DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-747

Anesta Corporation
C/O Cephalon, Inc.
145 Brandywine Parkway
West Chester, PA 19380-4245

Attention: Carol S. Marchione
Senior Director, Regulatory Affairs

Dear Ms. Marchione:

Please refer to the meeting between representatives of your firm and FDA on July 14, 2004. The purpose of the meeting was to discuss the issues related to the safety and promotional aspects of Actiq (oral transmucosal fentanyl citrate) .

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kimberly Compton at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Date/Time: July 14, 2004 / 1:00 – 2:30 PM
Location: Potomac Room
Sponsor: Cephalon, Inc.

Meeting Chair: Bob Rappaport, M.D., Director
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

Drug/Dosage Form/Doses: Actiq (fentanyl citrate)

Minutes Recorder: Parinda Jani, Chief, Project Management Staff, HFD-170

Cephalon, Inc Attendees	
Robert Bader	Senior Director, Global Product Safety
Randy Bradway, R.Ph.	Vice President, Commercial Operations
Ed Berg, J.D.	Associate GC and TL of Cephalon Risk Minimization Strategy Team
Paul Blake, FRCP	Senior, Vice President, Clinical Research & Regulatory Affairs
Richard Civil, M.D.	Vice President, Global Product Safety
Richard Kaplan, Ph.D.	Vice President, Quality Assurance
Carol Marchione	Senior Director, Regulatory Affairs
Robert P. Roche, Jr.	Senior Vice President, Pharmaceutical Operations
Jeffrey A. Gudin, M.D.	Consultant
FDA Attendees	**Title**
Robert Meyer, M.D.,	Director, ODE II
Jane Axelrad	Associate Director, Office of Regulatory Policy
Bob Rappaport, M.D.	Division Director, HFD-170
Rigoberto Roca, M.D.	Deputy Division Director, HFD-170
Elizabeth McNeil, M.D.	Medical Officer, HFD-170
Ravi Harapanhalli, Ph.D.	Chemistry Team Leader, HFD-170
Leah Ripper	ADRA, ODE II
Deborah Leiderman, M.D.	Director, CSS
Silvia Calderon, Ph.D.	CSS Reviewer
Corinne Moody	CSS Project Manager
Thomas Abrams, R. Ph.	Director, DDMAC
Brenda Marques, Pharm. D.	DDMAC
Spencer Salis, R.Ph.	DDMAC
Jialynn Wang	DDMAC
Kristin Davis, J.D.	Legal counsel, DDMAC
Carol Barstow, J.D.	Legal counsel, DDMAC
Lanh Green, Pharm.D.	ODS Team Leader
Martin Pollock, R. Ph.	Safety Evaluator, ODS
Jo Wyeth, R.Ph.	Safety Evaluator, ODS

Terry Martin	Executive Secretary
Janice Steinschneider	Regulatory Councel
Kathy Miracco	Office of Compliance
Lynn Whipkey Mehler	Office of Chief Councel
Parinda Jani	CPMS, HFD-170

Meeting Objective: To get an update from the sponsor on information related to the pediatric exposure, abuse, diversion, misuse, overdose, death, and off-label use of Actiq, and any non-compliance issues that the sponsor is aware of related to the risk management program implementation of Actiq (i.e., sales representatives, other company employees, prescribers, dispensers and/or patients).

Minutes

After introductions, Dr. Rappaport stated that the Agency has received reports of drug abuse with Actiq. The Agency is concerned about the abuse and diversion of Actiq and would like to understand the steps Cephalon is taking to prevent abuse and implementation of the risk management program. Available data suggests considerable off-label use of Actiq and the Agency would like to understand the steps Cephalon is taking to discourage such use and ensure that off-label promotion is not occurring.

Cephalon presented the information (see attachment) as requested in the Agency's letter dated June 29, 2004. Cephalon requested that any questions/clarification/discussion take place after the presentation is completed. The Agency agreed.

The sponsor presented the data obtained by their Global Product Safety group, classified into several categories, including deaths, overdose, unintended pediatric exposures, abuse, misuse, diversion and off-label use. The sponsor indicated that they believe that the data showed a strong safety record evidenced by the absence of an increase in reporting rates for these events despite increased sales.

The sponsor described its sales and marketing practices for Actiq. The eligibility of a physician to be detailed by sales representatives for Actiq promotion is determined by branded opioid prescribing activity. To be included, prescribers must have written at least 24 prescriptions of specified opioid (C II) products in the preceding six months. By meeting this criterion, the prescriber is initially considered knowledgeable and experienced in the use of opioids for the management of pain and would be considered an appropriate target for promotion of Actiq, including visits by sales representatives. Physicians are not screened for whether they treat cancer patients. Targeted physicians who meet the criterion related to opioid prescribing would continue to be visited by sales representative even if they did not routinely treat cancer patients. Specialties related to surgery, pediatrics and dentistry are excluded from visits by the sales force regardless of opioid prescribing level. Sales representatives also call upon physicians known to use Actiq, including physicians who prescribe it for off-label uses. According to the sponsor, this is done to ensure that the physician is educated on the safety profile of the drug.

The sponsor also described the training requirements of its sales personnel. The sponsor stated that only promotional materials reviewed by DDMAC are used in sales activities promoting

Actiq. The sales managers are responsible for monitoring the activity of the sales representatives to ensure compliance with the Risk Management Program (RMP) and promotion guidelines. When potential violations are reported, an investigation is immediately launched. Non-compliance with the sales policies for Actiq is grounds for disciplinary action. No employees have been terminated as a result of not complying with guidelines to promote Actiq; however, one area manager resigned.

The sponsor also described its activities and recent efforts, beyond those specified in the RMP, to further ensure that necessary and appropriate steps are being taken to minimize the risks of abuse, diversion, inappropriate prescribing and accidental pediatric exposure. These efforts are managed by Cephalon's Risk Minimization Strategy Team that has been formed under the mandate of its Executive Committee.

This concluded the sponsor's presentation. The Agency requested clarification for several issues.

1. The use of the Welcome Kit:
   The sponsor clarified that sales representatives are trained to promote the product only for its labeled indication (i.e., for breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy). The sales representatives are not specifically trained to tell prescribers to avoid the use of the product outside of breakthrough cancer pain because this decision remains the prerogative of the physician in his or her practice of medicine.

   The Agency suggested that in addition to providing the kit on requested basis via an 800 number that is published on the product's labeling and packaging, the sponsor should investigate ways to increase its distribution. The sponsor agreed to evaluate this proposal.

2. For the upcoming EOP 2 meeting to discuss an expanded indication beyond breakthrough cancer pain, the Agency stated that the sponsor will need to provide evidence that breakthrough pain exists outside of the labeled indication. In addition, it would be necessary to provide support demonstrating that the benefits of Actiq in the specific patient population for label expansion outweigh the potential risks of the product.

3. The sponsor stated that they would like a meeting with DDMAC regarding concerns about the review process for draft promotional materials. DDMAC expressed concerns about the information provided at this meeting and in the background materials regarding the sponsor's promotional practices as they relate to off-label use, and DDMAC recommended further discussion on this issue. DDMAC and the sponsor agreed to have a subsequent meeting to discuss these issues.

Post-Meeting Note: A meeting between representatives from DDMAC and Cephalon was held on August 30, 2004.

Action Items:

None at this time.

Minutes prepared by: Parinda Jani
Chief, Project Management Staff

Minutes concurred by Chair: Bob Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products

ATTACHMENT:

Slides for Overview of Items to be Presented for Discussion

- *FDA's intent of RMP*
  - *Accidental ingestion by children*
  - *Improper patient selection (prescription to and usage by opioid non-tolerant patients)*
  - *Diversion or abuse*
- *Results of RMP implementation at Cephalon*
  - *Strong safety record*
  - *Well-trained sales forces certified in the elements of the RMP*
  - *Integrity of the supply chain*
  - *Positive interaction with DEA*
  - *Access of Welcome Kit to all patients*
- *Ongoing communication requested with FDA*

Slides for Topic 1 (Actiq Safety Review)

Data: Deaths, Overdose, Pediatric exposure, Abuse, Misuse, Diversion, Off-label use
Time Period: 04-Nov-98 (US approval) to 15-June-04
Source: Post-marketing safety data, Professional Services (product complaints, medical inquiries), pharmacy callback, news media, law enforcement

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ACTIQ FATAL OUTCOME (04-Nov-98 through 15-Jun-04)		
	Spontaneous	*TESS*
Disease Progression	*1*	*0*
Overdose, Intentional	*3*	*2*
Overdose, Accidental	*4[1]*	*1*
Misuse	*8*	*0*
Abuse	*1*	*0*
CVA	*1*	*0*
Unknown	*2*	*0*
Total	*20*	*3*

1 Two accidental overdoses appear to involve a patch formulation

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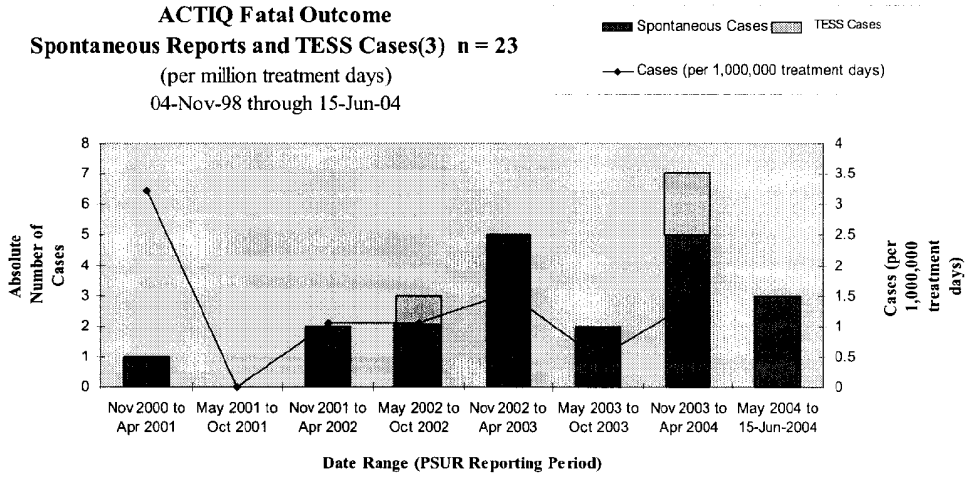
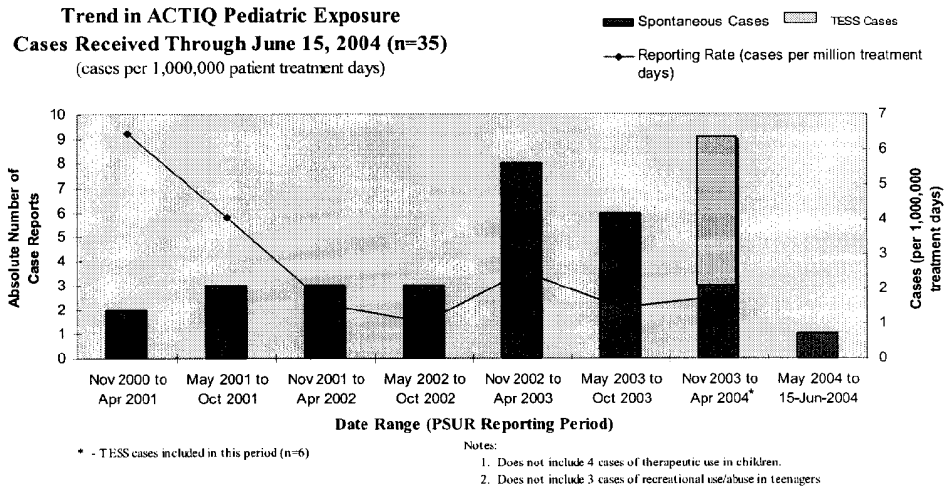


Slides for Topic 2
Accidental Pediatric Exposure-

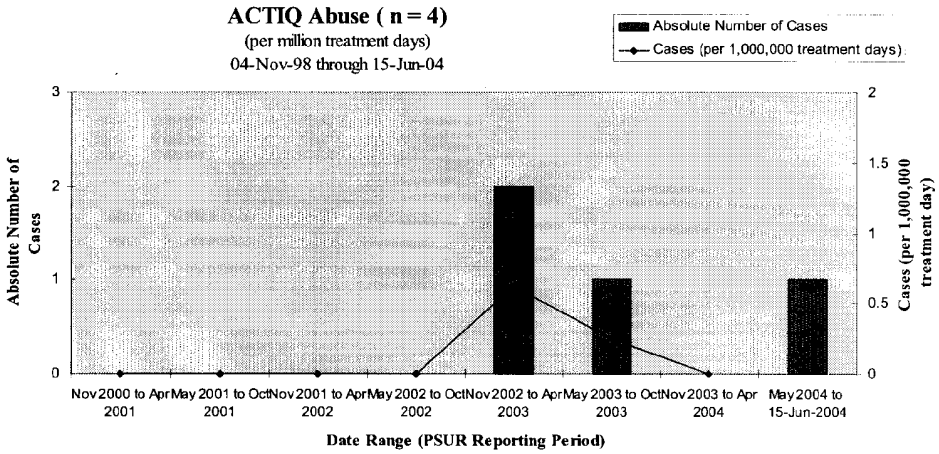
All accidental pediatric exposures, with pediatric age group defined as ≤ 16 years, including misguided uses or use facilitated by a non-healthcare professional, excluding intentional recreational use by an adolescent. (RMP)



Slides for Topic 3
Reports of Abuse-

1. *The "As reported approach"*
2. *The "Case definition approach"*
   Drug abuse is persistent or sporadic, intentional excessive use of drugs which is accompanied by harmful physical or psychological effects. (Notice to Applicants)

   This definition excludes reports of tolerance and physical dependence (withdrawal syndrome) that occur in the absence of other abuse related behaviors. These effects are inevitable consequences of chronic opioid therapy, and by themselves do not imply abuse or addiction.



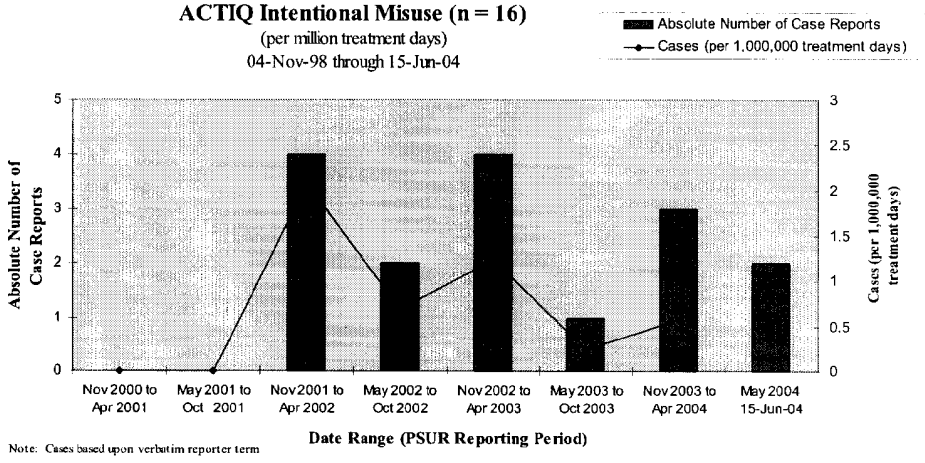
Slides for Topic 4
Reports of Misuse-

1. *The "As reported approach"*
2. *The "Case definition approach"*

Use for unintended or unprescribed purposes. (Diversion may be involved in obtaining medication for misuse).

*Examples include: **

- *Self-medication - used for therapeutic purposes, but without MD's knowledge or Rx*
- *Doctor-shopping – involves deceit by patient*
- *Unit sharing – for non-illicit purposes*
- *Illicit use – used for recreational or psychic effects (may involve manipulation of route of administration)*

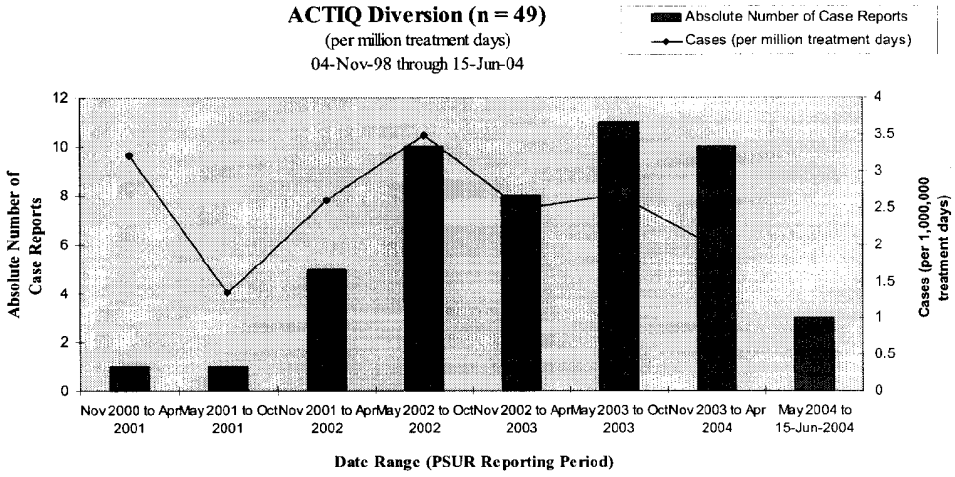


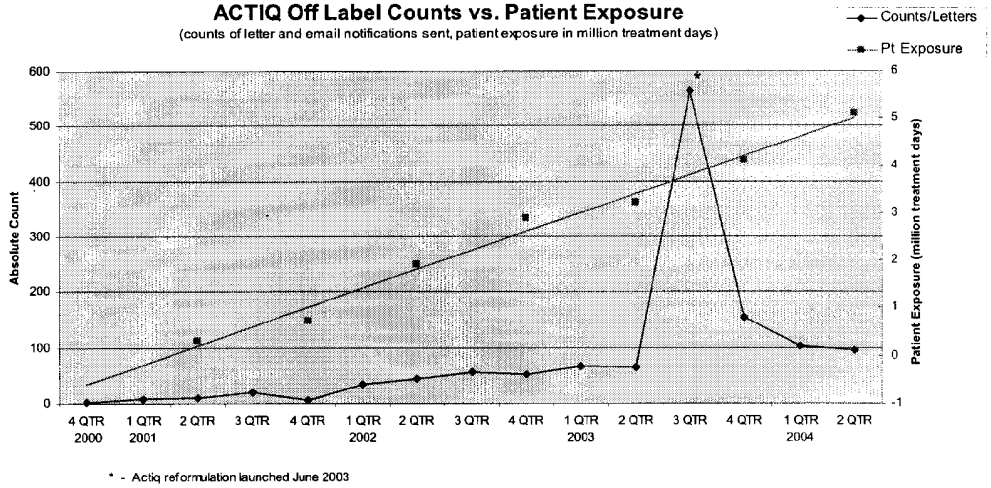
Slides for Topic 5
Diversion-

The willful transfer of a drug from legitimate supply (manufacture, distribution, or storage) and/or patients for whom the drug has been prescribed to unauthorized use and/or illegal sale. (RMP)

NOTE: Diversion refers specifically to how the medication is obtained; its subsequent use can be either misuse or abuse depending on the circumstances of use.

DIVERSION CASES (04-Nov-98 through 15-Jun-04)	
Total Cases	49
Fatal cases	5
Misuse	12
Abuse	0
Report Source:	
Direct	16
Indirect	33
Law/DEA	26
Poison Control	3
News media	4
Indication:	
On-label	1
Off-label	2
Unknown	46

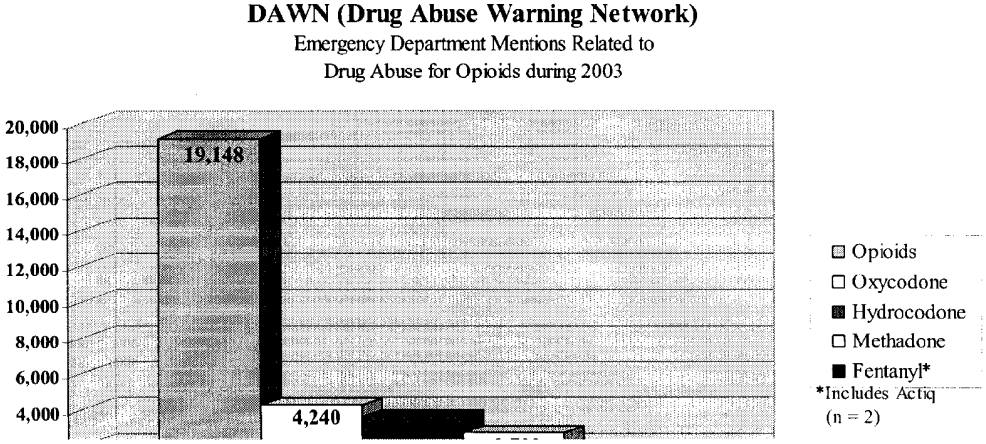




Slides for Topic 6
SAEs by Indication-

- *Actiq approved in the USA in November 1998*
- *Actiq approved in the EU in October 2000*
- *Over 700,000 TRx1*
- *Over 44,000,000 individual units sold2*
- *Over 18,000,000 patient treatment days2*
- *48 spontaneous SAEs related to diversion or off-label use3*
- *49 spontaneous SAEs related to on-label use4*

1April 1999- March 2004: IMS NPA
2November 2000-April 2004: Cephalon Sales Dept.
3April 1999 to June 2004: Cephalon 21th Quarterly RMP Report 404-Nov-98 to 15-Jun-04: Cephalon Global Product Safety



Conclusion-

- *Strong Safety Record*
- *No evidence of increasing reporting rates for deaths, pediatric exposure, abuse, misuse, or diversion despite increased sales*

Slides for Topic 7

Actiq Commercial Support-

- *Targeting and audience selection*
- *Sales Force activity*
- *Actiq education and promotion*
- *Training and compliance*
- *Involvement with RMP*

Cancer Pain Treatment-

- *30-40% of patients with cancer suffer breakthrough pain*
- *Multidisciplinary HC team manages cancer sufferers and their pain*
  - *Oncology*
  - *Anesthesiology*
  - *Other Pain Specialists*
  - *Neurologists, Psychiatrists & Psychologists*
  - *Primary Care Physicians*
  - *Nurses and others*
- *No database exists on Tx of cancer pain*

Actiq Physician Universe-

- *Determined by opioid prescribing activity*
- *Identified using NDC Prescriber syndicated prescription data for:*
  - *ACTIQ*
  - *Duragesic*
  - *Long Acting Opioids (Branded)*
  - *Short Acting Pure Opioids (Branded)*
  - *Percocet + Vicodin + Lortab*
- *Required to write at least 24 TRxs of these opioid products in the latest six months*

- *By meeting these criteria, MD is initially considered knowledgeable and experienced in the use of opioids to manage pain, including cancer pain*
- *Specialties related to Surgery, Pediatrics (including Child Neurology, Child Psychiatry) & Dentistry are excluded from all targeting regardless of opioid prescribing levels*
- *All other physicians are initially included in the potential physician call universe*
- *These physicians are called on by Cephalon sales specialists who determine their appropriateness for an Actiq presentation*
- *Spontaneous Actiq prescribers are included*

Physician Universe & Call Activity-2004 YTD

Specialty	*Cephalon Physician Universe Count*	*Specialty % of Total*	*Physicians Called on 2004*	*% Physicians Reached 2004*	*Total Actiq Calls*	*% Total Calls 2004*
Family Practice (FP)	*8943*	*29%*	*2247*	*25%*	*7534*	*15%*
Internal Medicine (IM)	*7840*	*26%*	*1824*	*23%*	*6209*	*12%*
Oncology-Medical (ON)	*1696*	*6%*	*691*	*41%*	*1970*	*4%*
Anesthesiology (AN)	*1656*	*5%*	*1279*	*77%*	*9329*	*18%*
Physical Medicine (PM)	*1593*	*5%*	*1111*	*70%*	*7309*	*14%*
Neurology (N)	*1060*	*3%*	*706*	*67%*	*3809*	*7%*
General Practice (GP)	*931*	*3%*	*281*	*30%*	*1046*	*2%*
Hematology/Oncology (HO)	*799*	*3%*	*292*	*37%*	*888*	*2%*
Anesthesiology-Pain Management (APM)	*786*	*3%*	*634*	*81%*	*5148*	*10%*
All Other Oncology	*781*	*3%*	*298*	*38%*	*969*	*2%*
Rheumatology (RHU)	*659*	*2%*	*333*	*51%*	*1504*	*3%*
All Other Specialties Combined	*3765*	*12%**	*1085*	*29%*	*5832*	*11%*
Total	*30509*	*100%*	*10781*	*35%*	*51547*	*100%*

**All Other Specialties Combined: no single specialty currently exceeds 1%*

Sales Force Activity-

- *Sales Specialists call on those physicians who frequently use opioids to treat pain and who are likely to treat patients with cancer*
- *Call on all physicians who spontaneously write prescriptions for Actiq to ensure they understand the approved indication and important safety information*
- *Approach is highly educational in BTCP and its management*
- *Present Actiq, only its approved indication, safety issues (including RMP), contraindications and other product information during their discussions*
- *Are repeatedly trained that they must not suggest Actiq be used for other than its approved indication or engage in discussion on this topic*
- *Actiq promoted from 1999-2003 by a specialized force of up to 70 sales specialists exclusively focused on Actiq*

- *Actiq promoted since 4th Quarter of 2003 by 435 sales representatives responsible for Provigil, Gabitril, and Actiq*
    - *Interact with all appropriate physicians for all products in their territory*
- *Sales Bulletin #9 issued in December 2003 to clarify limits of call universe for Actiq*
- *Overall Actiq promotional activity has not substantially changed since the sales force expansion*

Slides for Topic 8
Actiq Promotion-

- *Only to identified call universe*
    - *Knowledgeable and experienced in use of opioids*
- *Only with approved branded materials*
- *Specific to indication of BTCP*
- *Unbranded materials may be presented in a call where Actiq is discussed but are not designed to be used in promotion*
    - *Provide patient information to be conveyed by physicians*

Slides for Topic 9
Compliance Summary-

- *Compliance Program*
    - *Corporate guidelines for the conduct of Cephalon's business by its representatives (Standards of Conduct), as well as procedures to implement those standards (Implementation). The Compliance Program applies to directors, employees, agents and consultants of Cephalon and its subsidiaries, wherever located*
- *Business Ethics Review Questionnaire*
    - *Annual requirement for all Cephalon employees to answer questions on their knowledge of company compliance with all laws*

Slides for Topic 10
Sales Force Training-

- *Initial training on hire*
    - *Product Specific*
    - *In-house and in-field*
    - *Proper promotional practices and the requirement to comply with Cephalon policy strictly prohibiting off-label promotion*
    - *Procedures to handle frequent physicians questions relating to potential off-label use*
    - *Full Compliance training*

- *Additional product and compliance training regularly conducted for all Sales and Marketing personnel*

Sales Specialist Compliance with RMP Behavior Monitoring-

- *Sales Management monitors and observes Sales Specialist activity to ensure compliance with RMP and all promotion guidelines*
- *When potential violations are reported, an investigation is immediately launched*
- *Non-compliance with the policy by a Sales Specialist would be grounds for termination as per company policy*

Slides for Topic 11
Compliance Investigations
Based on alleged Sales Specialist violation of the Actiq Risk Management Program or Cephalon Promotional Policy-

Year	*Number of Investigations*
2001	*4*
2002	*2*
2003	*8*
2004 (YTD)	*1*

Conclusion-

- *Physician targeting based on available data sources and sales specialist interaction*
- *Great majority of calls made on bona fide targets*
  - *Oncologists and specialists in pain management*
- *Great majority of TRx come from this audience*
- *Sales personnel properly trained and monitored*
  - *Understand and implement RMP*
- *Promotion done solely with materials reviewed by DDMAC*
- *Compliance deeply ingrained in our culture and strictly enforced*

Slides for Topic 12
Risk Minimization Strategy Team (RMST-)

- *Formed early May 2004*
- *Sponsored by Cephalon Executive Committee*

RMST Purpose-

- *To ensure the Company, in a coordinated fashion, is taking necessary and appropriate steps to minimize the risks of abuse, diversion, inappropriate prescribing and accidental pediatric ingestion with present/future Scheduled Cephalon compounds*
- *Current focus is on ACTIQ and abuse liability issues*

RMST Membership-

- *Chair: Edward Berg- Associate General Counsel*
- *Members by Department*
  - *Global Product Safety*
  - *Regulatory Affairs*
  - *Regulatory Counsel*
  - *Worldwide Product Planning*
  - *Marketing*
  - *Corporate Communications*
- *Extended Team*
  - *Quality Assurance*
  - *Medical Affairs*
  - *Government Affairs*
  - *Commercial Operations*
  - *Chief Sponsorship*
    - *Paul Blake- Senior Vice President, Clinical Research and Regulatory Affairs*
    - *John Osborn- Senior Vice President and General Counsel*

RMST Activities to date-

- *Weekly update by Global Product Safety on new reports of abuse and diversion*
- *Review/discussion of proposed RMP update changes*
- *Review of previous activities by various Company Departments aimed at understanding the potential for and the prevention of diversion and misuse or abuse of ACTIQ*
- *Discussion with various expert consultants to determine range of possible steps to:*
  - *Detect signals of abuse/diversion of ACTIQ*
  - *Respond to instances of abuse/diversion of ACTIQ*
  - *Reduce likely future abuse/diversion of ACTIQ*
- *Meetings with Consultants to Date:*
  - *Best Practices (Jerome Jaffe, Roger Meyer)*
  - *Inflexxion (Simon Budman, Nathaniel Katz)*
  - *Drug & Chemical Advisory Group (Terrance Woodworth, Frank Sapienza)*
  - *ParagonRx (Jeffrey Fetterman)*
- *Issues Considered*
  - *Sources for monitoring abuse/diversion, including new sources*
  - *Government/industry partnerships to foster education, proper opioid prescribing*
  - *Sales force activity and its effect on proper patient selection*

- *The sales force as a resource to detect signals abuse/diversion*
- *Improvements to RMP*
- *Identification of and appropriate response to signals of diversion as well as abuse/misuse*

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/s/

Parinda Jani
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