



The Institute for Safe Medication Practices

A Nonprofit Organization Educating the Healthcare
Community and Consumers About Safe Medication Practices

QuarterWatch: 2008 Quarter 4

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Serious Adverse Drug Event Reports Increase 25% in 2008

Executive Summary

Fatal, disabling and serious adverse drug events reported to the Food and Drug Administration increased by 25% for the full year of 2008, compared to the previous year. The FDA received domestic reports of 100,789 cases of severe injury in 2008, compared to 80,598 reports in 2007. This was the largest one-year increase since the beginning of our historical data in 1998, although large increases were also reported in 2002 and 2003.

The biggest identifiable safety factor behind the 2008 increase was reports associated with massive generic drug recalls in 2008 because of product quality assurance problems that according the FDA posed a “reasonable probability” of serious injury or death.¹ The consumer-level recalls included more than half of the nation’s supply of heparin in vial form, about 50% of the nation’s supply of the heart drug digoxin, and still undetermined quantities of morphine, isosorbide and propafenone.

A second major factor explaining the increase was more voluntary reporting both directly to the FDA for numerous drugs and, in specific cases by manufacturers who learned of more events through increased contact with patients. We estimate that approximately one-half of the 25% increase in 2008 was explained by more voluntary reporting.

In the 4th quarter of 2008 alone, we identified 24,609 reported cases of death, disability and other serious adverse drug events, a total of 18.6% higher than the same quarter one year earlier, and slightly less than the previous calendar quarter.

In the quarter we saw warning flags about two drug safety problems. Fentanyl, a narcotic 100 times more potent than morphine, was the suspect drug in more cases of preventable medication error than any other drug. Product recalls from KV Pharmaceutical of St. Louis for possibly over strength tablets of seven different generic drugs were associated with reports of death or serious injury in 458 cases in the 3rd and 4th quarters. We discuss these signals in the full report.

The ISMP QuarterWatch pilot monitoring program evaluates computer excerpts of all serious, disabling and fatal adverse drug events reported to the FDA for patients in the

United States. The US system for postmarket safety surveillance relies on voluntary reports submitted by consumers, doctors, pharmacists and other health professionals. The submission of a report does not in itself prove that the suspect drug caused the event described. There are no reliable estimates of what fraction of serious adverse drug events are ever reported, and small studies and our own investigations show wide variation between drugs and among different types of adverse reactions. Although we have occasionally documented instances where injuries for a drug may be over reported, the events reported to the FDA are believed to be a relatively small fraction of the drug-related injuries actually occurring.

Updates

- Varenicline (CHANTIX). In July 2009 the FDA and Pfizer greatly strengthened the warnings regarding the risks of violence to self and others associated with this aid to stopping smoking. But in a step backward, weak and potentially misleading language about the risk of accidents was added to the patient Medication Guide. Given the accumulating evidence that varenicline causes violent and aggressive behavior, its use should be further restricted in the military, as well as for police and other emergency workers.
- Montelukast (SINGULAIR). We previously reported a large surge in adverse event reports of psychiatric side effects, apparently in response to an FDA advisory notice posted after Merck reported a small number of cases of suicidal behavior. In August 2009 the FDA and Merck added precautionary language to the prescribing information for doctors. Merck also provided a clear alert for patients on its SINGULAIR web site. The alert was also expanded to include additional psychiatric side effects including aggression, abnormal dreams and hallucinations.

Adverse Event Reporting System

We observed substantial increases in the 4th quarter for two Biogen Idec products, interferon beta (AVONEX brand) and natalizumab (TYSABRI). The company said one factor in the increase was that it had begun submitting its reports electronically in the 4th quarter and because of software compatibility problems with the FDA, duplicate reports were being generated.

Conclusions

Although the dangers of fentanyl transdermal systems have been documented in numerous reports and subject to previous FDA regulatory action, the new data show that the risks of this high alert drug are not under adequate control. We believe measures are needed to insure that every patient receives education on the risks and safe use of this medication.

The FDA and Pfizer need to strengthen and clarify the accident warning for varenicline to make clear to all patients that severe adverse effects may occur when the drug is started, after a few weeks, or even on discontinuation. In addition, because the drug can cause violent behavior, interrupt muscle control and cause blackouts, we believe the Department of Defense should extend its ban from aircraft and missile crews to all active duty military personnel. Its use should also be limited in police and emergency personnel.

We continue to have concern about the massive recalls of generic drugs, mainly because defective quality assurance resulted in companies distributing potentially over strength tablets for drugs in which a small overdose can be life-threatening. We have also noted that neither the FDA nor the manufacturer will reveal the size of some large recalls, and that manufacturers are often left to handle any public announcement.

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Background

QuarterWatch is a pilot program designed to improve patient safety by monitoring serious adverse drug event reports submitted to the Food and Drug Administration. The goals of the program are: 1) To examine overall trends in reported deaths and injury associated with drug therapy, 2) To identify signals for specific drugs that might indicate a new risk to patient safety, 3) To improve the quantity and quality of reports flowing through the voluntary system.

QuarterWatch is based on adverse drug event reports best known to consumers and health professionals as FDA MedWatch reports. These reports are submitted by consumers and health professionals directly to the FDA, or to drug manufacturers who then forward the completed reports to the agency. Manufacturers are required to submit an expedited report within 15 days if it contains at least one event that is not currently described in the product labeling and the patient outcome is serious. Manufacturers also submit periodic reports of other events. Manufacturers submit periodic reports to FDA quarterly for newer drugs (FDA-approved for three years or less) and annually for older drugs. Not all of the reports that the FDA receives for drug and therapeutic biologic products are entered into the FDA's Adverse Event Reporting System (AERS) database. Manufacturers may obtain waivers for submitting reports that are not serious and involve older drugs. The FDA publishes computer extracts of all reports for research use after removing personal identifying information. QuarterWatch evaluates these reports on a quarterly basis.

The serious adverse drug event reports analyzed for QuarterWatch have a unique set of strengths and weaknesses that must be considered when interpreting results of this program. The system relies on voluntary reports rather than any form of systematic surveillance. What fraction of all adverse drug events that occur is ever reported has not been determined, and may vary widely over time, between drugs, and among different kinds of adverse events. This means the totals for deaths and injury in this report are a small proportion of those actually occurring. In addition, the submission of an adverse event report does not in itself prove that the suspect drug caused the adverse event--it only shows that an observer suspected a link. In addition, some reports may contain details suggesting that a causal relationship was unlikely. Other factors, however, may strengthen the evidence of a causal link, and adverse drug event reports form the basis for many official actions by the FDA and drug manufacturers, including major warnings and drug withdrawal.

One strength of the system is its sensitivity. With millions of patients and hundreds of thousands of health professionals as observers, and no restrictive rules for reporting, the system is capable of detecting adverse drug effects that may have been overlooked or underestimated in clinical testing prior to approval. Doctors, pharmacists and patients may also identify an adverse effect overlooked by experts who may have preconceptions about the drug's properties, or who were bound by restrictive testing protocols.

We have examined the system in greater depth in previous reports.² Typically the data produce what we describe as signals of a problem that often requires further investigation.

Methodology

Computer excerpts of all adverse event reports received by the FDA since November 1997 are maintained with open-source database software MySQL (www.mysql.com) and analyzed with an open-source statistical program, the R Package for Statistical Computing (www.r-project.org).

QuarterWatch screens all adverse event reports received by the FDA in the quarter under study. From these reports we select for analysis new cases that involved a serious, disabling, or fatal outcome, and that originated in the United States. We have described our criteria and classification scheme in previous reports.^{3 4} Approximately four out of five reports received in the quarter are excluded from our analysis. The most important reasons were: a) reported injuries were not serious, b) the reports were from foreign sources, and c) the reports were updates of cases previously reported.

We made no changes in methodology since our previous report except that we revised our historical tables to correct a software error. In reviewing previous results we discovered that we had omitted from historical tables cases that had been revised or updated by drug manufacturers in calendar quarters after they were submitted. In the previous report for the third quarter of 2008 this led an overstatement of the growth in reports compared to the previous quarter.⁵ We reported a 30.5% increase from the same quarter in previous year while our corrected figures indicated a 13.4% increase.

In rebuilding our historical tables we have also learned that future comparisons will not be exact and are also subject to change. When the FDA distributes the computer files of new reports for a calendar quarter it includes some late reports from the previous quarter and hundreds of follow up reports from manufacturers that update previously submitted reports, some of which were several years old. Because both the FDA and ISMP analyze the most recent report for every known event, the late follow up reports mean that event totals may change over time. In addition, ISMP revises and updates the drug name dictionary from time to time. Finally, the industry revises the dictionary of medical terms used to describe events twice a year and ISMP updates its terminology once a year.

Results

From October through December 2008 the FDA received 24,609 domestic reports of serious, disabling or fatal injuries associated with drug therapy. The report total was little changed from the previous quarter (24,921 cases), but an increase of 18.6% over the 4th quarter of 2007, or 3,788 additional cases.

For the entire year of 2008, the FDA experienced a 25% increase over 2007, an increase of 20,191 cases compared to the previous year. A historical table shows that the growth rate declined in 2005 and 2006, and resumed climbing in 2007 and 2008. (Figures 1 and 2)

Figure 1. Reported Serious Events

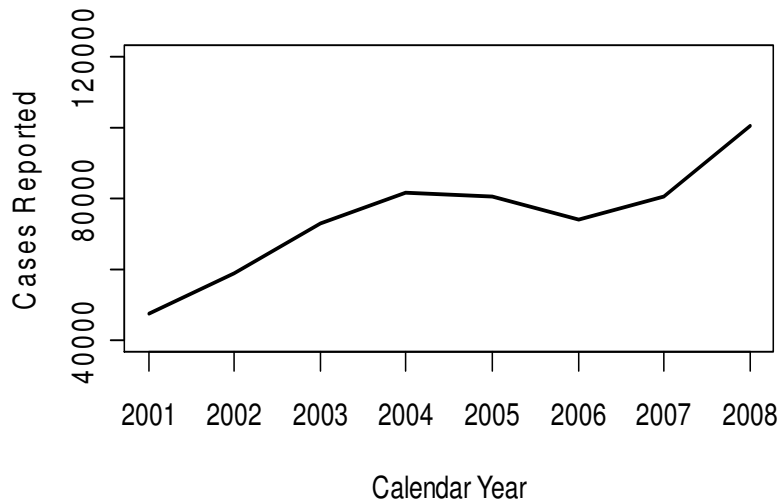
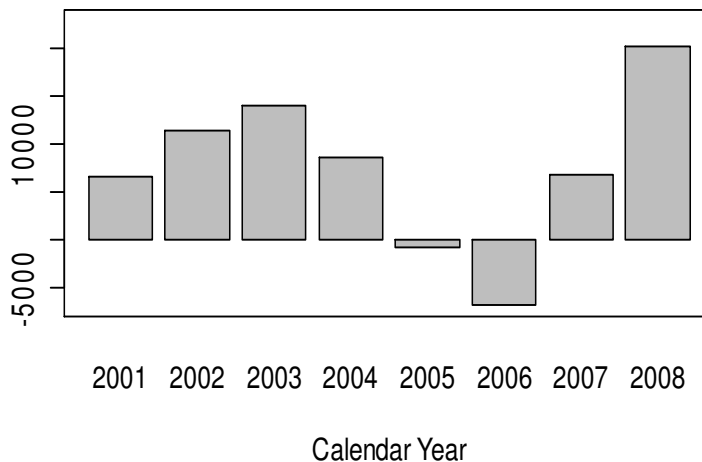


Figure 2. Annual Change in Cases



Reports of patient deaths, included in the totals above, increased even more rapidly with 15,189 deaths reported in 2008, compared to 9,728 the previous year, a 56% increase. This increase followed four years of declining numbers of reported fatalities and was slightly less than the previous high year, 2003, when 15,935 patient deaths were reported as drug adverse events.

Effect of Drug Recalls

We also examined the influence of several large scale generic drug recalls on the 25% growth in 2008 reports. In the first quarter we observed a large surge in reports associated with the recall of heparin, a drug to prevent unwanted blood clots. In the second quarter we saw an even larger increase associated with the recall of digoxin, a drug to prevent heart rhythm disturbances and increase the cardiac output of failing hearts; in the third and fourth quarters we examined three drugs recalled by KV Pharmaceutical, isosorbide, a drug to relieve chest pains in heart disease patients, propafenone, a drug for serious heart rhythm disturbances, and morphine, the narcotic. Heparin, a drug usually administered intravenously in medical facilities, was recalled because of contamination that was triggering severe allergic reactions.⁶ The contaminant was identified as oversulfated chondroitin sulfate introduced by a supplier in China that provided the raw heparin to several US drug manufacturers, but most notably to Baxter Healthcare. The other drugs were recalled because of manufacturing defects seen in US plants of Actavis Group and KV Pharmaceutical,^{7 8} leading to the possibility of over strength (or under strength) tablets. The drugs were recalled to the consumer level and classified as potentially life threatening because in each case an under- or overdose could lead to life threatening consequences. The two companies also recalled scores of other drug products, but these did not lead to large numbers of adverse drug event reports with serious and fatal outcomes.

We found that about one-quarter of the approximately 20,000 case increase in reported deaths and serious injury in 2008 could be linked to these drug recalls, notably digoxin and heparin as shown in the next two figures. The five drugs accounted for 5,549 reports in 2008 compared to 114 cases reported in the previous year. Heparin and digoxin alone accounted for 5,099 (92%) of the cases.

Figure 3. Heparin Reports

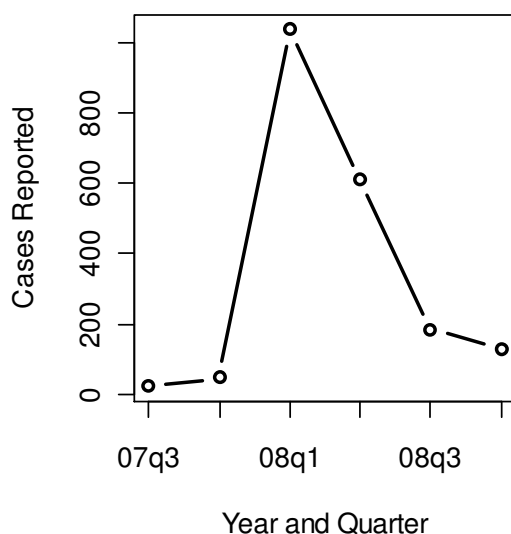
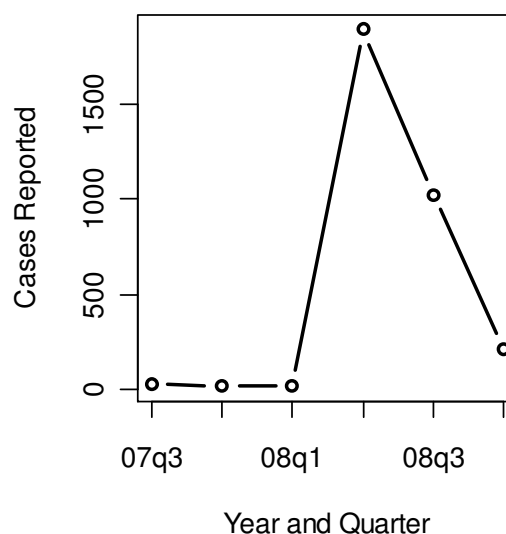


Figure 4. Digoxin Reports



Unfortunately, we believe the total of approximately 5,000 reports associated with product quality recalls does not provide a reliable estimate of the number of patients seriously injured or killed because of over strength tablets or other product problems. The true number could be substantially higher, or markedly lower. It is impossible to know how many cases might have occurred but neither consumers nor health professionals thought to make the connection to the recalled product. On the other hand, even without a defective product, all five drugs shared the property that a small overdose could have potentially fatal consequences. Without a program of extensive testing of returned tablets, it cannot be known how many of the reported injuries were caused by a defective tablet, and how many occurred because of an unintentional overdose.

We discuss the most recent product recall—all tablets manufactured by KV Pharmaceutical—in a separate section below.

Increased Reporting in 2008

Reports of serious injury and death associated with drug therapy reach the FDA through two markedly different routes. Health professionals and consumers may report adverse events directly to the FDA under the agency’s MedWatch Safety Information and Adverse Event Reporting Program, by telephone or online. (1-800-332-1088. <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>) While this is the part of the reporting program that receives the most publicity, in fact the agency receives relatively few reports directly--few thousand every calendar quarter. All the other reports are submitted through drug manufacturers, who collect the information and report the cases of which they are informed. For many years the increasing number of adverse event cases reported each year came entirely, or largely from drug manufacturers. In 2008 that picture changed, and direct reports increased markedly.

In 2008, the FDA received 24,267 direct reports of serious, disabling and fatal injury associated with drug therapy, a 43% increase over the 16,936 case reports it received the previous year. This increase all by itself accounts for nearly half of the overall growth in reporting from 2007 to 2008. Nevertheless, the share of case reports made directly to the FDA remains relatively small, but rose from 21% of all cases in 2007 to 24% of all cases in 2008.

It should be noted, however, that increased volume of reports received by the FDA in 2008 also included specific drugs producing signals we have discussed elsewhere, notably varenicline, heparin, digoxin and montelukast.

We believe one reason for the increase in direct reports to the FDA is the growing number of internet links to the MedWatch site. For example, FDA public health advisories and more preliminary “Early Communications” specifically encouraged reporting adverse events and provide a link.^{6 9 10} Drug company sites may also contain a similar link to the FDA MedWatch Internet site rather than its own program.¹¹

The pattern was somewhat different for drug manufacturers, where we identified large effects limited to a small number of drugs, and specific company policies. We found at least three instances in 2008 where we believe the increased volume of reports was primarily a result of high levels of company contact with its customers for business reasons. This led the companies to “learn” of more adverse events.

DIANEAL Dialysis Solution

A notable example was the drug Dianeal, which is a special solution used for kidney dialysis at home in patients with failing kidneys. To remove toxins from the blood the dialysis solution is circulated through the abdominal cavity—a treatment called intraperitoneal dialysis. This is an alternative treatment to the more familiar hemodialysis, where patients go to special dialysis centers several times a week to have their blood pumped through special filtration machines.

While half the drugs we monitor produce six or fewer reports a calendar quarter, in the 4th quarter of 2008, we identified 609 reports of serious injury in Dianeal patients, including 149 patient deaths. The most prominent injuries reported were infections of various types in the peritoneal cavity. The manufacturer of Dianeal, Baxter Healthcare, told us that the drug was being used by a small patient population, approximately 22,000 patients. The reported cases increased rapidly throughout the year, and by the end of 2008 totaled 1,225 cases. This one drug contributed substantially to the annual increase previously noted.

Baxter Healthcare provided the following explanation for this unusual volume of reports: The company maintains monthly contact with every patient through special case managers. It has further contact, the company said, when its drivers deliver the product to the homes of dialysis patients. During the fourth quarter of 2008 the company completed a training program for drivers, instructing them to report as adverse drug events cases where the drivers learned the patients had died or had been hospitalized. We believe this level of intensive patient contact may equal or exceed formal clinical studies where the investigators are required to account for all patients.

Interferon Beta (AVONEX brand)

Similar circumstances account for some of the continued growth of serious adverse event reports for the Avonex brand of interferon beta, a biological product for treatment of multiple sclerosis. In the 4th quarter of 2008, interferon beta products accounted for more serious adverse drug events than any other drug, or 1,557 cases. Of these 1,018 (65%) were the Avonex brand manufactured by Biogen Idec. As with Dianeal the company said it employed case managers to maintain monthly contact with each patient.

The most prominent adverse drug events reported were relapses of the underlying disease, multiple sclerosis. While these events might be expected in a relapsing, remitting disorder, the company policy was to report relapses as a serious adverse event. As with Dianeal the patient population was relatively small: the 1,018 case reports for Avonex came from a relatively small patient population of approximately 68,000 patients.

As noted above, the company also believed that some of the 2008 increase occurred because of software compatibility problems between the FDA system and the company's new electronic submissions, causing duplicate reporting of the same event. The same problem also may have increased reporting from natalizumab.

Taken together, increased reporting for just these two special cases contributed a significant fraction of the increase, and we suspect other cases of increased reporting may also have occurred.

Fentanyl Patches (DURAGESIC) Medication Errors

A synthetic opioid narcotic approximately 100 times more potent than morphine,^{12(p594)} fentanyl is available as a transdermal system or patch (DURAGESIC), as a lozenge or lollipop (ACTIQ), as a tablet (FENTORA), and as an injection. While it is an essential medication for the most intractable and persistent pain, it also has a daunting array of risks and problems. As with other narcotics, patients develop tolerance and may call for ever-increasing doses. This can lead to drug dependence or overdose and death through depression of the respiratory system. Because it is so potent, it should be used only in patients who have already developed tolerance for morphine or other opioids; otherwise it can produce overdose and death. However, the risk of fatal overdose with the patch can occur in numerous other ways: accidental exposure of children, who get access to a new or used patch,¹³ applying patches too frequently, failing to remove the previous patch, or applying heat (e.g. heating pad, sun tanning) to the area where the patch has been placed. Continued reports of deaths and serious injuries from fentanyl medication error has led to led to urgent health advisories from the FDA^{14 15} and repeated warnings and information for health professionals from ISMP. ISMP has also reported on prescribing errors by physicians (erroneously prescribing it for short-term pain in patients without tolerance for opioids), by other health professionals (nurses overlooking and failing to remove previously applied patches), and improper alteration of the product—cutting patches with the intention of reducing the dose, but instead causing overdose by triggering a leak in certain kinds of patches.¹⁶ In March and April of 2008 a whole new area of safety concern occurred when manufacturing problems led to the recall of millions of fentanyl patches that

might leak.² The FDA is developing a new risk management program for this high alert drug.

In our first look at serious, disabling and fatal adverse drug events specifically described as medication errors, fentanyl ranked first with 80 cases of serious or fatal injury reported; second was acetaminophen (41 cases) and third was insulin (40 cases). It is worth noting that all three of the most frequently reported drugs for medication errors have substantial risks of injury from overdose. Of the reported fentanyl cases, 75 (94%) of cases concerned the product delivered through patches applied to the skin.

We discussed our findings with Ortho-McNeil, which manufactures the brand name product (DURAGESIC) and accounted for 73% of the medication error cases involving the patch in the 4th quarter.

The company told us it was reporting to the FDA as “serious” any medication error involving the patch, even if it did not result in a serious injury, such as hospitalization, or other life threatening event. As a result, we adjusted the fentanyl medication error case totals reported above to eliminate medication error cases that did not result in serious injury by the conventional definition. For example, Ortho-McNeil reported as “serious” events cases where a patient applied a patch and found it did not adhere to the skin and taped it in place, which could affect how the drug was delivered but did not result in injury. Even after adjusting the medication error total for fentanyl patches to exclude cases without a serious health outcome, the drug still accounted for twice as many reports of serious injury or death than the second ranked drug.

Additional measures are still required to assure safe use of this high alert medication. We believe new prescriptions for this drug should not be dispensed without patient education by a doctor or pharmacist who has received special training in the safe use of this drug.

KV Pharmaceutical Recall

The case of KV Pharmaceutical and its generic drug subsidiary, Ethex Corporation, graphically illustrates the ongoing quality control problems among US manufacturers of generic drugs. A series of escalating drug recalls has led to the near collapse of KV Pharmaceutical. In May and June of 2008 KV Pharmaceutical recalled a large but unspecified quantity of morphine tablets exported to Canada because of “super-potent; oversized tablets.”¹⁷ In October 2008 it recalled dextroamphetamine tablets in the United States “due to the possible presence of oversized tablets.”¹⁸ In November it began recalling morphine, isosorbide, dextroamphetamine, and propafenone, again because of oversized tablets.¹⁹ The company noted that overdoses of any of these drugs “can have serious or life threatening consequences.” In December, the company suspended shipments of all FDA-approved drug products in tablet form,⁸ and fired its long-time CEO and major shareholder “for cause.”²⁰ In January 2009 the company announced it was recalling “most of its products.” In February, it expanded its product recall from the wholesale to the retail level for the same four products it had begun to recall the previous November.²¹ In March KV Pharmaceutical operations were placed under federal court

supervision as part of a stepped-up FDA enforcement program, and agreed to destroy all recalled products and hire an independent expert in good manufacturing practices to examine the company's operations.²²

This long series of product recalls also generated a surge in serious adverse event reports to KV Pharmaceutical involving three products with the highest health risks through overdose: isosorbide, morphine and propafenone. In the 4th quarter the company received 181 case reports for its isosorbide tablets, 101 for morphine and 40 for propafenone. There were also single reports for diltiazem, nitroglycerin and potassium and two reports for metoprolol. In product recalls for drugs with high risks for overdose, the computer excerpts do not have sufficient detail to distinguish between proven cases linked to a defective tablet and overdose injuries that might have had some other cause. For the last two quarters of 2008 we identified 458 reports of serious injury or death associated with the company's recalled products.

Varenicline (CHANTIX) Update

We note two steps forward and one misstep in managing the risks of varenicline, a drug to help people stop smoking. We have previously reported extensively on the risks of this drug, including suicidal acts, hostility/violence, and the risk of accidents.^{23 5}

In July 2009 the FDA required the addition of its strongest form of warning for "changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior," a black box warning for physicians and a Medication Guide for patients.²⁴ In the 4th quarter of 2008, varenicline continued to account for more serious psychiatric side effects than any other prescription drug. However, total serious events for varenicline were approximately half of those reported for the same quarter one year earlier, as were the product sales. The Medication Guide for patients also included a new warning of severe skin reactions, about which we have previously reported.

The misstep involved an inadequate and misleading warning about motor vehicle and other accident risks. The FDA and Pfizer did add a warning about accident risk to the patient Medication Guide, one year after ISMP called for a prominent patient alert following reports of numerous road traffic accidents, and of other serious adverse events (such as convulsions and impaired vision) with the potential to cause serious accidents. The new patient Medication Guide contains this statement:

"Use caution driving or operating machinery until you know how CHANTIX may affect you. Some people who use CHANTIX may feel sleepy, dizzy or have trouble concentrating that can make it hard to drive or perform other activities safely."²⁵

We object to this warning on factual grounds. The adverse effects we have seen reported that contribute to accident risk include blackouts, convulsions, muscle spasms, and hallucinations--an order of magnitude different from feeling sleepy or dizzy.

The warning is also misleading in saying “use caution driving or operating machinery until you know how CHANTIX may affect you.” This presumes that patients will “know” how the drug might affect them after a few days treatment. However, the FDA has noted that the severe psychiatric adverse effects occur when starting the drug, after several weeks, or when discontinuing the drug after many weeks. One problematical risk of this drug is that it is simply not clear when a person would “know how Chantix” is going to affect them.

The FDA and Pfizer should immediately revise this misleading and inadequate warning about accident risk. To date we have identified reports of 61 road traffic accidents, 207 reported cases of loss of consciousness, 142 cases of convulsions, 153 reports of hallucinations, 124 cases of muscle spasms, 135 instances of blurred vision and 33 cases of temporary blindness.

Taken together three different characteristics of varenicline make this drug unsuitable for individuals in sensitive occupations where serious injuries to others may occur. First, varenicline has unpredictable onset, which could be in a matter of days, or possibly weeks or on discontinuation. Second, it is associated with dangerous array of psychiatric side effects that include suicide, violence to others and hallucination. Third, it may cause blackouts, convulsions and interruption of motor control or vision.

When ISMP first raised these issues in May of 2008 the Federal Aviation Administration and the Department of Defense responded promptly by banning varenicline for pilots, air controllers and missile crews.³ Also in May, the US Federal Motor Carrier Safety Administration, which oversees the interstate trucking and bus industry, followed suit, issuing a warning advising medical examiners to not qualify anyone currently using varenicline for commercial motor vehicle licenses.²⁶ We believe this ban should be extended to all uniformed military personnel, as well as police and firefighters. Other professionals who require high levels of coordination should also be cautious in using varenicline.

Montelukast (SINGULAIR) and Psychiatric Side Effects

In August 2009, the FDA updated its information for montelukast for healthcare professionals, urging them to be aware of the potential for psychiatric side effects, including agitation, aggression, abnormal dreams, suicidal thinking and behavior.²⁷ The notice also covered two similar asthma drugs, zafirlukast (ACCOLATE) and Zileuton (ZYFLO). It also urged health professionals to consider discontinuing the medication if these symptoms develop. The FDA, however, limited its alert to healthcare professionals and did not provide a Medication Guide or other information that would be readily accessible to patients. Merck, the manufacturer of montelukast, however, did update its information for patients to provide a clear alert.¹¹

In the 2d quarter of 2008 we observed a large surge in adverse events that followed a low-key FDA Early Communication that it had received 24 adverse event reports of psychiatric side effects and was investigating a possible connection to the drug. In the

months following the notice, the FDA received a flood of such reports—more than 600 in the next six weeks. The original small group of reports had been identified by Merck’s safety surveillance unit and brought to the attention of the FDA in a regular report.

Merck told us, and the FDA later concluded that the clinical studies of montelukast had not shown psychiatric side effects. But the asthma drug studies were not designed to study this problem and lacked any checklist to ascertain psychiatric side effects. However, the large volume of adverse event reports persuaded the FDA and the company that an alert was nevertheless required.

We commend Merck for including a clear, prominent and unambiguous statement about the possibility of psychiatric side effects in its web-based information for patients. It is also an object lesson showing that psychiatric adverse events may be overlooked if caregivers or patients do not suspect such a drug connection might exist. It took just 24 reports over several years to suggest the possibility of a relationship; once made public, hundreds of confirming reports were received in the subsequent months.

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