anti-diversion programs to this day."

The proposed $35 million settlement comes as the nation's prescription opioid epidemic continues to worsen, with nearly 180,000 lives lost to overdoses since 2000.



Source: Centers for Disease Control and Prevention

GABRIEL FLORIT/THE WASHINGTON POST

The Post reported in October that the DEA's civil and administrative enforcement efforts against the mammoth wholesale distributors that deliver painkillers to pharmacies stalled in the face of a stepped-up lobbying campaign by the drug industry.

The Mallinckrodt case was something different: an aggressive attempt to hold a drug manufacturer accountable.

Mallinckrodt was founded 150 years ago in St. Louis and became the leading supplier of chemicals for the emerging photography industry. Now based in the United Kingdom after corporate acquisitions, Mallinckrodt is one of the nation's largest manufacturers of oxycodone, a powerful opioid made from the natural painkiller found in poppies.

"When you get to the manufacturing level, it's hard to prove that they knew what was happening," another law enforcement official familiar with the investigation said.

"But they were making the product, they were selling it to the country's largest distributors, and they had a responsibility under the law to detect and report orders that were suspicious. These orders were beyond suspicious."

The DEA and federal prosecutors contended that Mallinckrodt manufactured 500 million pills that ended up in Florida between 2008 and 2012 — 66 percent of all oxycodone sold in the state.

THE INVESTIGATION BEGINS

The first hint that Mallinckrodt might pose a problem for the DEA came not from Florida but from Tennessee.

On July 7, 2009, members of a Tennessee drug task force in a sting operation seized several 100-tablet bottles of Mallinckrodt-made oxycodone. Task force agents alerted Mallinckrodt. The company's lot numbers were printed on the labels, allowing for easy tracking of the pills.

Three days later, Mallinckrodt responded that the oxycodone had been prescribed by Barry Schultz, a doctor who ran a medical clinic in Delray Beach, Fla. The company said that one of its distributors, Sunrise Wholesale of Broward County, Fla., had sent 20,400 tablets of oxycodone to Schultz in the previous year.

The Florida Department of Health had just issued an administrative complaint against Schultz for prescribing oxycodone outside "the course of his professional practice."

His medical office had become a thoroughfare for those seeking easy access to drugs, records show.

On July 27, a Mallinckrodt security director told DEA Supervisor Paul "Pete" Kleissle in St. Louis about the Tennessee connection. Kleissle recommended that Mallinckrodt conduct an audit of Sunrise and the company agreed, government documents show.

The investigation seemed to stall there, but the events in Tennessee would later prove significant.

At the time, the DEA's Diversion Control Division was ramping up enforcement efforts against the nation's wholesale drug distributors — including Sunrise — warning them and drug manufacturers that they would be held accountable if they failed to report suspicious orders. Under the DEA's "distributor initiative," the agency had begun to make cases against large and small wholesalers.

In 2010 and 2011, DEA investigators in several states started to see large amounts of Mallinckrodt's oxycodone being sent to Florida.

By then, Mallinckrodt's blue 30-milligram oxycodone tablets had become so popular among drug users and dealers that they had a street name — "M's," for the company's distinctive block-letter logo.

KeySource Medical, based in Cincinnati, sent 41 million tablets of Mallinckrodt-made oxycodone to Florida in 2010, documents show. One of the pharmacies KeySource supplied was Tru-Valu Drugs in Lake Worth. With lines out the door and security measures such as a guard dog, left, and guns, Tru-Valu came under investigation by the DEA. (Federal court records)

Florida's lax laws, dishonest doctors and unscrupulous pharmacists had turned the state into ground zero for the nation's prescription opioid crisis.

One distributor that caught the attention of the DEA for sending drugs to Florida was KeySource Medical, a regional company based in Cincinnati. In 2010, it sent 41 million tablets of Mallinckrodt-made oxycodone to Florida, documents show. That was nearly 2.5 pills for every man, woman and child in the state.

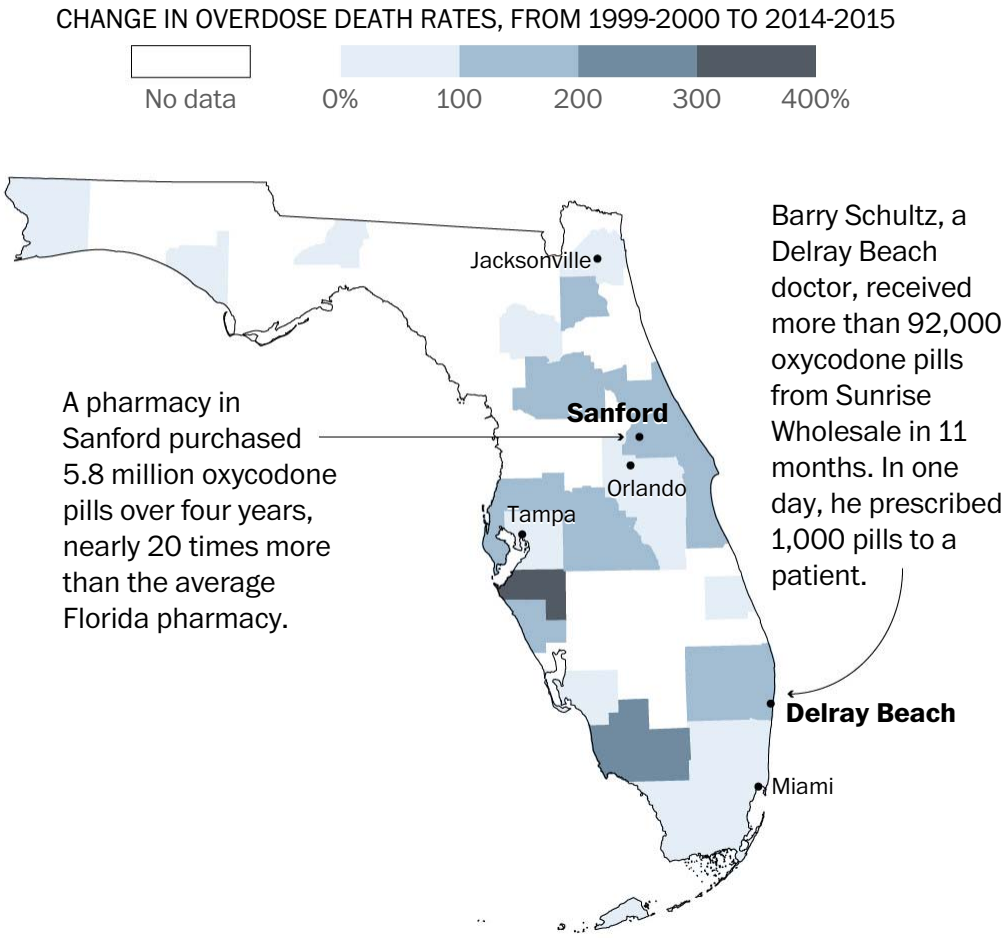
The DEA accused KeySource in June 2011 of trying to conceal the amounts of drugs it was shipping by splitting its orders and told the company to halt its oxycodone shipments.

Mallinckrodt's oxycodone cropped up again when the DEA looked at one of the nation's three largest drug distributors, Cardinal Health, which was sending vast quantities to four pharmacies in Florida.

The DEA had seen enough.

Florida's drug overdose deaths, county by county

Prescription opioids have played a key role in Florida's drug epidemic. Some counties have seen more than a threefold increase in overdose deaths since 2000.



Sources: Centers for Disease Control and Prevention; DEA GABRIEL FLORIT/THE WASHINGTON POST

On Aug. 23, 2011, DEA supervisors met with Mallinckrodt executives at the agency's headquarters in Arlington, Va., the day a rare 5.8-magnitude earthquake hit the

Washington region. People involved in the case still call the gathering "the earthquake meeting."

DEA officials showed the company the remarkable amounts of its oxycodone going to distributors and the number of arrests being made for oxycodone possession and distribution on the street, according to one participant in the meeting who also spoke on the condition of anonymity because the case is pending.

"There were a lot of follow-ups, and they said they would adjust their practices," the participant said.

The next day, the DEA's chief regulatory officer wrote to the agency's investigators and a federal prosecutor assigned to the case, Leslie Wizner, an assistant U.S. attorney in Detroit.

"I think we can all agree that yesterday's meeting was an eye opener for the company, and very successful, on so many levels, from DEA's perspective," Barbara J. Boockholdt wrote in an email obtained by The Post. She noted that there were "pending and proposed investigations" of Mallinckrodt.

Boockholdt declined to comment. Wizner did not return calls requesting an interview.

Three weeks after the Aug. 23 meeting, Mallinckrodt notified 43 of its distributors that they would no longer receive rebates from the company if they continued to supply certain pharmacies whose orders appeared to be suspicious.

But by then, the DEA and federal prosecutors had decided to take the investigation of the company to another level.

On Nov. 30, 2011, the DEA served a subpoena on Mallinckrodt, demanding documents related to its suspicious-order-monitoring program, according to the company's filings with the Securities and Exchange Commission.

Prosecutors said that the Mallinckrodt drugs that Sunrise sent to Schultz in the six weeks after Mallinckrodt was notified of the Tennessee sting were worth nearly $2.8 million on the street.

CONFIDENCE GROWS

The subpoena brought a windfall of information. The DEA gained access to data from Mallinckrodt's rebate or "chargeback" program, an industry-wide practice that provides reimbursements to wholesale distributors. That information and other records showed where Mallinckrodt's oxycodone was going — from the company to its network of distributors to retailers down the chain.

The significance of the Tennessee case started to become clear.

The DEA learned that in the six weeks after the Tennessee task force alerted Mallinckrodt to the drugs found in the 2009 sting operation, the company had shipped another 2.1 million tablets of oxycodone to Sunrise, the Florida distributor.

The DEA also discovered that Sunrise, over an 11-month period, had sent at least 92,400 tablets to Schultz, the Delray Beach doctor who prescribed the pills found in Tennessee. In one day, he had prescribed 1,000 tablets to one patient.

At the time, the street value of oxycodone was $30 a tablet. The Mallinckrodt drugs that Sunrise sent to Schultz after Mallinckrodt was notified of the Tennessee sting were worth nearly $2.8 million on the street, prosecutors said.

Barry Schultz was sentenced by Judge Jack Cox in West Palm Beach Friday, January 8, 2016. (Bruce R. Bennett / The Palm

Barry Schultz, a doctor who ran a medical clinic in Delray Beach, Fla., was sentenced to 25 years in prison in 2016. He was charged with drug trafficking and manslaughter after one of his patients died of an overdose. (Bruce R. Bennett/Palm Beach Post)

Prosecutors were becoming increasingly confident in their case. Under pressure from the DEA, Sunrise had surrendered its license to distribute narcotics. The Palm Beach County Sheriff's Office had arrested Schultz, charging him with drug trafficking and manslaughter because one of his patients died of a drug overdose. Schultz was later convicted and sentenced to 25 years in prison.

"Mallinckrodt knew through law enforcement reports that Barry Schultz was diverting controlled substances, and that the diverted oxycodone was supplied by Mallinckrodt through Sunrise," prosecutors later wrote in an internal document sent to the company. "When Mallinckrodt continued to distribute oxycodone to Sunrise for such purposes, and continued to pay incentives in the form of chargebacks for the product sales to Barry Schultz, Mallinckrodt was diverting oxycodone."

In Oct. 22, 2012, the DEA served Mallinckrodt with another subpoena for records relating to its suspicious-order-monitoring program, the company disclosed in SEC filings.

Those filings also showed that the DEA was examining Mallinckrodt's plant in Hobart, N.Y., about 70 miles southwest of Albany. Investigators documented scores of alleged violations, including the failure to secure narcotics, to keep accurate records or to document transfers of drugs, according to a confidential memo obtained by The Post.

Prosecutors said they considered 43,991 orders from distributors and retailers to be suspicious — orders that Mallinckrodt should have reported to the DEA. But the company said it was impossible

to monitor all of the 55,000 retail outlets where its drugs are delivered.

CONFLICTING RULES GUIDANCE

In 2014, Mallinckrodt, which is publicly traded and maintains its U.S. headquarters in St. Louis, notified its shareholders that it was under investigation by the federal government and had received subpoenas for documents.

But with no sign of civil action by the DEA, the company said it believed that "the ultimate resolution will not have a material adverse effect on our financial condition, results of operations and cash flows." In fiscal 2016, the company posted $3.4 billion in revenue and a $489 million profit.

Behind the scenes, however, the case against Mallinckrodt was growing more serious.

Prosecutors said in internal documents that they found the company's behavior so egregious that they initially considered framing it as a civil conspiracy.

"Mallinckrodt did knowingly, intentionally and unlawfully combine, conspire, confederate and agree with Sunrise and Barry Schultz to commit offenses against the United States," prosecutors wrote in a draft complaint against the company that was never filed. "That is, to knowingly, intentionally and unlawfully distribute, dispense or prescribe controlled substances, including but not limited to the Schedule II drug oxycodone 30 mg."

O'Connor, the Mallinckrodt lawyer, said that the draft document reflects "discredited allegations made in the heat of negotiations in 2015" and that the government and the company moved past those accusations.

"In particular, it is wrong to suggest Mallinckrodt was involved in any conspiracy related to Dr. Barry Schultz and Sunrise Wholesale," O'Connor said. "In reality, Mallinckrodt worked with law enforcement to investigate potential diversion by the physician and to audit Sunrise, and, importantly, the DEA praised the company's handling of the investigation."

Prosecutors weighed the strengths and weaknesses of their case in an internal summary they prepared Aug. 7, 2014.

"We will argue that thousands of orders from the distributors as well as tens of thousands of orders from these down-stream customers were suspicious because of the pattern of distribution to Florida," prosecutors wrote. In all, they said they considered 43,991 orders from distributors and retailers to be suspicious — orders that Mallinckrodt should have reported to the DEA.

A DEA agent walks out of the Cabana Pharmacy in Miami after raiding it along with police and the Florida Department of Health in October 2011. The owner and two of his employees were arrested after a six-month investigation by law enforcement in connection with the sale of oxycodone to those without a prescription. (Joe Raedle/Getty Images)

Prosecutors also acknowledged the weaknesses of their case in the summary. They noted that the DEA had provided conflicting guidance to Mallinckrodt about its responsibilities to report suspicious orders from retailers such as Schultz.

For example, Kleissle, the DEA supervisor in St. Louis, had told the company in 2010 after the Tennessee sting that it had a responsibility to keep close tabs on its customers, the distributors, as well as the distributor's customers, the pharmacies and doctors.

But that same year, a DEA investigator in New York, Heather White, told Mallinckrodt that no one in her region, including her supervisor, had heard anything about "know your customer's customer and that the regulations do not reflect such a requirement," according to the prosecutor's summary. White declined to comment for this article.

Mallinckrodt pushed back against the government's contention that it was responsible for the acts of downstream retail customers such as Schultz.

The company said during discussions with prosecutors that it was impossible to monitor all of the 55,000 retail outlets where its drugs are delivered. Mallinckrodt also said that the DEA was aware of the company's increased sales of oxycodone and could have acted by reducing the amount of narcotics the company is permitted to sell. The DEA sets quotas for the quantities of controlled substances that can be manufactured. The company also complained that the DEA has not provided guidance on how to track suspicious orders.

"Mallinckrodt has agreed to pay a settlement amount relating to orders from its distributors," prosecutors wrote in the summary. "However, it refuses to negotiate any settlement relating to the downstream customers orders."

The company put together a high-powered legal team to fight on its behalf. It included O'Connor, a former federal prosecutor who specialized in fraud and corruption cases, and D. Linden Barber, a former associate chief counsel for the DEA's diversion division who was one of the architects of the agency's crackdown on the pharmaceutical industry.

Following negotiations between Mallinckrodt's legal team and the U.S. attorney's office in Detroit, prosecutors dropped the civil conspiracy allegation, according to sources close to the talks. The negotiations then focused on the relationship between Mallinckrodt and its distributors, their customers and the amount of drugs that were going to Florida.

Prosecutors noted that the DEA had twice placed the industry on notice about its responsibility to report suspicious orders. They also said Mallinckrodt was aware of enforcement actions the agency had taken against distributors for failing to report the inordinate amounts of painkillers they were shipping to retail customers in states such as Florida.

"With respect to distributor orders," prosecutors wrote in a document, "Mallinckrodt's obligations to monitor and notify of suspicious sales were known to the company."

For a company the size of Mallinckrodt, a $35 million fine is "chump change," one government official said. In fiscal 2016, the company posted $3.4 billion in revenue and a $489 million profit.

ABOUT MORE THAN MONEY

On July 10, 2015, the U.S. attorney's office sent a proposed settlement offer to lawyers for Mallinckrodt.

Prosecutors said that they could fine the company as much as $2.3 billion because 222,107 orders to Florida were "excessive" and should have been reported as suspicious. Or they could fine the company up to $1.3 billion based on an analysis of the 217,022,834 Mallinckrodt 30 mg oxycodone tablets that were sold for cash in Florida in 2009 and 2010.

"As you are aware, significant cash sales are an indication of diversion," prosecutors wrote in their offer.

But the big buildup resulted in a much smaller proposed fine. Despite the billion-dollar figures bandied about, the prosecutors proposed settling the case for $70 million. They cited the "litigation risk" they faced if the case went to trial, Mallinckrodt's previous legal arguments and the size of other recent settlements with drug distributors.

This year, on Feb. 7, Mallinckrodt told its shareholders in an SEC filing that the investigation "will not have a material adverse effect on its financial condition" because it has set aside the money.

Sources close to the negotiations said that the two sides had recently reached a tentative agreement to settle the case for $35 million. With final approval pending from the Justice Department, some of those who worked on the case said they are deeply disappointed by the dollar amount of the proposed fine.

Drug manufacturers have paid much larger fines for other misdeeds. GlaxoSmithKline was fined $3 billion, and Pfizer was fined $2.3 billion for illegally promoting off-label drug use and paying kickbacks to doctors. Purdue Pharma paid a $600 million fine, and three of its executives pleaded guilty to charges that they misled regulators, doctors and patients about the risks of the painkiller that is widely blamed for setting off the nation's opioid crisis: OxyContin. All of those cases were initiated by the Food and Drug Administration.

The largest fine the DEA has levied against a drug distributor was the $150 million that McKesson, the nation's largest drug wholesaler, recently agreed to pay following allegations that it failed to report suspicious orders of painkillers.

For a company the size of Mallinckrodt, a $35 million fine is "chump change," one government official said.

"The problem you have is this was new ground, and it had never been done before," said another former law enforcement official with knowledge of the case. "There was a lot of back and forth over whether we could pull this off.

Is it ideal? No. Is this a number that everyone wants to see? No. People would probably like to see more. But this is about more than money. It's about holding a manufacturer accountable, and it will put the industry on notice."

Alice Crites contributed to this report.

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The DEA slowed enforcement while the opioid epidemic grew out of control

Enforcement cases dwindled to a "stunningly low" number after a change in policy by the agency.

How drugs intended for patients ended up in the hands of illegal users: 'No one was doing their job'

Wholesale distributors sent pills to drugstores that fueled the opioid epidemic.

Drug industry hired dozens of officials from the DEA as the agency tried to curb opioid abuse

Critics say the revolving door undercuts the agency's ability to curb the rising opioid epidemic.

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LawyerTom
8/18/2017 1:06 PM EDT

Treating the manufacturers as classic conveyors of dangerous substances backed by false and misleading advertising is an important tool that can help force changes of all sorts.

Like Reply Share

ThorazineDartGun
4/5/2017 9:44 AM EDT

The opioid epidemic was driven partly by the medical industry and largely by the federal government. The Joint Commission introduced standards for pain assessment and treatment in the 1990's, as it felt physicians were inadequately treating patients' pain. In 1996 the phrase, "the fifth vital sign" was introduced to emphasize the importance of this metric, that was included in the patient satisfaction surveys obtained by hospitals and required by CMS. In reality, "pain" is not and never was a vital sign—temperature, pulse, blood pressure and respirations are.

HCAHPS scores were formally introduced by CMS in 2002, codifying the standards Big Gov felt hospitals needed to meet. Hospitals that failed to comply with obtaining these patient satisfaction surveys were financially penalized, obviously creating the incentive for them to spend more time, money and resources to conform to the government's dictates. The Affordable Care Act then created "value-based incentive payments", essentially tying reimbursement to hospitals not only to obtain HCAHPC surveys, but now to their results.

All this government meddling did was coerce hospitals and doctors to write more narcotics so that happy, doped-up patients would rate the treating physicians and facilities highly on satisfaction surveys, decreasing the likelihood that these entities would lose money by not meeting the government's arbitrary performance metrics.

So guess what happened? Doctors (with the blessing of the AMA, by the way) got much of country hooked on opiates, all because federal bureaucrats felt they knew better how to treat patients than physicians with 11-15 years of education and training.

NOW, Big Gov wants to put the genie back in the bottle, proposing even MORE regulations to try to fix the problem it created in the first place. Morons.

Like Reply Share

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dc_wolverine
4/4/2017 9:37 PM EDT

White collar crime pays in this country. Jail is never an option, not since the days of Enron, with only the only restitution being a fine paid by the company, not any of the corporate officers. And Republicans want to eliminate most lawsuits against companies, so even that pathetic amount of accountability will soon disappear. The U.S. is a great country to live in for someone who is rich and evil.

1 · Like Reply Share

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dc_wolverine
4/4/2017 8:27 PM EDT

"In a statement, a Mallinckrodt spokesman said the company has worked hard to fight drug diversion"....before falling to the floor laughing and say, "nah, actually we were too busy counting our billions and snorting cocaine off a hooker's body to give a rats @@s about anyone dying from our product."

3 · Like Reply Share

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iNgodWetrust-AllothersbringDATA
4/4/2017 8:21 PM EDT

... kinda suspected the " pendulum " would begin to swing the other way after viewing the 2009 BBC Panorama Doc: The OxyContin Express.
http://topdocumentaryfilms.com/oxycontin-express/
(http://topdocumentaryfilms.com/oxycontin-express/)

Like Reply Share

Divinity11
4/4/2017 11:14 AM EDT

F*ck synthetics.

Stick with the natural herb, that God intended for His people to cultivate.

2 · Like Reply Share

Walter Wilson
4/4/2017 1:08 AM EDT

I take oxycodone on a regular basis. I have degenerative-joint arthritis and I am in continuous pain. Artificial joints are out because I very tall and quite heavy So it is a constant battle to get by with even the under-prescribed amount I use. Why? Government is unable to effect control without putting hospitals and doctors in fear of practice busting license issues. All to my detriment. The pain sometimes gets so bad I dread facing the day knowing if I take as little as one extra I will have even less toward the end of my prescription and hurt even more with no chance in hell of getting even 1 or 2 pills more. That's not treatment, that's torture. And I am tired of it and must consider alternatives. If I load up on over-the-counter pain killers, I put my liver and kidneys in jeopardy. If I buy on the street, I put my freedom in jeopardy. Given these facts what would you do? Can you imagine being put in the position of stealing some more pills or of considering suicide? Well, I won't go there, so what do I do? Any productive, legal solution for less pain will be gratefully accepted. What would you do?

3 · Like Reply Share

MadamDeb
4/4/2017 4:05 AM EDT

Move to Colorado or Washington state where pot is legal? Would that help – I mean, pot?

Like Reply

Jacob Frie
4/4/2017 5:26 PM EDT

Sad that pain is always the opium addicts go to pitch. I am not saying you are not in pain but I am saying that pain is what everyone is in when they are not on opium. It physically hurts when you withdraw and there fore makes it difficult for the person to distinguish. I strongly suggest you seek medicinal pot even if it is just for a short period of time.

Like Reply

Lost in Carolina
8/4/2017 11:19 PM EDT

Walter Wilson – from what I understand, pills like Oxycontin do not help chronic pain – after a time, the nerves get used to sending signals regardless of whether there is pain. That is an oversimplified explanation but it might be worth looking into. I have heard some great information on a program called The People's Pharmacy – they had a program on about a spine doctor who had come up with an entirely new program for relieving pain. It sounds crazy but – if you are in so much pain, wouldn't it be worth a shot to try?
If this page will allow me to paste a link I will paste it to the page that has the podcast on it as well:
https://www.peoplespharmacy.com/2017/03/09/show-10...
(https://www.peoplespharmacy.com/2017/03/09/show-1071-how-you-can-get-relief-from-chronic-pain/)

Like Reply

Lost in Carolina
8/4/2017 11:31 PM EDT

I found an article talking about what I referenced above – it tells why talking narcotics for chronic pain may actually increase pain... of course, perhaps that is not true in your case but I think it is interesting information
http://www.sciencemag.org/news/2016/05/why-taking-...
(http://www.sciencemag.org/news/2016/05/why-taking-morphine-oxycodone-can-sometimes-make-pain-worse)

Like

teepartayruskay
4/3/2017 11:25 PM EDT [Edited]

In 2001, NO heroin was produced in Afghanistan, due to bad weather and Taliban opposition.

In 2002, when US troops arrived, and in each year thereafter, Afghanistan became the world's leading production center for heroin, organized crimes's number one product, supplying over 90% of the world's heroin, and a significant proportion of the base ingredients for other opioids as well.

Afghanistan is also the world's leading production center for cannabis/hashish since US troops arrived in 2002.

With all due respect to the US military, why has our occupation of Afghanistan coincided with the centralization and exponential expansion of organized crimes' production center for some of its leading products, heroin, and hashish?

This is a national disgrace for America.

2 · Like Reply Share

MadamDeb
4/4/2017 3:55 AM EDT

They were there to protect Big Pharma.

1 · Like Reply

dirtydiverdave
4/3/2017 10:35 PM EDT

Drug companies have ONE obligation, make drugs that are SAFE and EFFECTIVE when prescribed by a Doctor. That people can abuse the drugs they make is no different than trying to hold an automobile manufacturer liable for the misuse of their product. It is so fashionable to blame "big pharma" these days, but imagine what life would be like were it not for companies investing billions to create drugs that actually alleviate human suffering, which (oh, by the way) must pass strict Government Oversight (like the FDA) before being able to sell them. I would argue that it is most definitely NOT the responsibility of the drug manufacturers to be concerned at all by the misuse of their products. One last thing: To paraphrase Wild Bill in "Deadwood" - why don't we let people go to Hell in their own way?

2 · Like Reply Share

Amphibian62
4/3/2017 10:56 PM EDT

Then you're a troll for the drug companies. And you certainly didn't read the article; or you're incapable of understanding it. We send dealers on the street away for years, but overpaid corporate drug dealers get a free pass.

1 · Like Reply

Old Soldier Recovering Lawyer
4/3/2017 10:29 PM EDT [Edited]

Gee, Mallinckrodt Pharmaceuticals, a multinational manufacturer, should notice that Dr. Feel Good is prescribing enough pills to get all of Florida High and that Hole in the Wall Pharmacy in Smallville ordered enough to get the Great State a Florida zoned out. But the distributors who actually sold the pill to Hole in the Wall Pharmacy were not expected to note the oddity. Wonder why.

The answer is that the DEA backed off the distributors after lobbyists went to Congress. The whole War on Drugs is a 104 year old failure and the DEA a poor joke. Better to legalize all drugs. Darwinian selection will take care of the problem

3 · Like Reply Share

susancol
4/4/2017 7:28 PM EDT

The War on Drugs is directly responsible for the heroin epidemic. If doctors won't prescribe and pharmacies won't dispense pills made in safe and sanitary facilities and provided in verifiable and knowable dosages, the cost for illegal pills goes up and heroin (unsafe, unsanitary and unknowable dosage/strength) becomes the substitute.

1 · Like Reply

Floyd Zuber
4/3/2017 9:12 PM EDT

Nah! We don't need regulations.

Like Reply Share

canadianguy1
4/3/2017 8:17 PM EDT

It seems that little is mentioned about the legitimate users of the drugs. My wife is in pain 24/7 and has been on oxy contin - now oxy neo for quite a few years now. Because of the illegal distribution and the street drug problem, the drug once covered by Canadian provincial drug plans (for seniors) eliminated the drugs from their formulary meaning that the legitimate users are now not covered for the drug cost, while at the same time illicit drug users are now being provided at the taxpayers' expense with safe injection centres and free methodone clinics. Something wrong with this picture!

3 · Like Reply Share

dirtydiverdave
4/3/2017 10:41 PM EDT

The problem is that the "grown ups" are being treated like children by the government. Your wife should have unfettered access to whatever medications her doctor says she needs - regardless of how others may "abuse" these drugs. If anyone wonders why we're seeing such an uptick of deaths related to Fentanyl in Heroin these days, it's due to the Law of Unintended Consequences whereupon the govt. tries to crackdown on the excess use of prescription-grade drugs, forcing people who (for whatever reason) need those drugs to run to the corner dealers. This is stupid policy, enacted by stupid people who have zero concept of how the real world works. Just because my neighbor is an alcoholic shouldn't make buying Pino Grigio any harder for me. Let him go to Hell in his own way, and me mine. As long as no one else is being hurt (the purpose of drunk driving laws), let people BE.

3 · Like Reply

angriestmaninamerica
4/3/2017 7:06 PM EDT [Edited]

What alot of people commenting do not realize is that the pharma companies knew the pills were addictive but they suppressed that knowledge

Like Reply Share

memyselfandIII
4/3/2017 8:16 PM EDT

If you didn't know they were addictive you are an idiot.

2 · Like Reply

susancol
4/4/2017 7:30 PM EDT

ROFLMAO. I've heard of conspiracy theorists, but this takes the cake. EVERYBODY knows opioids are addictive and it was never "hidden".

1 · Like Reply

michael howe
4/3/2017 6:51 PM EDT

Reading some of the comments below, it seems there is a great misconception about the addictiveness of some medicines. Much like alcohol, every one who drinks doesn't become an alcoholic, and everyone given pain meds doesn't become addicted.
My wife, a retired pharmacist, points out another confusion that may arise from the article. It seems to be talking about the rise in Florida of "drive-thru" doctor offices, where Doctors

unprofessionally prescribe large amounts of Oxycodone for anyone. Most major Pharmacies (Walgreens, CVS, etc) and their Pharmacists would never fill any such prescription. Most Doctors would never prescribe these large amounts. The article also showed the picture of the Cabana pharmacy where drugs were sold without a Doctors prescription.
It appears the cause of the rise of abuse in Florida stems from possibly a lower level of drug monitoring by their state agencies, law enforcement, etc. Perhaps their laws have not been updated, perhaps there are other reasons.
It's also problematic when you mix profit and safety. Mallinkcrodt should have alerted DEA sooner.

1 · Like Reply Share

angriestmaninamerica
4/3/2017 7:04 PM EDT

My little town in fla had a small local pharmacy, not a walgreens or publix or cvs, and they were cashing presciptions left and right. Ride the gravy train as long as you can and hope you dont get busted

Like Reply

angriestmaninamerica
4/3/2017 6:49 PM EDT [Edited]

Here in fla rick scott and his hatchet woman pam biondi shut all the pill mills down. They did not do a thing about treatment because republicanism. Everybody who went to the pill mills are now using heroin and are now criminals problem solved. For profit jails make money state employees make money. Win win

1 · Like Reply Share

Amphibian62
4/3/2017 10:58 PM EDT

Scott's health care company paid a huge fine for medicare fraud, while Scott was CEO. Then he gets elected governor anyway. Flori-duhh.

3 · Like Reply

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EXHIBIT 104

Opioid epidemic: ex-DEA official says Congress is protecting drug makers

Joseph Rannazzisi accuses lawmakers of putting US pharmaceutical companies' $9bn-a-year trade in opioid painkillers ahead of a public health crisis

Chris McGreal

Monday 31 October 2016 09.26 EDT

A former top Drug Enforcement Administration (DEA) official has accused Congress of putting pharmaceutical company profits ahead of public health in the battle to combat the US's prescription opioid epidemic.

Joseph Rannazzisi, head of the DEA office responsible for preventing prescription medicine abuse until last year, said drug companies and their lobbyists have a "stranglehold" on Congress to protect a $9bn a year trade in opioid painkillers claiming the lives of nearly 19,000 people a year.

Rannazzisi, director of the agency's office of diversion control for a decade, said the drug industry engineered recent legislation limiting the DEA's powers to act against

pharmacies endangering lives by dispensing disproportionately large numbers of opioids. He also accused lobbyists, who have spent hundreds of millions of dollars in recent years to influence opioid legislation and policy, of whipping up opposition to new guidelines for doctors intended to reduce the prescribing of the painkillers with a close resemblance to heroin.

“Congress would rather listen to people who had a profit motive rather than a public health and safety motive,” said Rannazzisi. “As long as the industry has this stranglehold through lobbyists, nothing’s going to change.”

The former DEA official, who is a pharmacist, was particularly scathing about politicians he said claim to be at the forefront of fighting the opioid epidemic while doing the bidding of the pharmaceutical industry in Congress.

“These congressmen and senators who are using this because they are up for re-election, it’s a sham. The congressmen and senators who are championing this fight, the ones who really believe in what they’re doing, their voices are drowned out because the industry has too much influence,” he said.

Charges that Congress is too beholden to pharmaceutical companies have been levelled for years, particularly over controversial legislation such as the law that barred the government from negotiating lower prices for drugs bought for the Medicare and Medicaid systems. But Rannazzisi says the influence on opioid policies is particularly disturbing because so many lives are being lost and he sees members of Congress claiming to take the issue seriously during election campaigns but acting differently in Washington.

That’s a criticism echoed by Democrats in the Senate, who issued a report earlier this month criticising Republicans for passing sweeping legislation in July to combat addiction, the Comprehensive Addiction and Recovery Act (Cara), but refusing to fund it. The report, Dying Waiting for Treatment, likened the Republican response to the opioid crisis to “using a piece of chewing gum to patch a cracked dam”. “The bill was ‘comprehensive’ in name only; without funding, its policies are little more than empty promises,” the report said.

Senator Ron Wyden of Oregon, who released the report, acknowledged the influence of drug companies and their lobbyists on Congress but he has also been critical of their sway over federal institutions. “There is no question that the powerful opioid manufacturers have a disproportionate voice, a disproportionate amount of influence, in these debates,” he said.

Rannazzisi clashed with Congress over a law passed in April reducing the DEA’s power to suspend the licenses of distributors and pharmacists accused of dispensing excessive amounts of opioids without abiding by regulations.

The Ensuring Patient Access and Effective Drug Enforcement Act was initiated by an industry-funded group, the Healthcare Distribution Management Association, which

claimed that the DEA was misusing its powers to go after pharmacists and drug distributors which made minor mistakes in their paperwork. Rannazzisi said the agency only targeted those that were “sending millions of drugs down the street”.

Several states have sued pharmaceutical distributors, including West Virginia, which accused a dozen companies of dumping 200m opioid pills on the state knowing many were dispensed to addicts able to get prescriptions from crooked doctors and pharmacists.

The new law requires the DEA to warn pharmacies and distributors if they are in breach of regulations and to give them a chance to comply before licenses are withdrawn. Rannazzisi said that amounts to a “free pass” for institutional drug traffickers.

“This doesn’t ensure patient access and it doesn’t help drug enforcement at all. What this bill does has nothing to do with the medical process. What this bill does is take away DEA’s ability to go after a pharmacist, a wholesaler, manufacturer or distributor,” he said. “This was a gift. A gift to the industry.”

Rannazzisi riled some members of Congress by telling them they were “supporting criminals” with the law. Representative Tom Marino of Pennsylvania said he was immensely offended by the comment and told the DEA to “seek collaboration with legitimate companies that want to do the right thing”.

“Corporations have no conscience,” Rannazzisi told the Guardian. “Unfortunately, with my job, I was the guy who had to go out and talk to families that lost kids. If one of those CEOs went out there and talked to anybody, or if one of those CEOs happened to lose a kid to this horrible, horrible domestic tragedy we have, I’d bet you they’d change their mind.

“When you sit with a parent who can’t understand why there’s so many pharmaceuticals out in the illicit marketplace, and why isn’t the government doing anything, well the DEA was doing something. Unfortunately what we’re trying to do is thwarted by people who are writing laws.”

Asked why he thinks the bill passed over the objections of the DEA, Rannazzisi gave a short derisive snort.

“The bill passed because ‘Big Pharma’ wanted it to pass. The DEA is both an enforcement agency and a regulatory agency. When I was in charge what I tried to do was explain to my investigators and my agents that our job was to regulate the industry and they’re not going to like being regulated,” he said.

Industry groups have spent hundreds of millions of dollars in lobbying to stave off measures to reduce prescriptions and therefore sales of opioid painkillers. Among the most influential drug industry groups is the Pain Care Forum, co-founded by a top executive of Purdue Pharma - the manufacturer of the opioid which unleashed the addiction epidemic, OxyContin - and largely funded by pharmaceutical companies. It

spent $740m lobbying Congress and state legislatures over the past decade according to the Center for Public Integrity.

Recipients of political donations from the industry included Senator Orrin Hatch, chairman of the finance committee, who took $360,000 and Representative Mike Rogers, who received more than $300,000, according to the CPI. The two politicians were instrumental in legislation establishing a panel to examine treatment of pain that critics said had close ties to industry-funded groups.

Wyden has been critical of what he says is pharmaceutical company influence over policy through other expert panels, including the government-run Interagency Pain Research Coordinating Committee (IPRCC). The senator said it had been used to "weaken" guidelines drawn up by the Centers for Disease Control and Prevention (CDC) that discouraged doctors from prescribing opioids so widely.

Earlier this year, Wyden wrote to the secretary of health and human services, Sylvia Burwell, protesting about the presence on the IPRCC of experts and activists he said had close links to pharmaceutical companies, including a scientist who holds a chair funded by a $1.5m endowment from Purdue.

"You've got a panel that's certainly got a fair number of people that have a vested interest in this problem of overprescribing. That's something you've got to root out," said Wyden. "The role of the pharmaceutical companies on these advisory panels troubles me greatly. Science is getting short shrift compared to the political clout of these influential interests."

Wyden criticised the presence of others on the IPRCC including Penney Cowan, founder of the American Chronic Pain Association, which he said "receives corporate support from 11 companies that manufactured opioid-based drugs" and Cindy Steinberg, national policy director of the US Pain Foundation which he said "receives substantial funding from opioid manufacturers".

Cowan, who founded her association 36 years ago before prescription opioids were widely available, said the organisation is focused on education and relies on funding from drug companies because it is not available from other sources.

"Unfortunately no one cares about pain so they don't fund it," she said. "[Pharmaceutical companies] don't have any influence over us. I don't know that we would have survived the last 36 years if they did."

Steinberg, who has lived with chronic pain for 15 years after she was crushed under a filing cabinet, said the US Pain Foundation receives "unrestricted educational grants" from pharmaceutical companies and other foundations but these do not influence policy.

"These companies have no input into the materials the foundation creates," she said.

Steinberg said she was “honoured to serve on the IPRCC” and that its criticisms of the CDC guidelines were legitimate.

“These included the fact that the guidelines were based on ‘weak’ or ‘very weak’ scientific evidence,” she said. “As a result of the IPRCC comments, the guidelines were subsequently put out for public comment, went to a larger group for review and revised to some extent which was a good thing.”

In December, a congressional committee piled pressure on the CDC by launching an investigation into how it drew up the guidelines. Other members of Congress suggested it was the job of the Food and Drug Administration (FDA), which is more sympathetic to the position of the pharmaceutical companies, not the CDC to advise doctors on prescriptions.

In the end the committee turned up no evidence of wrongdoing but the pressure led to changes to the CDC guidelines and a delay in their release that Rannazzisi said weakened their impact.

“The industry got Congress to put pressure on the CDC over their prescribing guidelines. That was just a farce,” he said.

Dr Andrew Kolodny, director of Physicians for Responsible Opioid Prescribing, said resistance to the CDC guidelines is part of a pattern of opposition to measures that reduce sales of opioid pills. “The opioid lobby has very actively blocked interventions that might result in more cautious prescribing or reduced prescribing. They’ve very clearly defended their financial stake in the status quo,” he said.

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EXHIBIT 105

Red Flags: Pharmacists Anti-Abuse Video

Mallinckrodt Pharmaceuticals

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Published on May 27, 2014

The National Association of Boards of Pharmacy (NABP) and the Anti-Diversion Industry Working Group (ADIWG), a consortium of pharmaceutical manufacturers and distributors, has created this educational video for pharmacists to help them identify the warning signs of prescription drug abuse and diversion

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EXHIBIT 106

Mallinckrodt to Pay $35M in Deal to End Feds' Opioid Probe

A top maker of brand-name and generic narcotic painkillers has agreed to pay the U.S. government $35 million to resolve a probe of its distribution of those drugs.

April 3, 2017, at 6:47 p.m.

FILE - This Jan. 18, 2013, file photo shows a bottle of Morphine Sulfate, made by the pharmaceutical company Mallinckrodt PLC, in Carmichael, Calif. The Dublin, Ireland-based company, which sells a number of powerful opioid painkillers, has agreed to pay the U.S. government $35 million to resolve a probe of its distribution of those drugs. Mallinckrodt didn't admit any wrongdoing, as is common with deals ending federal probes of companies. (AP Photo/Rich Pedroncelli, File) The Associated Press

AP

By LINDA A. JOHNSON, AP Medical Writer

TRENTON, N.J. (AP) — A top maker of brand-name and generic narcotic painkillers has agreed to pay the U.S. government $35 million to resolve a probe of its distribution of those drugs.

Mallinckrodt PLC said Monday it has reached an agreement with the U.S. Drug Enforcement Administration and the U.S. attorneys for the Eastern District of Michigan and Northern District of New York. The deal is subject to further review and approval by the DEA and Justice Department.

Best States

Mallinckrodt didn't admit any wrongdoing, as is common with deals ending federal probes of companies.

Prosecutors and lawmakers have been investigating possible connections between marketing of addictive painkillers and the epidemic of opioid and heroin deaths.

Dublin, Ireland-based Mallinckrodt sells a number of powerful opioid painkillers including generic pills containing fentanyl, morphine and oxycodone. Its brand-name narcotic painkillers include extended-release Exalgo, Xartemis and Roxicodone pills. Mallinckrodt also makes medicines for treating narcotic addiction.

In a statement, Mallinckrodt said that its "innovative suspicious order monitoring program" exceeds DEA requirements.

Numerous companies that sell addictive opioid painkillers have been accused by politicians, lawyers and others of contributing to the U.S. epidemic of people who become addicted to the pills, often after having them prescribed following surgery or injury. Many eventually turn to much-cheaper heroin as a replacement.

More than 33,000 Americans died of an opioid overdose in 2015, the most of any year, according to the Centers for Disease Control and Prevention. Nearly half of the opioid overdose deaths involve a prescription opioid.

In one of the latest probes, Sen. Claire McCaskill, D-Missouri, last week began an investigation by seeking marketing information, sales records and studies from manufacturers of top-selling opioid products. She noted sales of prescription opioids have quadrupled since 1999.

President Donald Trump also promised to increase efforts to combat the opioid addiction crisis and picked New Jersey Gov. Chris Christie to head the project.

—

Follow Linda A. Johnson at https://twitter.com/LindaJ_onPharma

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Tired of sitting in traffic? Move to these states for a quicker trip to the office.

Fort Carson Soldiers Return Home After European Deployment (https://www.usnews.com/news/best-states/colorado/articles/2017-10-10/fort-carson-soldiers-return-home-after-european-deployment?int=news-rec)
Oct. 10, 2017

U.S. Army soldiers from Fort Carson's 3rd Brigade Combat Team are returning to Colorado after a nine-month deployment in central and eastern Europe.

North Dakota Lawmakers Get Report on Marsy's Law Impacts (https://www.usnews.com/news/best-states/north-dakota/articles/2017-10-10/north-dakota-lawmakers-get-report-on-marsys-law-impacts?int=news-rec)
Oct. 10, 2017

North Dakota prosecutors, law enforcement to discuss impacts of new law incorporating victims' rights in the state constitution.

Longtime Democratic Activist Joins 2018 Race for Governor (https://www.usnews.com/news/best-states/south-carolina/articles/2017-10-10/longtime-democratic-activist-joins-2018-race-for-governor?int=news-rec)
Oct. 10, 2017

A long-time Democratic activist and consultant is entering the race for South Carolina governor.

Woman Seeks Answers in Slaying of Father in 2000 (https://www.usnews.com/news/best-states/alabama/articles/2017-10-10/woman-seeks-answers-in-slaying-of-father-in-2000?int=news-rec)
Oct. 10, 2017

An Alabama veteran is seeking answers about her father's unsolved killing 27 years ago.

Abilene Police Investigate 3 Apparent Drug Overdose Deaths (https://www.usnews.com/news/best-states/texas/articles/2017-10-10/abilene-police-investigate-3-apparent-drug-overdose-deaths?int=news-rec)
Oct. 10, 2017

Abilene police are investigating three apparent overdose deaths on the same day and trying to determine where the victims got the drugs.

Woman Injured in Eastern Idaho Drive-By Shooting (https://www.usnews.com/news/best-states/idaho/articles/2017-10-10/woman-injured-in-eastern-idaho-drive-by-shooting?int=news-rec)
Oct. 10, 2017

Police in the eastern Idaho town of Chubbuck are investigating after a woman was injured in a drive-by shooting.

2 Drown on Alabama Coast Trying to Save Child (https://www.usnews.com/news/best-states/alabama/articles/2017-10-10/2-drown-on-alabama-coast-trying-to-save-child?int=news-rec)
Oct. 10, 2017

Two men who were trying to save a child in rough surf on the Gulf Coast have drowned.

Turtle That Swallowed Fishing Line Released in Ocean (https://www.usnews.com/news/best-states/south-carolina/articles/2017-10-10/turtle-released-in-atlantic-ocean-after-successful-surgery?int=news-rec)
Oct. 10, 2017

A sea turtle that underwent surgery to remove more than 4 feet (1 meter) of fishing line she had swallowed has been released in the Atlantic Ocean off South Carolina's coast.

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EXHIBIT 107

JUSTICE NEWS

Department of Justice

Office of Public Affairs

FOR IMMEDIATE RELEASE Tuesday, July 11, 2017

Mallinckrodt Agrees to Pay Record $35 Million Settlement for Failure to Report Suspicious Orders of Pharmaceutical Drugs and for Recordkeeping Violations

Mallinckrodt LLC, a pharmaceutical manufacturer and one of the largest manufacturers of generic oxycodone, agreed to pay $35 million to settle allegations that it violated certain provisions of the Controlled Substances Act (CSA) that are subject to civil penalties, Attorney General Jeff Sessions of the Justice Department and Acting Administrator Chuck Rosenberg of the Drug Enforcement Administration (DEA) announced today.

This is the first settlement of its magnitude with a manufacturer of pharmaceuticals resolving nationwide claims that the company did not meet its obligations to detect and notify DEA of suspicious orders of controlled substances such as oxycodone, the abuse of which is part of the current opioid epidemic. These suspicious order monitoring requirements exist to prevent excessive sales of controlled substances, like oxycodone in Florida and elsewhere. The settlement also addressed violations in the company's manufacturing batch records at its plant in Hobart, New York. Both sets of alleged violations impact accountability for controlled substances, and the compliance terms going forward are designed to help protect against diversion of these substances at critical links in the controlled substance supply chain.

"In the midst of one of the worst drug abuse crises in American history, the Department of Justice has the responsibility to ensure that our drug laws are being enforced and to protect the American people," said Attorney General Sessions. "Part of that mission is holding drug manufacturers accountable for their actions. Mallinckrodt's actions and omissions formed a link in the chain of supply that resulted in millions of oxycodone pills being sold on the street. Thanks to the hard work of our attorneys and law enforcement, Mallinckrodt has agreed to do everything they can to help us identify suspicious orders in the future. And as a result of today's settlement, we are sending a clear message to drug companies: this Department of Justice will hold you accountable for your legal obligations and we will enforce our laws. I believe that will prevent drug abuse, prevent new addictions from starting, and ultimately save lives."

"Manufacturers and distributors have a crucial responsibility to ensure that controlled substances do not get into the wrong hands," said DEA Acting Administrator Chuck Rosenberg. "When they violate their legal obligations, we will hold them accountable."

The government alleged that Mallinckrodt failed to design and implement an effective system to detect and report "suspicious orders" for controlled substances – orders that are unusual in their frequency, size, or other patterns. From 2008 until 2011, the U.S. alleged, Mallinckrodt supplied distributors, and the distributors then supplied various U.S. pharmacies and pain clinics, an increasingly excessive quantity of

oxycodone pills without notifying DEA of these suspicious orders. Through its investigation, the government learned that manufacturers of pharmaceuticals offer discounts, known as “chargebacks,” based on sales to certain downstream customers. Distributors provide information on the downstream customer purchases to obtain the discount. The groundbreaking nature of the settlement involves requiring a manufacturer to utilize chargeback and similar data to monitor and report to DEA suspicious sales of its oxycodone at the next level in the supply chain, typically sales from distributors to independent and small chain pharmacy and pain clinic customers.

The government also alleged that Mallinckrodt violated record keeping requirements at its manufacturing facility in upstate New York. Among other things, these violations created discrepancies between the actual number of tablets manufactured in a batch and the number of tablets Mallinckrodt reported on its records. Accurate reconciliation of records at the manufacturing stage is a critical first step in ensuring that controlled substances are accounted for properly through the supply chain.

In addition to the significant monetary penalty, this settlement includes a groundbreaking parallel agreement with the DEA, as a result of which the company will analyze data it collects on orders from customers down the supply chain to identify suspicious sales. The resolution advances the DEA’s position that controlled substance manufacturers need to go beyond “know your customer” to use otherwise available company data to “know your customer’s customer” to protect these potentially dangerous pharmaceuticals from getting into the wrong hands. DEA’s Memorandum of Agreement with Mallinckrodt also sets forth specific procedures it will undertake to ensure the accuracy of batch records and protect loss of raw product in the manufacturing process.

By entering into these agreements, elements of which Mallinckrodt is already implementing, the company is becoming part of the solution to this public health epidemic.

This lengthy investigation was led by DEA’s Detroit Field Division on the suspicious order issues and the New York Field Division on the manufacturing record keeping issues.

U.S. Attorneys’ Offices for the Eastern District of Michigan and the Northern District of New York, along with DEA Office of Chief Counsel and Diversion Control Division, led the civil settlement negotiations. The Criminal Division’s Narcotic and Dangerous Drug Section (NDDS) also coordinated and assisted in negotiating the settlement.

Component(s):
Criminal Division
Drug Enforcement Administration (DEA)

Updated July 11, 2017

EXHIBIT 108

United States Department of Justice

THE UNITED STATES ATTORNEY'S OFFICE
DISTRICT of MARYLAND

U.S. Attorneys » District of Maryland » News

Department of Justice

U.S. Attorney's Office

District of Maryland

FOR IMMEDIATE RELEASE Friday, December 23, 2016

Cardinal Health Agrees to $44 Million Settlement for Alleged Violations of Controlled Substances Act

Settlement resolves multiple investigations against Cardinal in Maryland, Florida, New York and Washington

Baltimore, Maryland – Cardinal Health, Inc. agreed to pay $44,000,000 to the United States to resolve allegations that it violated the Controlled Substances Act (CSA) in Maryland, Florida and New York by failing to report suspicious orders of controlled substances to pharmacies located in those states. The settlement also resolves a civil investigation in the Western District of Washington concerning alleged violations of CSA record keeping requirements. Contemporaneously, the Southern District of New York has entered into a separate settlement agreement with Cardinal in which Cardinal agreed to resolve allegations that Kinray, Inc., a subsidiary distributor, failed to report suspicious orders by pharmacies in the Kinray service area.

The settlement agreement was announced today by United States Attorney for the District of Maryland Rod J. Rosenstein and Special Agent in Charge Karl C. Colder of the Drug Enforcement Administration - Washington Field Division.

"Pharmaceutical suppliers violate the law when they fill unusually large or frequent orders for controlled substances without notifying the DEA," said U.S. Attorney for the District of Maryland Rod J. Rosenstein. "Abuse of pharmaceutical drugs is one of the top federal law enforcement priorities. Cases such as this one, as well as our $8 million settlement with CVS in February 2016, reflect the federal commitment to prevent the diversion of pharmaceutical drugs for illegal purposes."

"DEA is responsible for ensuring that all controlled substance transactions take place within DEA's regulatory closed system. All legitimate handlers of controlled substances must maintain strict accounting for all distributions and Cardinal failed to adhere to this policy," stated Special

Agent-in-Charge Karl C. Colder of the Drug Enforcement Administration's Washington Division. "Oxycodone is a very addictive drug and failure to report suspicious orders of oxycodone is a serious matter. The civil penalty levied against Cardinal should send a strong message that all handlers of controlled substances must perform due diligence to ensure the public safety," stated Colder.

The CSA requires distributors of pharmaceuticals, such as Cardinal, to identify and report suspicious orders of controlled substances, such as orders of unusual size, unusual frequency or those that substantially deviate from a normal pattern. If the distributor fails to report suspicious orders to the DEA, civil penalties can be imposed against the distributor.

The settlement resolves allegations arising from an investigation in Maryland as well as an administrative proceeding related to conduct in Florida. According to the settlement agreement, Cardinal admitted that from January 1, 2009 to May 14, 2012, it failed to report suspicious orders to the DEA as required by the CSA. The settlement also resolves allegations that Cardinal failed to maintain effective controls against diversion.

U.S. Attorney Rod J. Rosenstein commended the DEA's Office of Diversion Control, Washington Division, Baltimore District Office for its work in the investigation. U.S. Attorney Rosenstein also thanked U.S. Attorney for the Middle District of Florida A. Lee Bentley, III and Division Chief, Katherine Ho and Civil Chief, Randy Harwell; as well as U.S. Attorney for the Southern District of New York Preet Bharara, and Assistant United States Attorney Tony Pellegrino for their collaborative work. Mr. Rosenstein thanked Assistant United States Attorney Thomas F. Corcoran, who handled the case for the District of Maryland.

Component(s):
USAO - Maryland

Updated December 23, 2016

EXHIBIT 109

AmerisourceBergen

AmerisourceBergen Corporation is an American drug wholesale company that was formed by the merger of Bergen Brunswig and AmeriSource in 2001.[2] They provide drug distribution and related services designed to reduce costs and improve patient outcomes, distribute a line of brand name and generic pharmaceuticals, over-the-counter (OTC) health care products and home health care supplies and equipment to a wide variety of health care providers located throughout the United States, including acute care hospitals and health systems, independent and chain retail pharmacies, mail-order facilities, physicians, clinics and other alternate site facilities, as well as skilled nursing and assisted living centers. They also provide pharmaceuticals and pharmacy services to long-term care, workers' compensation and specialty drug patients.

AmerisourceBergen is a market leader in pharmaceutical distribution handling about 20% of all of the pharmaceuticals sold and distributed throughout the country and ranked 16th on the Fortune 500 list for 2015 with over $100 Billion in annual revenue.[3] In terms of revenue (79.49 billion in 2012) the firm is the largest based in Pennsylvania.[4][5]

AmerisourceBergen Corporation

Type	Public
Traded as	NYSE: ABC (https://www.nyse.com/quote/XNYS:ABC) S&P 500 Component
Industry	Pharmaceutical
Founded	Merger between AmeriSource Health and Bergen Brunswig in 2001
Headquarters	Chesterbrook, Pennsylvania, U.S.
Area served	North America United Kingdom
Key people	Richard C. Gozon (Chairman) Steven H. Collis (President), (CEO) & (Director)
Products	Pharmaceuticals and pharmacy services
Revenue	▲ US$135.9 billion (2015)[1]
Operating income	▼ US$386 million (2015)[1]
Net income	▼ US$-134 million (2015)[1]
Total assets	▲ US$27.73 billion (2015)[1]
Total equity	▼ US$633 million (2015)[1]
Number of employees	16,500 (2015)[1]
Website	AmerisourceBergen.com (http://www.amerisourcebergen.com/)

Contents

History

AmerisourceBergen was formed in 2001 following the merger of AmeriSource Health Corporation and Bergen Brunswig Corporation.[6] AmeriSource and Bergen were both successful pharmaceutical distributors that served similar markets but covered somewhat different geographies. Bringing the two together gave the company a strong national presence that was geared especially towards serving independent community pharmacies, regional retail chain pharmacies, hospitals, physician offices, clinics and other alternate care facilities.

AmerisourceBergen has 26 pharmaceutical distribution centers in the US, nine distribution centers in Canada, four specialty distribution centers in the US, and over 1 million square feet of packaging production capacity in the US and the UK. With the addition of World Courier, the largest specialty courier company in the world, over 150 company-owned offices around the globe were added to the company.

Lawsuit

In 2012 the state of West Virginia filed a lawsuit against AmerisourceBergen[7] On 5/17/2015, the West Virginia Gazette reported, "AmerisourceBergen, the nation's third largest drug wholesaler, shipped 80.3 million hydrocodone pills and 38.4 million oxycodone pills to West Virginia over the five-year span — the highest totals for both drugs by any company named in the state's lawsuit, according to the filing.[8] and that "The lawsuit alleges that the companies have helped fuel the state's pain pill epidemic by shipping excessive amounts of prescription painkillers to southern West Virginia pharmacies."

Corporate structure

AmerisourceBergen operates its pharmaceutical distribution business under four primary units: AmerisourceBergen Drug Corporation (ABDC), AmerisourceBergen Specialty Group (ABSG), AmerisourceBergen Consulting Services (ABCS) and World Courier. In March 2016 Walgreens Boots Alliance Inc. announced it would exercise an option to purchase 22.7 million shares of AmerisourceBergen stock and thereby control 15% of the company.[9]

Good Neighbor Pharmacy

Good Neighbor Pharmacy is an American retailers' cooperative network of more than 3,400 independently owned and operated pharmacies. It has a business affiliation with AmerisourceBergen, which sponsors the network and owns the name "Good Neighbor Pharmacy" Good Neighbor Pharmacy is the sponsor for "Thought Spot" the annual trade show held in Las Vegas.

ThoughtSpot

ThoughtSpot is a four-day trade show put on by Good Neighbor Pharmacy held in or around July in Las Vegas aimed for and limited to community and independent pharmacies.[10][11]

Exhibitors are represented throughout the healthcare industry including, brand name, generic and over the counter products. ThoughtSpot 2013 was hosted at the MGM Grand, Las Vegas from July 24 to July 27. Special guest musical performance by Bret Michaels capped off the week on July 27 at a special attendee-only closing event.[12]

KnowledgeDriven

KnowledgeDriven is a resource site sponsored by AmerisourceBergen.[13]

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External links

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- AmerisourceBergen Specialty Group (http://www.absg.com/)
- Business data for AmerisourceBergen: Google Finance (https://www.google.com/finance?q=ABC) · Yahoo! Finance (https://finance.yahoo.com/q?s=ABC) · Reuters (https://www.reuters.com/finance/stocks/overview?symbol=ABC) · SEC filings (https://www.sec.gov/cgi-bin/browse-edgar?action=getcompany&CIK=ABC)

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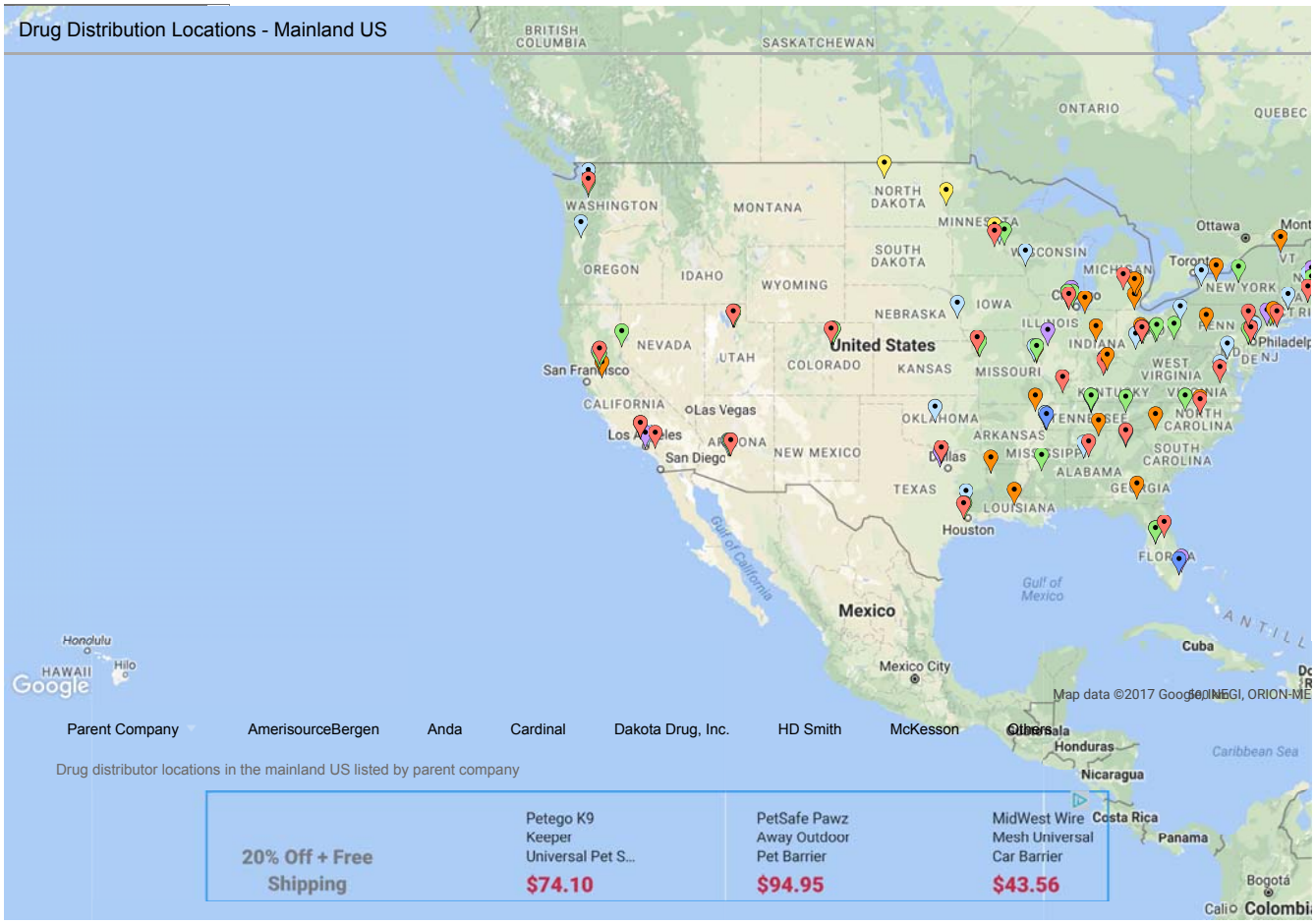
EXHIBIT 110



Actavis Mid Atlantic, LLC*
1860 Outer Loop Rd Louisville, Kentucky 40219
Distribution Center: Actavis Mid Atlantic, LLC

AF Hauser Inc.
4401 East US Hwy 30 Valparaiso, Indiana 46383
Distribution Center: AF Hauser Inc.

AmerisourceBergen
5100 Jaindl Blvd Bethlehem, Pennsylvania 18017
Distribution Center: ABC Bethlehem

AmerisourceBergen
345 International Blvd Brooks, Kentucky 40109
Distribution Center: ABC Brooks ASD

AmerisourceBergen
2550 John Glenn Ave, Ste #A Columbus, Ohio 43217
Distribution Center: ABC Columbus AHP

AmerisourceBergen
11200 N Congress Ave Kansas City, Missouri 64153
Distribution Center: ABC Congress

AmerisourceBergen
1851 California Avenue Corona, California 92881
Distribution Center: ABC Corona

AmerisourceBergen

501 W 44th Denver, Colorado 80216
Distribution Center: ABC Denver

AmerisourceBergen
6810 Shady Oak Drive Eden Prairie, Minnesota 55344
Distribution Center: ABC Eden Prairie

AmerisourceBergen
9900 JEB Stuart Pwy Glen Allen, Virginia 23060
Distribution Center: ABC Glen Allen

AmerisourceBergen
19220 64th Ave South Kent, Washington 98032
Distribution Center: ABC Kent

AmerisourceBergen
Columbus - 6305 LaSalle Drive Lockbourne, Ohio 43137
Distribution Center: ABC LaSalle

AmerisourceBergen
101 Norfolk Street Mansfield, Massachusetts 2048
Distribution Center: ABC Mansfield

AmerisourceBergen
120 Trans Air Drive Morrisville, North Carolina 27560
Distribution Center: ABC Morrisville

AmerisourceBergen
2100 Directors Row Orlando, Florida 32809
Distribution Center: ABC Orlando Division

AmerisourceBergen
322 N. 3rd Street Paducah, Kentucky 42001
Distribution Center: ABC Paducah

AmerisourceBergen
172 Cahaba Valley Pk Pelham, Alabama 35124
Distribution Center: ABC Pelham Birmingham

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1825 South 43rd Avenue Phoenix, Arizona 85009
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Distribution Center: ABC Roanoke

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1001 W. Taylor Road Romeoville, Illinois 60446
Distribution Center: ABC Romeoville

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1325 W. Striker Ave Sacramento, California 95834
Distribution Center: ABC Sacramento Striker

AmerisourceBergen
1765 Freemont Drive Salt Lake City, Utah 84104
Distribution Center: ABC Salt Lake City

AmerisourceBergen
12727 W Airport Blvd Sugar Land, Texas 77478

Distribution Center: ABC Sugarland

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1085 N Satellite Blvd Suwanee, Georgia 30024
Distribution Center: ABC Suwanee

AmerisourceBergen
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Distribution Center: ABC Thorofare

AmerisourceBergen
24903 Avenue Kearney Valencia, California 91355
Distribution Center: ABC Valencia

AmerisourceBergen
One Industrial Pk Dr Williamston, Michigan 48895
Distribution Center: ABC Williamston

Anda
2915 Weston Road Weston, Florida 33331
Distribution Center: Anda Pharmaceuticals

Anda
8644 Polk Lane Olive Branch, Mississippi 38654
Distribution Center: Anda Pharmaceuticals

Anda
6500 Adelaude Ct Groveport, Ohio 43125
Distribution Center: Anda Pharmaceuticals

Associated Phar, Inc.*
211 Lonnie Crawford Blvd Scottsboro, Alabama 35769
Distribution Center: Associated Phar, Inc.

AmerisourceBergen
5500 New Horizons Blvd. North Amityville, New York 11701
Distribution Center: Bellco Drug Corp "Division of AmerisourceBergen

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Burlington Drug Company
92 Catamount Drive Milton, Vermont 5468
Distribution Center: Burlington Drug Co

Capital Wholesale Drug
873 Williams Avenue Columbus, Ohio 43212
Distribution Center: Capital Wholesale Drug

Cardinal
801 C St NW, Ste #B Auburn98001, Washington 98001
Distribution Center: Cardinal Auburn

Cardinal
2353 Prospect Drive Aurora, Illinois 60504
Distribution Center: Cardinal Aurora

Cardinal
11 Centennial Drive Peabody, Massachusetts 1960
Distribution Center: Cardinal Boston

Cardinal
4875 Florence Street Denver, Colorado 80238

Distribution Center: Cardinal Denver

Cardinal
160 Tower Drive Burr Ridge, Illinois 60527
Distribution Center: Cardinal DIK Drug Company

Cardinal
3238 Dwight Road Elk Grove, California 95758
Distribution Center: Cardinal Elk Grove

Cardinal
4 Cardinal Health Court Greensboro, North Carolina 27407
Distribution Center: Cardinal Greensboro

Cardinal
Ingram Boulevard #140 La Vergne, Tennessee 37086
Distribution Center: Cardinal Health 108 Inc (Novis)

Cardinal
2901 Eeloe Street Hudson, Wisconsin 54016
Distribution Center: Cardinal Hudson

Cardinal
7601 NE Gardner Avenue Kansas City, Montana 64120
Distribution Center: Cardinal Kansas City

Cardinal
2512 Westcott Boulevard Knoxville, Tennessee 37931
Distribution Center: Cardinal Knoxville

Cardinal
2045 Interstate Drive Lakeland, Florida 33805
Distribution Center: Cardinal Lakeland

Cardinal
15 Ingram Blvd, Ste 140 LaVergne, Tennessee 37086
Distribution Center: Cardinal LaVergne (SPD)

Cardinal
1240 Gluckstadt Road Madison, Mississippi 39110
Distribution Center: Cardinal Madison

Cardinal
5995 Commerce Center Drive Groveport, Ohio 43125
Distribution Center: Cardinal NLC

Cardinal
3540 East Pike Zanesville, Ohio 43701
Distribution Center: Cardinal NPP

Cardinal
850 Airport Dist. Drive Zanesville, Ohio 43701
Distribution Center: Cardinal NPP2

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6640 Echo Drive, Ste J Reno, Nevada 89506
Distribution Center: Cardinal Reno (SPD)

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Distribution Center: Cardinal Roanoke

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Distribution Center: Cardinal Wheeling

Dakota Drug, Inc.
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Dakota Drug, Inc.
4121 12th Avenue West Fargo, North Dakota 58103
Distribution Center: Dakota Drug

Dakota Drug, Inc.
28-32 N Main Street Minot, North Dakota 58701
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Eveready Wholesale Drugs*
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Distribution Center: Eveready Wholesale Drugs

Frank W. Kerr Company
43155 W Nine Mile Road Novi, Michigan 48375
Distribution Center: Frank W Kerr Co

Harvard Drug Group, LLC.
31778 Enterprise Drive Livonia, Michigan 48150
Distribution Center: Harvard Drug Group, LLC.

Harvard Drug Group, LLC.
5110 West 74th Street Indianapolis, Indiana 46268
Distribution Center: Harvard Drug Group, LLC.

HD Smith
1370 Victoria St Carson, California 90746
Distribution Center: HD Smith Drug Carson

HD Smith
1101 W Vickery Blvd Fort Worth, Texas 76104
Distribution Center: HD Smith Drug Fort Worth

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670 Belleville Turnpike Kearny, New Jersey 7032
Distribution Center: HD Smith Drug Kearny

HD Smith
6001 Global Distribution Way Louisville, Kentucky 40228
Distribution Center: HD Smith Drug Louisville

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1901 NW 25th Avenue Pompano Beach, Florida 33069
Distribution Center: HD Smith Drug Pompano Beach

HD Smith
4650 Industrial Dr Springfield, Illinois 62703
Distribution Center: HD Smith Drug Springfield

HD Smith
8 Marin Way Stratham, New Hampshire 3885
Distribution Center: HD Smith Drug Stratham

HD Smith
950 Lively Blvd. Wood Dale, Illinois 60191
Distribution Center: Smith Medical Partners, LLC

J.M. Smith Corporation
9098 Fairforest Road Spartanburg, South Carolina 29301
Distribution Center: J.M. Smith Corporation

J.M. Smith Corporation
1104 Jones Road Paragould, Arkansas 72451
Distribution Center: Smith Drug Company

J.M. Smith Corporation
1500 Commerce Drive Valdosta, Georgia 31601
Distribution Center: Smith Drug Company

Cardinal
152-35 10th Ave Whitestone, New York 11357
Distribution Center: Kinray Whitestone

Louisiana Wholesale Drug Company*
2085 I-49 S. Service Rd Sunset, Louisiana 70584
Distribution Center: Louisiana Wholesale Drug

McKesson
14500 E 39th Avenue Aurora, Colorado 80011
Distribution Center: McKesson Aurora

McKesson
1995 McKesson Street Aurora, Illinois 60502
Distribution Center: McKesson Aurora

McKesson
3301 Pollok Drive Conroe, Texas 77303
Distribution Center: McKesson Conroe

McKesson
400 Delran Pkwy Delran, New Jersey 8075
Distribution Center: McKesson Delran

McKesson
2975 Evergreen Drive Duluth, Georgia 30096
Distribution Center: McKesson Duluth

McKesson
710 132nd Street, SW Everett, Washington 98204
Distribution Center: McKesson Everett

McKesson
3003 Airport Road La Crosse, Wisconsin 54603
Distribution Center: McKesson La Crosse

McKesson
7009 S 108th Street La Vista, Nebraska 68128
Distribution Center: McKesson La Vista

McKesson
1515 W Bella Vista Street Lakeland, Florida 33805
Distribution Center: McKesson Lakeland

McKesson
7721 Polk Street Landover, Maryland 20785
Distribution Center: McKesson Landover

McKesson
38220 Plymouth Road Livonia, Michigan 48150
Distribution Center: McKesson Livonia

McKesson
6775 Jefferson Metropolitan Pkwy McCalla, Alabama 35111
Distribution Center: McKesson McCalla

McKesson
4836 S Ridge Blvd. Memphis, Tennessee 38115
Distribution Center: McKesson Memphis

McKesson
4853 Crumpler Street Memphis, Tennessee 38141
Distribution Center: McKesson Memphis RDC

McKesson
5960 East Shelby Drive Memphis, Tennessee 38141
Distribution Center: McKesson Memphis RDC

McKesson
4971 Southridge Blvd. Memphis, Tennessee 38141
Distribution Center: McKesson Memphis Repak

McKesson
9 Aegean Drive Methuen, Massachusetts 1844
Distribution Center: McKesson Methuen

McKesson

2798 New Butler Road New Castle,, Pennsylvania 16101
Distribution Center: McKesson New Castle

McKesson
#1 Commerce Drive O'Fallon, Missouri 63366
Distribution Center: McKesson O'Fallon

McKesson
4012 South Purdue Oklahoma City, Oklahoma 73179
Distribution Center: McKesson Oklahoma City

McKesson
8313 Polk Lane Olive Branch, Mississippi 38654
Distribution Center: McKesson Olive Branch

McKesson
401 Mason Road La Vergne, Tennessee 37086
Distribution Center: McKesson Plasma and Biologics

McKesson
280 Dividend Road Rocky Hill, Connecticut 6067
Distribution Center: McKesson Rocky Hill

McKesson
10504 McKesson Drive Ruther Glen, Virginia 22546
Distribution Center: McKesson Ruther Glen

McKesson
3230 Spruce Street Saint Paul, Minnesota 55117
Distribution Center: McKesson Saint Paul

McKesson
1900 South 4490 West Salt Lake City, Utah 84104
Distribution Center: McKesson Salt Lake City

McKesson
9501 Norwalk Blvd. Santa Fe Springs, California 90670
Distribution Center: McKesson Santa Fe Spgs

McKesson
401 Mason Road LaVergne, Tennessee 37086
Distribution Center: McKesson Specialty Care Dist

McKesson
495 S. 107th Tolleson, Arizona 85353
Distribution Center: McKesson Tolleson

McKesson
3775 Seaport Blvd West Sacramento, California 95691
Distribution Center: McKesson W Sacramento

McKesson
3000 Kenskill Ave Washington Court House, Ohio 43160
Distribution Center: McKesson Wash Court Hse

McKesson
2700 N. America West Seneca, New York 14224
Distribution Center: McKesson West Seneca

McKesson
9700 SW Commerce Circle Wilsonville, Oregon 97070

Distribution Center: McKesson Wilsonville

Midwest Medical Supply
13400 Lakefront Drive Earth City`, Missouri 63045
Distribution Center: Midwest Medical Supply

Morris Dickson Shreveport
10301 Highway 1 South Shreveport, Louisiana 71115
Distribution Center: Morris Dickson Shreveport

North Carolina Mutual Drug Company
816 Ellis Road Durham, North Carolina 27703
Distribution Center: North Carloina Mutual Whsle Drug

Pharmacy Buying Association
1825 NW Vivion Rd, Bldg "C Riverside, Missouri 64150
Distribution Center: Pharmacy Buying Association

Prescription Supply, Inc.
2233 Tracy Road Northwood, Ohio 43619
Distribution Center: Prescription Supply, Inc.

R & S Sales, Inc
256 Geiger Road Philadelphia, Pennsylvania 19115
Distribution Center: R & S Sales, Inc

Rochester Drug Cooperative, Inc
50 Jet View Drive Rochester, New York 14624
Distribution Center: Rochester Drug Cooperative, Inc

Valley Wholesale Drug Company
1401 W Freemont Blvd Stockton, California 95203
Distribution Center: Valley Wholesale Drug Company

Value Drug Company
1 Golf View Drive Altoona, Pennsylvania 16601
Distribution Center: Value Drug Company

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EXHIBIT 111

Drug firms poured 780M painkillers into WV amid rise of overdoses

Eric Eyre, Staff Writer

December 17, 2016

SAM OWENS | Gazette-Mail - Kay Mullins (left) and Tiffany Vincent, mother and daughter of Mary Kathryn Mullins, pose for a portrait in the dining room of the house where they both live and where Mary Kathryn died of a drug overdose on Dec. 23, 2015. Over the years, Kay has helped raise her granddaughter Tiffany, who has also battled drug addiction, and her great-granddaughters, Kylie and Madyson.

Related Stories

Congressional opioid investigation targets drug wholesaler Miami-Luken
Drug-addled WV county sues pain-pill shippers, doctor

Editor's Note: This is part one of a two-part series. For the second part, click here.

Follow the pills and you'll find the overdose deaths.

The trail of painkillers leads to West Virginia's southern coalfields, to places like Kermit, population 392. There, out-of-state drug companies shipped nearly 9 million highly addictive — and potentially lethal — hydrocodone pills over two years to a single pharmacy in the Mingo County town.

Rural and poor, Mingo County has the fourth-highest prescription opioid death rate of any county in the United States.

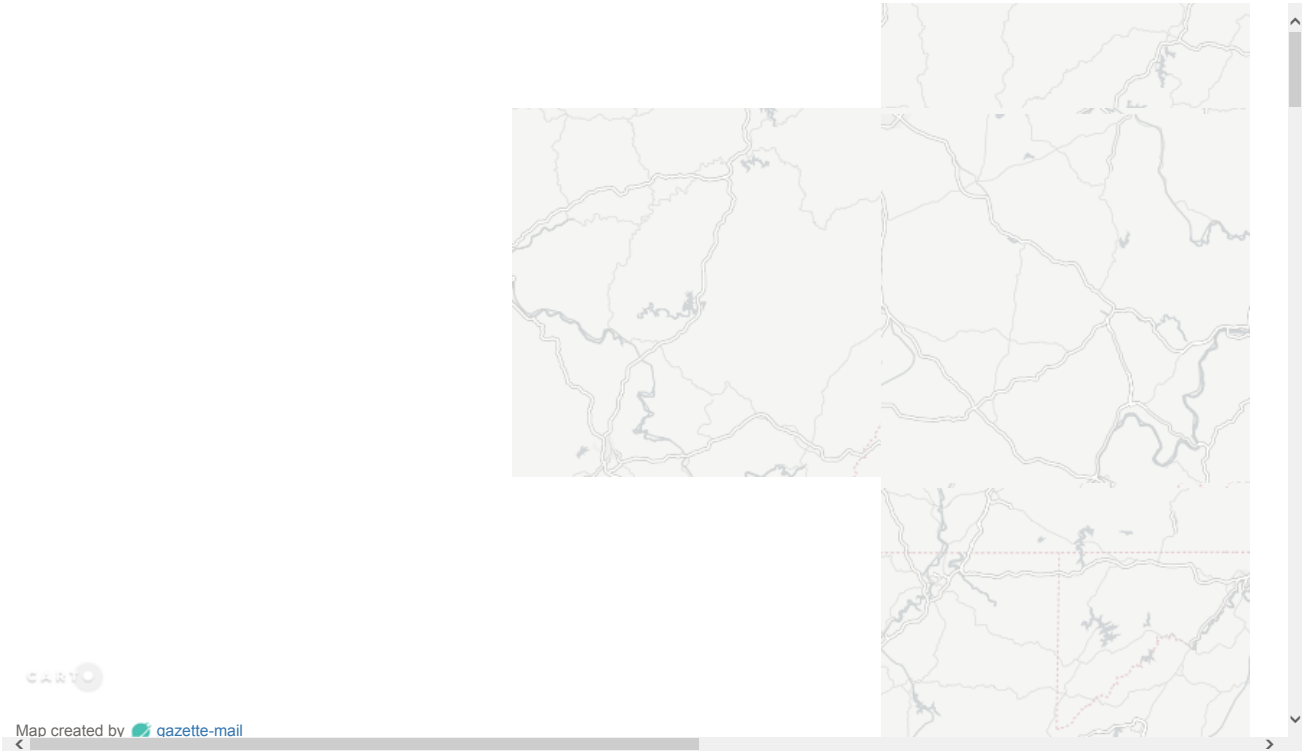
The trail also weaves through Wyoming County, where shipments of OxyContin have doubled, and the county's overdose death rate leads the nation. One mom-and-pop pharmacy in Oceana received 600 times as many oxycodone pills as the Rite Aid drugstore just eight blocks away.

In six years, drug wholesalers showered the state with 780 million hydrocodone and oxycodone pills, while 1,728 West Virginians fatally overdosed on those two painkillers, a Sunday Gazette-Mail investigation found.

The unfettered shipments amount to 433 pain pills for every man, woman and child in West Virginia.

“These numbers will shake even the most cynical observer,” said former Delegate Don Perdue, D-Wayne, a retired pharmacist who finished his term earlier this month. “Distributors have fed their greed on human frailties and to criminal effect. There is no excuse and should be no forgiveness.”

The Gazette-Mail obtained previously confidential drug shipping sales records sent by the U.S. Drug Enforcement Administration to West Virginia Attorney General Patrick Morrisey's office. The records disclose the number of pills sold to every pharmacy in the state and the drug companies' shipments to all 55 counties in West Virginia between 2007 and 2012.



The wholesalers and their lawyers fought to keep the sales numbers secret in previous court actions brought by the newspaper.

The state's southern counties have been ravaged by a disproportionate number of pain pills and fatal drug overdoses, records show.

The region includes the top four counties — Wyoming, McDowell, Boone and Mingo — for fatal overdoses caused by pain pills in the U.S., according to CDC data analyzed by the Gazette-Mail.

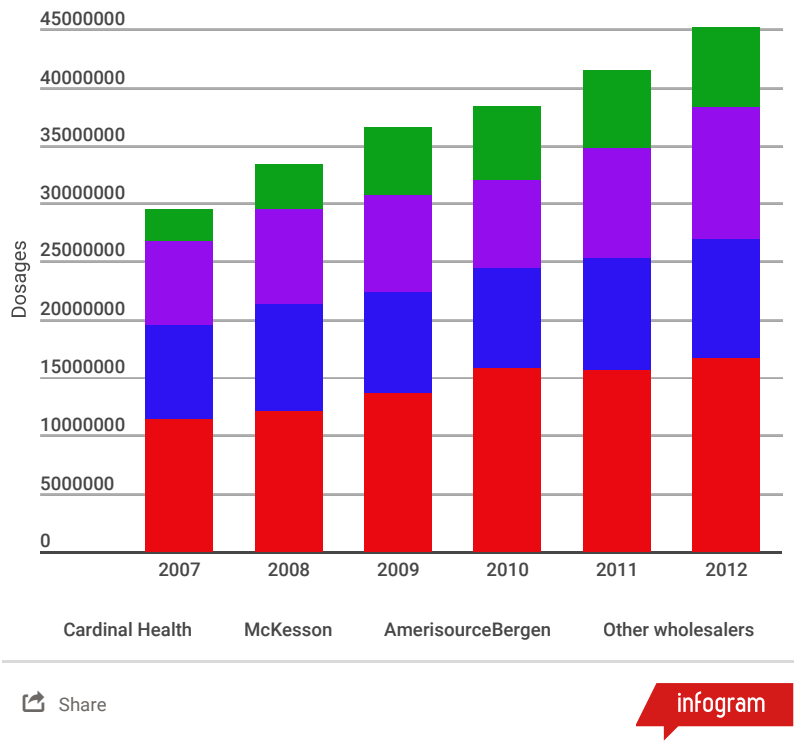
Another two Southern West Virginia counties — Mercer and Raleigh — rank in the top 10. And Logan, Lincoln, Fayette and Monroe fall among the top 20 counties for fatal overdoses involving prescription opioids.

While the death toll climbed, drug wholesalers continued to ship massive quantities of pain pills.

Mingo, Logan and Boone counties received the most doses of hydrocodone — sold under brand names such as Lortab, Vicodin and Norco — on a per-person basis in West Virginia. Wyoming and Raleigh counties scooped up OxyContin pills by the tens of millions.

The nation's three largest prescription drug wholesalers — McKesson Corp., Cardinal Health and AmerisourceBergen Drug Co. — supplied more than half of all pain pills statewide.

Oxycodone wholesalers



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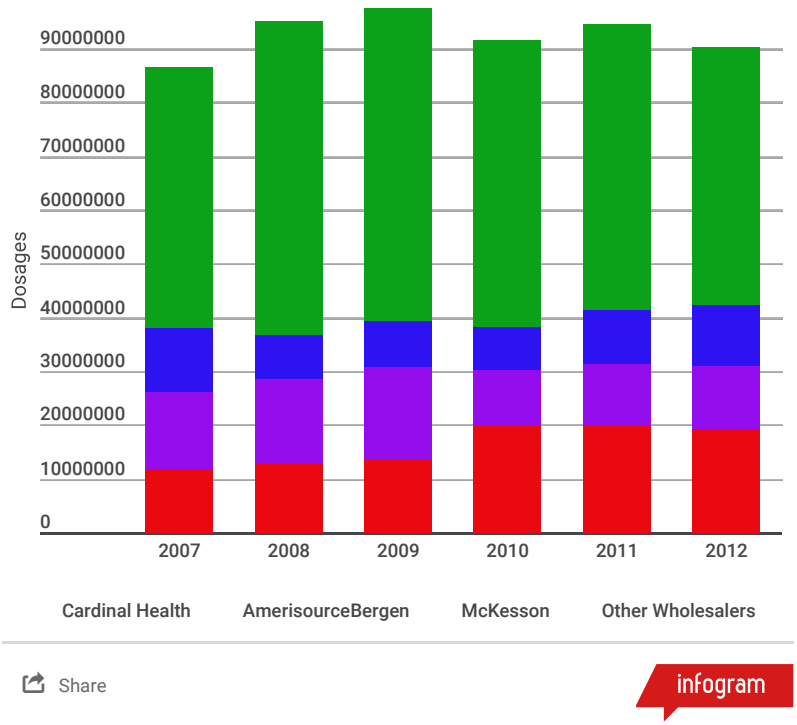
Oxycodone shippers
Create column charts



Hydrocodone wholesalers
Create column charts

For more than a decade, the same distributors disregarded rules to report suspicious orders for controlled substances in West Virginia to the state Board of Pharmacy, the Gazette-Mail found. And the board failed to enforce the same regulations that were on the books since 2001, while giving spotless inspection reviews to small-town pharmacies in the southern counties that ordered more pills than could possibly be taken by people who really needed medicine for pain.

As the fatalities mounted — hydrocodone and oxycodone overdose deaths increased 67 percent in West Virginia between 2007 and 2012 — the drug shippers' CEOs collected salaries and bonuses in the tens of millions of dollars. Their companies made billions. McKesson has grown into the fifth-largest corporation in America. The drug distributor's CEO was the nation's highest-paid executive in 2012, according to Forbes.

In court cases, the companies have repeatedly denied they played any role in the nation's pain-pill epidemic.

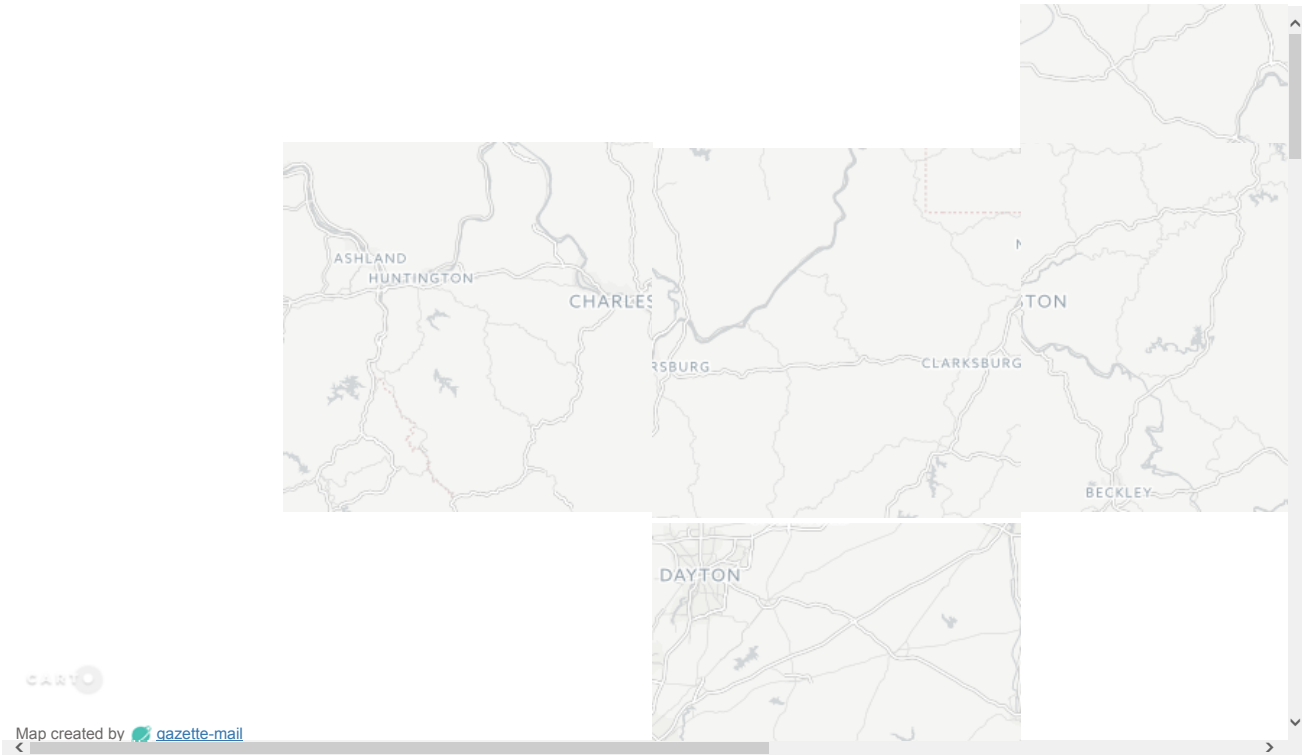
Their rebuttal goes like this: The wholesalers ship painkillers from drug manufacturers to licensed pharmacies. The pharmacies fill prescriptions from licensed doctors. The pills would never get in the hands of addicts and dealers if not for unscrupulous doctors who write illegal prescriptions.

In other words, don't blame the middleman.

“The two roles that interface directly with the patient — the doctors who write the prescriptions and the pharmacists who fill them — are in a better position to identify and prevent the abuse and diversion of potentially addictive controlled substance,” McKesson General Counsel John Saia wrote in a recent letter released by the company last week.

But the doctors and pharmacists weren't slowing the influx of pills.

Cardinal Health saw its hydrocodone shipments to Logan County increase six-fold over three years. AmerisourceBergen's oxycodone sales to Greenbrier County soared from 292,000 pills to 1.2 million pills a year. And McKesson saturated Mingo County with more hydrocodone pills in one year — 3.3 million — than it supplied over five other consecutive years combined.



Year after year, the drug companies also shipped pain pills in increasing stronger formulations, DEA data

shows. Addicts crave stronger pills over time to maintain the same high.

“It starts with the doctor writing, the pharmacist filling and the wholesaler distributing. They're all three in bed together,” said Sam Suppa, a retired Charleston pharmacist who spent 60 years working at retail pharmacies in West Virginia. “The distributors knew what was going on. They just didn't care.”

'She just got hooked'

Mary Kathryn Mullins' path of dependence took her to pain clinics that churned out illegal prescriptions by the hundreds, pharmacies that dispensed doses by the millions and, on many occasions, to a Raleigh County doctor who lectured her about the benefits of vitamins but handed her prescriptions for OxyContin.

“She'd get 90 or 120 pills and finish them off in a week,” recalled Kay Mullins, Mary Kathryn's mother. “Every month, she'd go to Beckley, they'd take $200 cash, no insurance, and the pills, they'd be gone within a week.”

Mary Kathryn Mullins' addiction, her mother said, started after a car crash near her home in Boone County. Her back was hurting. A doctor prescribed OxyContin.

“She got messed up,” Kay Mullins said. “They wrote her the pain pills, and she just got hooked.”

Kay Mullins has a hard time talking about the 10 years that followed, all the lies her daughter told to cover her addiction, stealing from her brother, the time she shot herself in the stomach in an attempt to end her life.

Mary Kathryn Mullins would go to dozens of doctors for prescriptions. She was a “doctor shopper.”

Her mother can't recall most of the doctors by name. She said she believes the doctor who talked to her daughter about vitamins was recently in the news after being charged with prescription fraud. Many rogue pain clinics have been shut down in recent years.

“She'd go to his house in the woods for prescriptions,” Kay Mullins said.

There also were stops at multiple pharmacies in Madison, Logan, Beckley and Williamson. Mary Kathryn Mullins always would find a way to get pills. She kept most for herself, but sometimes she sold them to others, her mother said.

“It tore my family up,” said Kay Mullins, who works at a flower shop in Madison. “You don't sleep. One time she would be OK, and you think she would come out of it, but then something else happens.”

Last December, Mary Kathryn Mullins' hunt for pain pills led her to South Charleston. A doctor prescribed her OxyContin and an anti-anxiety medication, her mother said. A pharmacy in Alum Creek filled it.

Two days later, she stopped breathing in her bed. Her brother, Nick Mullins, a Madison police officer, responded to the 911 call. He tried chest compressions, but he could not revive his sister.

At age 50, Mary Kathryn Mullins was dead.

After the funeral, her mother had one last thing to do. She found an appointment reminder card for Mary Kathryn Mullins' next scheduled visit to the doctor who wrote her final prescription. She dialed the phone number of the doctor's office and spoke to the receptionist.

“I told her my daughter was there Dec. 20,” Kay Mullins recalled. “I said, 'Y'all wrote these prescriptions, and she's gone Dec. 23. I just wanted to let you know she won't be back.'”

Drug wholesalers made billions

In the drug distribution industry, they're called the “Big Three” — McKesson, Cardinal Health, AmerisourceBergen — and they bear no resemblance to the mom-and-pop pharmacies that ordered massive quantities of the drugs the wholesalers delivered in West Virginia.

The Big Three wholesalers together are nearly as large as Wal-Mart, with total revenues of more than $400 billion. Their revenues account for about 85 percent of the drug distribution market in the U.S.

Between 2007 and 2012 — when McKesson, Cardinal Health and AmerisourceBergen collectively shipped 423 million pain pills to West Virginia, according to DEA data analyzed by the Gazette-Mail — the companies earned a combined $17 billion in net income.

Over the past four years, the CEOs of McKesson, Cardinal Health and AmerisourceBergen collectively received salaries and other compensation of more than $450 million.

In 2015, McKesson's CEO collected compensation worth $89 million — more money than what 2,000 West Virginia families combined earned on average.

“What's most remarkable is that the boards of the companies are paying the CEOs as if they were innovators and irreplaceable entrepreneurs, when in fact they are just highly paid middlemen, betting on market consolidation and ever-rising drug prices,” said Ken Hall, international secretary-treasurer of the Teamsters union.

Last month, the Teamsters sent a letter to McKesson board members urging them to investigate allegations raised by Morrisey in a lawsuit he filed against the company earlier this year. The complaint alleges McKesson “flooded” West Virginia with pain pills and gave bonuses and commissions to employees based on sales of highly addictive prescription drugs. The Teamsters' pension funds hold a stake in McKesson.

In a letter to the Teamsters released by McKesson last week, the company denied it gave incentives to executives and other personnel for sales of controlled substances.

McKesson added Morrisey's lawsuit assigns blame to drug wholesalers for West Virginia's opioid crisis “without acknowledging the role played by doctors, pharmacists and the regulatory agencies that oversee doctors and pharmacists.”

“McKesson's shipments were in response to orders placed by these registered entities,” the company's chief lawyer wrote. “Thus, McKesson lawfully shipped controlled substances to registered pharmacies.”

A spokesman for AmerisourceBergen suggested health experts and law enforcement authorities would be better able to comment on whether there's a link between pain-pill volumes and overdose deaths.

Cardinal Health said it shipped 3.4 billion doses of medication in West Virginia between 2007 and 2012. So hydrocodone and oxycodone sales made up about 17 percent of the company's shipments.

“All parties including pharmacies, doctors, hospitals, manufacturers, patients and state officials share the responsibility to fight opioid abuse,” said Ellen Barry, a spokeswoman for Cardinal Health.

In Southern West Virginia, many of the pharmacies that received the largest shipments of prescription opioids were small, independent drugstores like ones in Raleigh and Wyoming counties that ordered 600,000 to 1.1 million oxycodone pills a year. Or they were locally owned pharmacies in Mingo and Logan counties, where wholesalers distributed 1.4 million to 4.7 million hydrocodone pills annually.

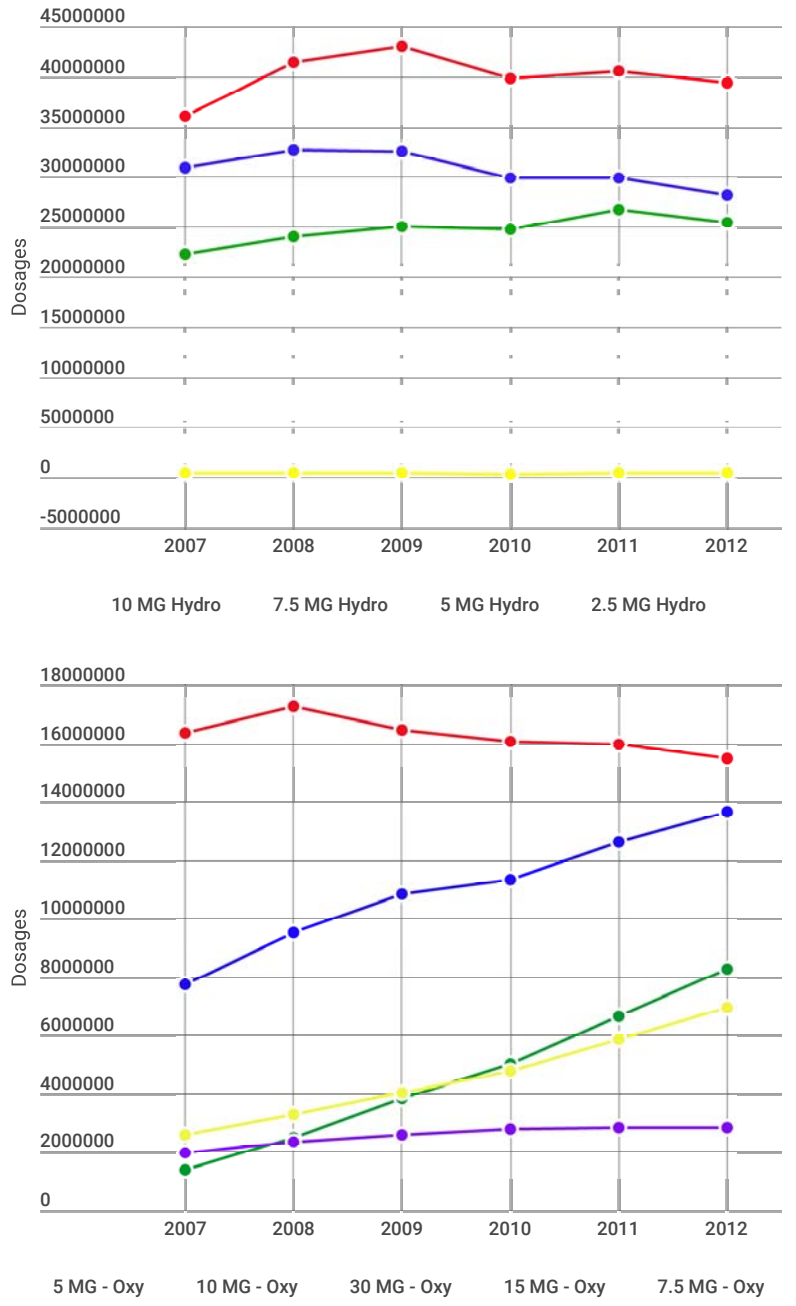
By contrast, the Wal-Mart at Charleston's Southridge Centre, one of the retail giant's busiest stores in West Virginia, was shipped about 5,000 oxycodone and 9,500 hydrocodone pills each year.

Firms shipped stronger pain pills

At the height of pill shipments to West Virginia, there were other warning signs the prescription opioid epidemic was growing.

Drug wholesalers were shipping a declining number of oxycodone pills in 5 milligram doses — the drug's lowest and most common strength — and more of the painkillers in stronger formulations.

Prescription opioid dosage strength



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Hydro strength
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A DEA agent warned Morrisey's aides about the disturbing trend in January 2015, according to an email released by the attorney general in response to a Freedom of Information Act request from the Gazette-Mail.

Between 2007 and 2012, the number of 30-milligram OxyContin tablets increased six-fold, the supply of 15-milligram pills tripled and 10-milligram oxycodone nearly doubled, the DEA records sent to Morrisey's office show.

In the email to Morrisey, DEA agent Kyle Wright said the higher-strength oxycodone pills were commonly abused.

The DEA agent sent Morrisey's office a separate email about hydrocodone shipments to the state. West Virginia pharmacies were mostly buying 10-milligram hydrocodone tablets — the most potent dosage at the time.

Once hooked on painkillers, addicts typically demand higher and higher doses.

Chelsea Carter, a recovering 30-year-old addict who now works as a therapist at a drug treatment center in Logan County, remembers crushing, snorting and injecting OxyContin — always wanting the strongest pills she could get her hands on. She once shot up with eight to 10 doses of oxycodone, passed out and woke up with the needle still stuck in her arm.

“You're turned on to this potent substance, and your tolerance grows,” said Carter, who quit using pills in 2008, the day she went to jail after taking part in a theft ring that sold stolen goods for painkillers.

“When they handcuff you, and you walk through the doors, and you're in an orange jumpsuit and they slam the doors behind you, that's when you wonder, 'is two to 20 years worth it for one OxyContin?'” Carter said. “That's when I hit my knees and prayed, 'Lord, if you ever bring me out of this, I'll never touch another drug again.'”

The addicted come to see Carter at the clinic just off Main Street in downtown Logan. They want to get off pain pills or heroin — a street drug causing more and more overdose deaths in West Virginia every year.

They talk to Carter, eight to 10 of them a day. They've lost children, parents, grandparents. They've lost homes. They're tired of living that way.

Carter listens and tells them her story, how every day she wakes up and makes a decision not to use pills.

“I've buried a lot of friends from drug addiction,” Carter said. “I don't want to bury another one.”

Her trail follows the direction of hope.

Gazette-Mail staff writer Andrew Brown contributed to this story.

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AP Top 25 Poll
Poll Released: Oct 8

RANK	TEAM	PV RANK
1	Alabama (43)	1
2	Clemson (18)	2
3	Penn State	4
4	Georgia	5
5	Washington	6

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TUE 10 **BLUE YONDER**
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