From:	Adams, Jessica </O=CEPHALON/OU=USO1 ADMINISTRATIVE GROUP/CN=RECIPIENTS/CN=JADAMS>
To:	'Bailey, J. Elise'
CC:	'Dart, Richard'; Marcolbe, Carol
Sent:	9/8/2006 2:25:15 PM
Subject:	RE: DRAFT template for FENTORA RiskMap quarterlies
Attachments:	FDALetter8-30-06.pdf; FDALetter9-7-06.pdf; FDALetter28-08-06.pdf; Response 9-7-06.pdf; RiskMAP sept20changes.doc; Template Elise.doc

Hi Elise,

The documents that we discussed are attached. In the template example the highlighted text is what we're trying to fill in with authoring notes and samples tables. The sections to focus on are 2.1.1 and 4.5. The correspondences that are attached are: two letters from FDA on 8/30, our response yesterday, and a letter from FDA yesterday, which we have not yet responded to. The actual RiskMAP that is attached is a version from 7/25, so it will also need to be updated per our agreements in our letters and coming letter (Penny Levin is working on this. I am trying to coordinate the templates.

I will let my colleagues in Regulatory, Penny and Carol, know that you will be seeing what you can recommend for Monday morning, especially in light of Rick traveling today.

Thank you!,
Jessica

From: [illegible]
Sent: [illegible]
To: [illegible]
Cc: [illegible]
Subject: [illegible]

Hi Jessica,

As discussed, here is an "example" report. I have removed all identifying information, but it should provide you with all you need. You will receive one of these reports for each signal detection system. There will be some slight variances between reports by each signal detection system. For example, this example report is from the Poison Control Center Study, and you will see that we will provide you with tablet identification information in the report. The PCC study is the only one that captures tablet identifications, so you will not be getting this information from the other signal systems. Please feel free to call me if you have any questions.

Also, as discussed, we do use a signal threshold of 2/100,000 population for the methadone clinic signal detection system. We would appreciate it if that change could be made to the Fentora document so our methodology can remain consistent. In addition, after review of the methadone clinic data, this does appear to be the more appropriate signal threshold.

Let us know if there is anything else we can do for you
Elise

[illegible]

From: [illegible]
Sent: [illegible]
To: [illegible]
Cc: [illegible]
Subject: [illegible]

Jessica,
We'll be happy to work on this, but I'm not sure what you want. I'm out of town, but the RADARS coordinator Elise Bailey should be able to help and she generates the requests anyway.

It appears that are referring to graphical and narrative presentations. I'm not sure what that means. There are several graphical representations in the report we send of course, so I guess that is not what you need? For example, we have maps or tables showing where the system showed a signal rate greater than 5.0 for poison centers, etc.

If you could just give a little description of what you need and perhaps have a quick call with Elise, I believe we should be able to help you.

Rick

From: [illegible]
Sent: [illegible]
To: [illegible]
Cc: [illegible]
Subject: [illegible]
Importance: [illegible]

Hi Rick,

I work with Penny in Regulatory at Cephalon (we met when you visited on site). Would you be able to provide information pertaining to the request below for detailed Radars data and presentation of the data that we've been discussing via email (see below)? If you can send what you have now and provide some timings for more information this would greatly help. Apologies for the timings, but we are trying to respond to the Agency in time for them to review and keep an action date of Sep. 25[th].

Thank you!,
Jessica

From: [illegible]
Sent: [illegible]
To: [illegible]
Cc: [illegible]
Subject: [illegible]

Hi Sid,

Thanks for your edits. I was really also looking for some graphical and narrative presentations to expect of the actual data to follow the introductory paragraph that you edited. The introductory paragraph is taken directly from the RiskMAP so I'm not sure we'll be editing this (unless Penny you would like to also fine tune the RiskMAP with it). Is the graphical and narrative presentations of the data something that you can provide or do you recommend I contact Rick at RADARS (if I recall correctly)?

Further graphs and narrative would be pulled from the RADARS report, so a depiction of this would be very helpful.

Thanks again for the quick reply given the crucial time factor!
Jessica

From: [illegible]
Sent: [illegible]
To: [illegible]
Cc: [illegible]
Subject: [illegible]

Jessica: attached are my edits to section 2.1.1. Is there a reason why you are calling the Drug Diversion study Drug Suspected diversion? The data from this study are based on arrests. All of RADARS data can be called suspected. I would recommend you drop that designation. If you have any questions, let me know.

Sid

From: [illegible]
Sent: [illegible]
To: [illegible]
Cc: [illegible]
Subject: [illegible]
Importance: [illegible]

Hi Sid,

I work with Penny in Regulatory Affairs at Cephalon (we met when you were on site). She provided your contact information to see if you can provide feedback to the attached template for our quarterly RiskMAP reports for FENTORA that we are preparing for a submission very soon. Can you provide information for the RADARS section 2.1.1? Your assistance is greatly appreciated.

Regards,
Jessica
(610) 883-5715

From: [illegible]
Sent: [illegible]
To: [illegible]
Cc: [illegible]
Subject: [illegible]
Importance: [illegible]

Hi everyone,

Please review and provide your feedback to the attached DRAFT template for the FENTORA quarterly RiskMAP report to submit to the Agency as previously discussed following our telecon. Please keep in mind this is a very draft version that has not yet been reviewed by Penny or Carol, so there may be substantial changes to this version. Given the timings for our response, I wanted to get your feedback early.

Bob and Ray: Please review for any revisions or clarification that may need to be made since the latest discussions with the Agency. Please also provide information for section 2.1
Mark: Please review the survey section. I think that some clarification around the timings of the surveys may need to be made either in the template or in Penny's cover letter. There also may need to be revisions or clarification since the latest discussions with the Agency.

I am also forwarding this to Sid Schnoll for information around RADARS in section 2.2.

If possible, we may aim to include this in a submission to the Agency tomorrow, so your feedback ASAP (and hopefully by 10 a.m. tomorrow) would be greatly appreciated. I will get help from Reg Ops with formatting and generation of a TOC.

Thank you!
Jessica
x5715

PLAINTIFFS TRIAL EXHIBIT
P-19067

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-947

DISCIPLINE REVIEW LETTER

Cephalon, Inc
c/o CIMA Labs
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Carol S. Marchione
Senior Director, Regulatory Affairs

Dear Ms. Marchione:

Please refer to your August 31, 2005, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fentora (fentanyl buccal tablets).

We also refer to your complete response dated July 25, 2006.

The Controlled Substances Staff (CSS) review of your submission dated July 25, 2006, is complete. The following deficiencies have been identified.

Package Insert

1. Effervescent Technology

    a. Under the "Description" section, third paragraph, first sentence, delete the end of the sentence that associates the oravescent technology with a rate and extent of absorption of fentanyl. This sentence, which currently reads "utilizing an effervescent reaction which is thought to enhance the rate and extent of fentanyl absorbed through the buccal mucosa," does not contribute to the safe and effective use of Fentora.

    b. In the June 23, 2006 teleconference, you agreed not to use the term "effervescent" in describing the formulation. You also agreed not to make reference to the "rapid onset of action" of Fentora. Proposed language such as "enhance the rate and extent of fentanyl absorbed through the buccal mucosa" in the label may increase the appeal for abuse by certain individuals who abuse or use opioids recreationally. CNS active drugs with rapid onsets of action are associated with greater subjective effects that relate to increased likelihood of drug abuse.

    c. Promotional claims related to the "effervescent speed" of the formulation should be removed. Considering the risk of fatal overdose associated with the misuse and abuse of Fentora, any claims that refer to a rapid effervescent onset of action of

fentanyl should not be allowed. These claims defeat the purpose and goals of the RiskMAP.

2. Quantities of tablets dispensed during titration and maintenance

   a. Titration-CSS recommends inclusion of the following paragraph under "ADMINISTRATION OF FENTORA" section, as proposed by you in your June 16, 2006 submission. The purpose of the paragraph was to maximize patient convenience, enhance patient safety, and minimize the risk of abuse and diversion: *"Patients should be prescribed an initial supply of no more than 28 (100mcg) tablets, thus limiting the number of tablets in the home during titration. Patients should use up all tablets before increasing to a higher dose."*

   b. Maintenance-CSS recommends including a statement related to the quantity of Fentora that will be dispensed and available in the patient's home during both titration and maintenance. Add a sentence to recommend the dispensing of no more than a one month supply of Fentora. CSS is concerned about the risks associated with abuse and misuse stemming from the availability of large amounts of Fentora in the patient's house. CSS is also concerned about the "mock up" or example of prescriptions presented by you in the proposed marketing brochures. The brochures indicate the dispensing of "**one hundred forty tablets**" to be used "one tablet **PRN**." Once again, this type of promotional activity defeats the goals of the RiskMAP.

3. Editorial change to clarify the potential misunderstanding that Fentora had been administered intravenously

   Under the "CLINICAL PHARMACOLOGY" section, "Respiratory System" subsection, second paragraph, modify the second sentence that reads, "Although not observed with oral transmucosal fentanyl products, in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration."

4. Type of information offered through the toll-free number listed in the label

   Provide information regarding the type of advice that will be provided through the toll free number listed under "Information for Patients and Their Caregivers," item 10.

Medication Guide

5. CSS recommends strengthening warnings against sharing Fentora and the risk of respiratory depression and death associated with misuse and abuse

   a. Under the "What is FENTORA" section, the warning that "FENTORA should not be given to anyone else, even if they have the same symptoms, because this medication may harm or even kill the person for whom it has not been prescribed," should be more prominent and deserves a separate paragraph.

b. The medication guide should clearly state the risk of respiratory depression and death associated with the misuse (taking not as prescribed) and abuse of this product.

c. Respiratory depression should be explained clearly in lay language.

d. Under the "How should I store Fentora?" section, modify first bulleted paragraph to indicate that Fentora should always be stored in a secure place, away from children and from anyone for whom it has not been prescribed.

e. All educational materials provided by you should include warnings not to share Fentora or use it to treat other types of pain, such as pain not associated with cancer.

RiskMAP

6. Submit proposed format and content (draft outline of the tables and data elements) of the quarterly report for FDA review. The proposed RiskMAP does not clearly indicate what kind of events will be included in the quarterly submissions.

7. Commit to submit expedited reports for the following:

   a. All reports of death as the outcome

   b. All pediatric (0-16 years of age) exposure reports, regardless of intention and outcome

   c. All serious adverse events associated with medication errors, misuse, abuse and addiction

8. Describe the procedures that will be used to assess off-label use of the product. Include assessment of off-label use in quarterly reports as done with Actiq.

9. Clearly propose interventions and specify quantitative thresholds for signals that will prompt those interventions and revisions to the RiskMAP during the postmarketing surveillance period.

10. Clarify the role and responsibilities of the Cephalon External Advisory Board as well as its interaction with the FDA.

11. Quarterly reporting is acceptable for the first two years. Frequency of the reporting after the first two years will be determined in consultation with the FDA based upon post-marketing experience.

12. You propose to use DAWN Live! as a source of medical examiners' (ME) data. This proposal is unacceptable because DAWN Live! does not provide access to medical examiner/coroner data (SAMHSA limits access to the ME data to the

medical examiners who submit the data).

13. You propose to use DAWN Live! to monitor emergency department (ED) admissions for their product in comparison to other opioid products, and to analyze patterns regarding geographic locations, age groups, drug combinations and other risk factors. This proposal is methodologically flawed in that DAWN Live! data generally cannot be used to measure trends because participation of hospitals, and the completeness of their data, vary. The unweighted DAWN data are not representative. In addition, pharmaceutical companies can use DAWN Live! only to look at their own products at the brand level. Sponsors cannot make comparisons with other companies' brands and don't get access to any geographic location information. DAWN Live! does not have the capacity to provide information about drug combinations (polydrug ED visits).

14. Utilize DAWN Live! data as a warning system to track ED visits associated with the use of Fentora in comparison to Actiq which is also their product.

15. Provide information on how you plan to capture fatalities associated with the use of your product.

16. Educational materials for both the physician and patient should be revised and you should honor commitments made at the June 23, 2006 teleconference.

17. Overall, the educational pieces should incorporate a stronger message to convey the risks of overdose associated with the product.

Proposed Website

18. Provide more emphasis on risks of overdosing or sharing this medication.

19. Remove tag line "Relief at Effervescent Speed".

20. It has been noted that the Fentora health care providers' web site incorrectly states that "onset of pain relief in as little as 15 minutes." This claim should take under consideration wide variability among patients. Patients might get the erroneous idea that if pain is not relieved within 15 minutes, they should take an additional tablet, and this behavior might lead to overdose.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sara Stradley
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
9/7/2006 11:58:23 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-947

DISCIPLINE REVIEW LETTER

Cephalon, Inc
c/o CIMA Labs
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Carol S. Marchione
Senior Director, Regulatory Affairs

Dear Ms. Marchione:

Please refer to your August 31, 2005, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fentora (fentanyl buccal tablets).

We also refer to your complete response dated July 25, 2006.

The Office of Surveillance and Epidemiology (OSE) review of your proposed RiskMAP dated July 25, 2006, is complete and we have identified the following deficiencies.

Post-Marketing Reporting

1. The RiskMAP does not include a plan to submit the following types of reports to the Agency in an expedited fashion:

    a. Any report with an outcome of death

    b. Any report in a child or adolescent (ages 0-16), whether or not the exposure was intended or unintended, and regardless of the outcome.

    c. Any medication error reports regardless of patient outcome (this would include reports involving accidental exposures)

    Per our letter of May 19, 2006, and your June 2, 2006 agreement to this request, revise the final RiskMAP to reflect this commitment.

2. The RiskMAP is not specific with regard to the type of data that will be submitted in the quarterly report. Per our letter of May 19, 2006, revise the final RiskMAP to include the following in your quarterly reports to the Agency:

    a. Extent of use (denominator estimates)

b. Indicators of off-label use or inappropriate prescribing (i.e., opioid-naïve)

c. Summary of reports involving medication errors and inadvertent pediatric exposures

d. Summary of adverse events involving opioid naïve patients

e. Rates of misuse, abuse, addiction, or diversion observed

f. Results of any investigation or surveys conducted

g. Outcome of any interventions, such as targeted educational interventions and anti-diversion programs conducted.

We note that you plan to purchase patient longitudinal data to help assess the degree to which Fentora is prescribed to patients who have a recent prescription for another opioid medication; share the details and updated information from this planned analysis with the Agency. Include this information in the quarterly reports to the Agency.

Education and Outreach Tools

3. Use of Effervescent, Bubbles, and Rocket (graphics and statements)

   The statement "*FENTORA* employs OraVescent® drug delivery technology, which utilizes effervescence to enhance the rate and extent of fentanyl delivery across the buccal mucosa" (HCP Introductory Letter) implies that the tablet is an effervescent tablet rather than a buccal tablet. Furthermore, the bubble graphics presented next to the proprietary name and at the bottom of the letter in addition to the statement "effervescent speed" under the proprietary and established names imply that the tablet is effervescent.

   The aforementioned statements and graphics in addition to other references of effervescence appear throughout the Fentora product information (e.g., HCP letter, Medication Guide, product monograph, website, sales aids, etc). Remove all references to effervescence and bubble and rocket graphics should be removed from the product information.

4. Use of Abbreviations

   The abbreviations BTP (breakthrough pain), OTFC (oral transmucosal fentanyl citrate), and ATC (around the clock) are used throughout the Fentora product information (e.g., product monograph, Questions and Answers About Fentora for Healthcare Professions, etc). Often when abbreviations are used in labeling, the abbreviations are carried over to physician prescribing practices, which increases the potential for confusion.

   The FDA in conjunction with the Institute for Safe Medical Practice (ISMP) launched a campaign on June 14, 2006 to reduce medication mistakes caused by unclear medical

abbreviations. Remove all uses of the abbreviations "BTP," "ATC," and "OTFC," from all Fentora product information in order to comply with this campaign.

5. Mock Prescriptions

   The mock prescriptions contained in the promotional materials are concerning. Often prescribers follow examples such as these when prescribing said products. The examples used for Fentora increase the potential for overdoses, diversion, or unintended exposures due to vague directions (e.g., one tablet PRN) and quantity prescribed (e.g., 140 tablets). Revise these prescriptions so that they accurately reflect prescribing practices which help to ensure safe use of this product.

6. Onset & Duration of Relief

   The "Core Sales Aid" states "Onset of relief in as little as 15 minutes" and "Duration of relief demonstrated for up to 60 minutes." These statements may lead to overdoses if (1) patient does not feel relief in 15 minutes and (2) patient takes another tablet after 60 minutes to prevent onset of breakthrough pain. Remove these statements.

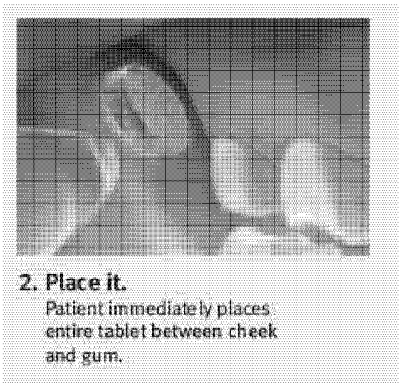
7. Tablet Color

   The "Core Sales Aid" has pictures of all white tablets while the website presents pictures of different color tablets. Revise pictures to the correct color scheme.

8. Correct Administration

   a. Fentora is to be placed above a rear molar tooth between the upper cheek and gum. However, the picture below from the website (Tool 24) shows the tablet being placed above a tooth closer to the front of the mouth. Patients often heavily rely on pictures with regard to correct administration of drug products. Revise this picture to reflect correct administration of the tablet.

   b. In the picture below from the sales aids, the tools demonstrates correct placement of the tablet in the mouth: however, the wording below the picture does not state where in the mouth the patient is supposed to place the tablet between the cheek and gum (i.e., above rear molar tooth). Revise the statement to reflect correct placement of the tablet.



9. Counseling Aid to Pharmacists and Prescribers (Tool 14)

   The brochure titled "Questions and Answers About FENTORA for Patients" can be easily confused with the Medication Guide (MG). If you desire to have additional information for patients in the form of a brochure, any reference to safety information or use of Fentora should be consistent with the MG. We suggest that the brochure include the MG (exact reproduction of content and format) with any supplementary educational information at the end of the brochure. Inform the Agency of your plan to disseminate this brochure (e.g., via a call-in number, in the doctor's office, etc.).

10. Fentora Website

    As part of your educational plan, you submitted the Fentora website. OSE reviewed the website for clarity and consistency. As with the Brochure noted above, the content and language is not consistent with the Medication Guide.

    Replace the three sections of the website that are dedicated to safety information (sections: "About Fentora," "Safety, Storage, and Disposal," and "Important Information") with the Medication Guide. The sections of the website that are not addressed in the Medication Guide (sections: "Breakthrough pain in patients with cancer," "For Caregivers," and "Resources") can remain as additional education.

Surveillance and Measuring Effectiveness of the RiskMAP

11. Active Surveillance

    The following are some inaccuracies with the surveillance activities:

    a. First, the data that is made available using DAWN Live! are counts of drug-related hospital emergency department (ED) visits, not medical examiner data. It will provide counts of all drug-related ED visits that are related to all of your marketed products at the brand level and generic level (e.g., Actiq and oral transmucosal fentanyl citrate on stick). The system does not provide information on location or on

drug combinations and will not provide information on other opioid products other than the ones you market.

b. Furthermore, this data is an on-line public health surveillance system that can be accessed at any time after gaining access to the system, therefore data can be evaluated more often than on a quarterly basis. It is not an appropriate tool to be used to compare with other opioid products or to examine trends since you would only have access to your own products. Because participation of hospitals and the completeness of data vary, unweighted DAWN data are not representative.

c. DAWN Live! should function more as an early warning surveillance system of possible cases of drug misuse abuse and problems with the drug. If you were to gain access to DAWN Live!, we recommend that you gain access to all your products and compare the counts of ED mentions per prescriptions sold for Actiq and use that as a baseline. If the counts of ED mentions for Fentora exceed this rate, evaluate the source of this increased risk and work with the FDA to develop more effective risk management strategies.

d. Little information was provided on how you plan to use data from TESS. We encourage you to purchase the more detailed data that includes fatality data from American Association of Poison Control Centers.

12. Surveys

a. General Survey Methodology - In several places in the submission (between pages 40-43), you indicate that you will evaluate and potentially modify the methodology: questions, sample frame, sample size, and time frames. Notify the Agency of these changes (including the rationale for the change) prior to change implementation.

b. Patient Survey Introduction - In the introduction of the Fentora Patient Call Back Survey the interviewer says, "Hello, my name is XXX on behalf of FENTORA, I'm a pharmacist....". Revise to say, "Hello, my name is XXX on behalf of the Manufacturer (or makers) of FENTORA. I'm a pharmacist..."

c. Pharmacist and Physician Survey Methodology - On page 42 of the July 25, 2006 submission, you indicate that "respondents for this survey will be recruited ahead of time." We question the need for this recruitment step. For purposes of reaching adequate sample size, it would decrease drop-out if you completed the interview as soon as the pharmacist/physician agrees to it.

d. Physician Survey Methodology - It is not clear in the submission how many of the 110 respondents in the physician survey will have been seen by a Cephalon sales representatives. Determine the sample regardless of whether the physician has seen a sales rep. If you choose to do a cohort study to determine the effectiveness of sales reps, it should be done outside of the RiskMAP-related survey.

e. Pharmacist and Physician Survey Instruments – The instruction to the interviewer administering the survey states "If the answer to any question (2 and beyond) is not yes or always, please instruct physician [or pharmacist] to visit website associated with FENTORA for full prescribing information."

   In addition to directing the respondent to the FENTORA website for the full prescribing information, issue a follow-up letter to be sent to the physician and pharmacist informing them of the importance of selecting and dispensing only to the appropriate opioid tolerant patient to ensure safe use of the product. The letter should be accompanied by a detailed definition of an opioid tolerant patient and the full prescribing information. Change the instructions to reflect this procedure.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, M.S.
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
8/29/2006 06:46:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-947

INFORMATION REQUEST LETTER

Cephalon, Inc
c/o CIMA Labs
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Carol S. Marchione
Senior Director, Regulatory Affairs

Dear Ms. Marchione:

Please refer to your August 31, 2005, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fentora (fentanyl buccal tablets).

We also refer to your complete response dated July 25, 2006.

We are reviewing your RiskMAP submitted July 25, 2006, and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Remove any element with a potential promotional quality from the RiskMAP. This would include references to effervescence as a means of both enhancing the extent of and rate of absorption of fentanyl and the appearance of a rocket, which is inherently promotional in nature.

2. Remove any presentation of information that implies a superiority claim relative to Actiq (OTFC) that is not supported by two adequate and well-controlled clinical trials. This includes presentations of pharmacokinetic (PK) characteristics of both products.

3. Reference is made to opioid-tolerant patients throughout the RiskMAP. To avoid any terminology that might promote off-label use of Fentora, replace the term "opioid-tolerant patient" with "opioid-tolerant cancer patient."

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, M.S.
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley

8/30/2006 08:34:58 PM

Cephalon
deliver more

www.cephalon.com

Cephalon, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355
Phone 610-344-0200
Fax 610-344-0065

September 7, 2006

Robert Rappaport, M.D., Director
Food and Drug Administration
Center for Drug Evaluation
Division of Anesthetic, Analgesia and
Rheumatology Products, HFD-170
5901-B Ammendale Road
Beltsville, MD 20704-1266

NDA 21-947
FENTORA™ (fentanyl buccal tablets) CII

Amendment to NDA: Response to FDA Correspondence Regarding the RiskMAP

Dear Dr. Rappaport:

Reference is made to our New Drug Application (NDA 21-947) for the use of FENTORA (fentanyl buccal tablets) for the treatment of breakthrough pain in opioid-tolerant patients with cancer. Reference is also made to the Discipline Review Letter (August 29, 2006), the Information Request Letter (August 30, 2006), and the teleconference between FDA and Cephalon that occurred on August 31, 2006 regarding the FENTORA proposed RiskMAP.

The purpose of this submission is to address each of the items delineated in the FDA's correspondences. For ease of review, we have restated the Agency's comments from the correspondences referenced above and have provided Cephalon's responses immediately after each question.

In addition, a separate submission will be provided to the Agency reflecting all of the modifications discussed in this communication.

Comments from Discipline Review Letter (August 29, 2006):

Post-Marketing Reporting

1. **The RiskMAP does not include a plan to submit the following types of reports to the Agency in an expedited fashion:**
    a. **Any report with an outcome of death**
    b. **Any report in a child or adolescent (ages 0-16), whether or not the exposure was intended or unintended, and regardless of the outcome**

c. **Any medication error reports regardless of patient outcome (this would include reports involving accidental exposures)**

Per our letter of May 19, 2006, and your June 2, 2006 agreement to this request, revise the final RiskMAP to reflect this commitment.

The RiskMAP, specifically Section 4.2, has been revised to acknowledge that we will be providing the requested reports. We will submit the revised RiskMAP under separate cover.

2. **The RiskMAP is not specific with regard to the type of data that will be submitted in the quarterly report. Per our letter of May 19, 2006, revise the final RiskMAP to include the following in your quarterly reports to the Agency:**
   a. **Extent of use (denominator estimates)**
   b. **Indicators of off-label use or inappropriate prescribing (i.e., opioid-naïve)**
   c. **Summary of reports involving medication errors and inadvertent pediatric exposures**
   d. **Summary of adverse events involving opioid naïve patients**
   e. **Rates of misuse, abuse, addiction or diversion observed**
   f. **Results of any investigation or surveys conducted**
   g. **Outcome of any interventions, such as targeted educational interventions and antidiversion programs conducted.**

Cephalon commits to include the above mentioned items in our quarterly reports. We would, however, like to clarify the information that we will be able to provide for Items b. and e.

In order to provide information to address Item b, Cephalon will use longitudinal data to assess whether patients receiving FENTORA are opioid tolerant, which (because of the associated medical risk) we believe is a useful indicator of the extent to which the product is being used inappropriately. This evaluation will specifically address one of the three key risks identified in the FENTORA RiskMap. Therefore, we suggest that Item b should more accurately be titled, "Indicators of inappropriate prescribing (i.e., prescribing to opioid non-tolerant patients)".

For Item e, we would like to clarify that the cases of misuse, abuse, addiction or diversion will not be confirmed at the time of the submission of the quarterly reports. Therefore, we are proposing to revise the title of Item e to be "Rates of suspected misuse, abuse, addiction or diversion reported".

Education and Outreach Tools

3. **Use of Effervescent, Bubbles, and Rocket (graphics and statements)**

The statement "FENTORA employs OraVescent drug delivery technology, which utilizes effervescence to enhance the rate and extent of fentanyl delivery across the buccal mucosa" (HCP Introductory Letter) implies that the tablet is an effervescent tablet rather than a buccal tablet. Furthermore, the bubble graphics presented next to the proprietary name and at the bottom of the letter in addition to the statement "effervescent speed" under the proprietary and established names imply that the tablet is effervescent.

The aforementioned statements and graphics in addition to other references of effervescence appear throughout the FENTORA product information (e.g., HCP letter, Medication Guide, product monograph, website, sales aids, etc.). Remove all references to effervescence and bubble and rocket graphics should be removed from the product information.

Cephalon is revising all of the tools included in the RiskMAP to remove the statements and graphics as noted above in accordance to the Agency's directions. The tools will be resubmitted to the Agency under separate cover.

4. **Use of Abbreviations**

The abbreviations BTP (breakthrough pain), OTFC (oral transmucosal fentanyl citrate), and ATC (around the clock) are used throughout the FENTORA product information (e.g., product monograph, Questions and Answers About FENTORA for Healthcare Professionals, etc.). Often when abbreviations are used in labeling, the abbreviations are carried over to physician prescribing practices, which increases the potential for confusion.

The FDA in conjunction with the Institute for Safe Medical Practice (ISMP) launched a campaign on June 14, 2006, to reduce medication mistakes caused by unclear medical abbreviations. Remove all uses of the abbreviations "BTP", "ATC", and "OTFC" from all FENTORA product information in order to comply with this campaign.

All other documents containing product information associated with FENTORA are being revised to remove these abbreviations. The documents identified as RiskMAP tools will be submitted under a separate cover and will reflect the removal of the abbreviations.

As mentioned during the teleconference of August 31, 2006, Cephalon has manufactured one packaged lot of each strength of FENTORA containing a package insert and Medication Guides. The text in the package insert, agreed upon at the time of receipt of our approvable letter, dated June 29, 2006, contain the abbreviations mentioned above. It will take approximately 3-9 months, depending on the dosage strength, to deplete this supply of inventory. Cephalon commits to revising the

package insert to remove "BTP", "ATC", and "OTFC" at the next printing. We will submit revised labeling documents for your review in a separate submission.

5. **Mock Prescriptions**

The mock prescriptions contained in the promotional materials are concerning. Often prescribers follow examples such as these when prescribing said products. The examples used foe FENTORA increase the potential for overdoses, diversion, or unintended exposures due to vague directions (e.g., one tablet PRN) and quantity prescribed (e.g., 140 tablets). Revise these prescriptions so that they accurately reflect prescribing practices which help to ensure safe use of this product.

Promotional materials containing mock prescriptions have been revised in response to the Agency's concerns. Specifically, for the initial dose of FENTORA, the mock prescription now states, "FENTORA 100mcg; disp twenty-eight; sig: place tablet above a rear molar between the upper cheek & gum; Take 1 tablet per breakthrough pain episode. May be repeated once if pain not relieved after 30 minutes." For the maintenance dose, it has been modified to the following: "FENTORA 400mcg; disp one hundred twelve tablets; sig; take 1 tablet per breakthrough pain episode." It should be noted that the RiskMAP tools will not contain mock prescriptions.

6. **Onset & Duration of Relief**

The "Core Sales Aid" states "Onset of relief in as little as 15 minutes" and "Duration of relief demonstrated for up to 60 minutes." These statements may lead to overdoses if (1) patient does not feel relief in 15 minutes and (2) patient takes another tablet after 60 minutes to prevent onset of breakthrough pain. Remove these statements.

The "Core Sales Aid", though not a tool of the RiskMAP, will be modified to include the addition of the statement "Redosing may occur 30 minutes after the start of administration of FENTORA and the same dosage strength should be used". As discussed during the teleconference with the Agency, Cephalon believes that the addition of this information should provide better context of the onset of relief as requested by the Agency. If this is acceptable, this statement will be added to pertinent RiskMAP tools and promotional pieces.

7. **Tablet Color**

The "Core Sales Aid" has pictures of all white tablets while the website presents pictures of different color tablets. Revise pictures to the correct color scheme.

The website has been modified to reflect pictures of all white tablets. A copy of the revised website content will be submitted under separate cover with the other RiskMAP tools.

8. **Correct administration**
   a. **Fentora is to be placed above a rear molar tooth between the upper cheek and gum. However, the picture below from the website (Tool 24) shows the tablet being placed above a tooth closer to the front of the mouth. Patients often heavily rely on pictures with regard to correct administration of drug products. Revise this picture to reflect correct administration of the tablet.**

      The picture on the website has been revised to reflect correct administration of the tablet. A copy of the revised website content will be submitted under separate cover with the other RiskMAP tools.

   b. **In the picture below from the sales aids, the tools demonstrates correct placement of the tablet in the mouth; however, the wording below the picture does not state where in the mouth the patient is supposed to place the tablet between the cheek and gum (i.e., above rear molar tooth). Revise the statement to reflect correct placement of the tablet.**

      As previously noted, the sales aid is not a tool associated with the RiskMAP. However, we did revise the sales aid and all of the other pieces to ensure that a statement has been added below the picture to reflect the correct placement of the tablet. The RiskMAP tools containing this revision will be provided in a forthcoming submission.

9. **Counseling Aid to Pharmacists and Prescribers (Tool 14)**

   The brochure titled "Questions and Answers About FENTORA for Patients" can be easily confused with the Medication Guide (MG). If you desire to have additional information for patients in the form of a brochure, any reference to safety information or use of FENTORA should be consistent with the MG. We suggest that the brochure include the MG (exact reproduction of content and format) with any supplementary educational information at the end of the brochure. Inform the Agency of your plan to disseminate this brochure (e.g., via a call-in number, in the doctor's office, etc.).

   As clarified during the August 31st teleconference, the above mentioned aid pertains to Tool 15, not Tool 14. Subsequent to our teleconference, we reviewed and modified the Patient Brochure to ensure that it is consistent with the content of the Medication Guide and that the safety information is balanced throughout. This tool will have a Medication Guide attached. It will be disseminated by the sales representatives to healthcare providers.

10. FENTORA Website

As part of your educational plan, you submitted the FENTORA website. OSE reviewed the website for clarity and consistency. As with the Brochure noted above, the content and language is not consistent with the Medication Guide. Replace the three sections of the website that are dedicated to safety information (sections: "About FENTORA", "Safety, Storage, and Disposal", and "Important Information") with the Medication Guide. The sections of the website that are not addressed in the Medication Guide (sections: "Breakthrough pain in patients with cancer", "For Caregivers", and "Resources") can remain as additional information.

The website has been revised to incorporate the changes indicated above. A copy of the revised website content will be submitted under separate cover with the other RiskMAP tools.

Surveillance and Measuring Effectiveness of the RiskMAP

11. Active Surveillance

The following are some inaccuracies with the surveillance activities:

a. **First, the data that is made available using DAWN Live! Are counts of drug-related hospital emergency department (ED) visits, not medical examiner data. It will provide counts of all drug-related ED visits that are related to all of your marketed products at the brand and generic level (e.g., Actiq and oral transmucosal fentanyl citrate on stick). The system does not provide information on location or on drug combinations and will not provide information on other opioid products other than the ones you market.**

   In accordance with our teleconference of August 31, 2006, the FDA confirmed that the above information was provided to Cephalon as background and that no action is warranted.

b. **Furthermore, this data is an on-line public health surveillance system that can be accessed at any time after gaining access to the system; therefore data can be evaluated more often than on a quarterly basis. It is not an appropriate tool to be used to compare with other opioid products or to examine trends since you would only have access to your own products. Because participation of hospitals and the completeness of data vary, unweighted DAWN data are not representative.**

In accordance with our teleconference of August 31, 2006, the FDA confirmed that the above information was provided to Cephalon as background and that no action is warranted.

c. **DAWN Live! Should function more as an early warning surveillance system of possible cases of drug misuse abuse and problems with the drug. If you were to gain access to DAWN Live!, we recommend that you gain access to all your products and compare the counts of ED mentions per prescriptions sold for Actiq and use that as a baseline. If the counts of ED mentions for FENTORA exceed this rate, evaluate the source of this increased risk and work with the FDA to develop more effective risk management strategies.**

In accordance with the Agency's recommendations, Cephalon will be obtaining access to DAWN Live! and analyzing the data as described above. Section 4.1 of the FENTORA RiskMAP document, containing this methodology, will be submitted under separate cover.

d. **Little information was provided on how you plan to use data from TESS. We encourage you to purchase the more detailed data that includes fatality data from American Association of Poison Control Centers.**

In accordance with the Agency's recommendations, Cephalon will purchase the more detailed data from TESS including the fatality data from American Association of Poison Control Centers. Cephalon will be able to utilize this information to conduct surveillance and to analyze subsets of the data to assess whether further interventions are warranted in a particular demographic segment (e.g., age), geographic area, etc.

12. Surveys

a. **General Survey Methodology- In several places in the submission (between pages 40-43), you indicate that you will evaluate and potentially modify the methodology: questions, sample frame, sample size, and time frames. Notify the Agency of these changes (including the rationale for the change) prior to change implementation.**

Cephalon commits to notifying the FDA of any changes to the surveys, including the rationale for the change, prior to change implementation.

b. **Patient Survey Introduction – In the introduction of the FENTORA Patient Call Back Survey the interviewer says, "Hello, my name is XXX on behalf of FENTORA, I'm a pharmacist...". Revise to say, "Hello, my name is XXX on behalf of the Manufacturer (or makers) of FENTORA. I'm a pharmacist..."**

Cephalon has modified the Patient Call Back Survey as directed above. A modified copy of this survey will be provided under separate cover with the RiskMAP tools.

c. **Pharmacist and Physician Survey Methodology –on page 42 of the July 25, 2006 submission, you indicate that "respondents for this survey will be recruited ahead of time." We question the need for this recruitment step. For purposes of reaching adequate sample size, it would decrease drop-out if you completed the interview as soon as the pharmacist/physician agrees to it.**

As summarized on our teleconference, the market research vendor conducts their research in a step-wise manner; one resource conducts the recruitment phone calls, while another resource subsequently conducts the interview. Therefore, we will not be able to have the respondents that are recruited ahead of time interviewed at the time of their recruitment.

d. **Physician Survey Methodology – It is not clear in the submission how many of the 110 respondents in the physician survey will have been seen by a Cephalon sales representatives. Determine the sample regardless of whether the physician has seen a sales rep. If you choose to do a cohort study to determine the effectiveness of sales reps, it should be done outside of the Risk MAP-related survey.**

In accordance with the Agency's instruction, participation in the physician survey is not dependent on whether a physician was seen by a Cephalon sales representative. Therefore, any number from 0-110 of the respondents in the physician survey may have (or may not have) been seen by a Cephalon sales representative. In addition, we concur with the Agency that the effectiveness of sales reps, if evaluated, should be conducted in a cohort study outside of the RiskMAP-related survey.

e. **Pharmacist and Physician Survey Instruments – The instruction to the interviewer administering the survey states "If the answer to any question (2 and beyond) is not yes or always, please instruct physician [or pharmacist] to visit website associated with FENOTRA for full prescribing information."**

In addition to directing the respondent to the FENTORA website for the full prescribing information, issue a follow-up letter to be sent to the physician and pharmacist informing them of the importance of selecting and dispensing only to the appropriate opioid tolerant patient to ensure safe use of the product. The letter should be accompanied by a detailed

definition of an opioid tolerant patient and the full prescribing information. Change the instructions to reflect this procedure.

In accordance with the FDA's direction above, Cephalon commits to having a third-party independent vendor issue a follow-up letter to those physicians and pharmacists informing them of the importance of selecting and dispensing only to the appropriate opioid tolerant patients to ensure safe use of the product. The letter will be accompanied by a detailed definition of an opioid tolerant patient as well as the full prescribing information. The survey instructions have been modified to reflect the change to this procedure. A copy of the modified survey will be submitted under separate cover with the RiskMAP tools.

Comments from Information Request Letter (August 30, 2006):

1. **Remove any element with a potential promotional quality from the RiskMAP. This would include references to effervescence as a means of both enhancing the extent of and rate of absorption of fentanyl and the appearance of a rocket, which is inherently promotional in nature.**

   Elements with a potential promotional quality have been removed from the RiskMAP. Additionally, two tools previously included with the RiskMAP, the product monograph (Tool 9) and the Healthcare Professional FAQ (Tool 14), were removed. After considering your comments from the teleconference, we removed these tools as we believe that pieces oriented specifically with risk-related information better relay the messages of the FENTORA RiskMAP.

2. **Remove any presentation of information that implies a superiority claim relative to Actiq (OTFC) that is not supported by two adequate and well-controlled clinical trials. This includes presentation of pharmacokinetic (PK) characteristics of both products.**

   In accordance with the Agency's comments, we have modified our RiskMAP materials to ensure the presentation of information with respect to Actiq is identical to that contained in the package insert. The revised RiskMAP tools are being submitted under separate cover.

3. **Reference is made to opioid-tolerant patients throughout the RiskMAP. To avoid any terminology that might promote off-label use of FENTORA, replace the term "opioid tolerant patient" with "opioid tolerant cancer patient."**

   The RiskMAP document as well as all of the RiskMAP tools have been modified to replace the term "opioid tolerant patient" with "opioid tolerant cancer patient." The revised RiskMAP and associated tools are being submitted under separate cover.

This letter constitutes our formal response to the FDA Discipline Review and Information Request Letters (August 29 and August 30, 2006, respectively) and serves as our commitment to fulfill the items delineated in the FENTORA RiskMAP (SECURE Program). A follow-up submission will be provided to the Agency next week consisting of a revised RiskMAP document that will be supplied to you both in 'track/changes' mode and 'clean' to facilitate ease of review. Also included in this forthcoming submission will be the revised RiskMAP tools, surveys, and a sample quarterly report template reflecting the commitments noted in this correspondence.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 738-6742 or Ms. Carol Marchione at (610) 738-6237.

Sincerely,

Penny S. Levin, MS

Penny S. Levin, MS
Associate Director
Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Cephalon,Inc. c/o CIMA Labs	September 7, 2006
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(610) 344-0200	(610) 738-6642
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
41 Moores Road P.O. Box 4011 Frazer, PA 19355	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 21-947

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Fentanyl buccal tablet	Fentora™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Propanamide, N-phenyl-N-[(1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:)	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Buccal tablet	100, 200, 400, 600, and 800 mcg	oral transmucosal

(PROPOSED) INDICATION(S) FOR USE:
Management of breakthrough pain in opiod tolerant patients with cancer

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Response to FDA Request

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Information previously submitted, available upon request

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 65-447 Oravescent fentanyl citrate, OTFC
NDA 20-747 Oral transmucosal fentanyl citrate
DMF 5038 Fentanyl Citrate)
DMF 6684 Alcan Packaging - Shelbyville, KY
DMF 15067 Alcan Packaging - Kreuxlingen, AG

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Response to FDA Request

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Carol S. Marchione	Carol S. Marchione Senior Director, Regulatory Affairs	9/7/2006

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
41 Moores Road, P.O. Box 4011 Frazer, PA 19355	(610) 344-0200

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Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
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Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

1 BACKGROUND

1.1 Rationale for the RiskMAP

Fentanyl citrate is marketed in the U.S. in a variety of formulations including those for intravenous and intramuscular administration as well as those intended for transdermal or oral transmucosal delivery and has a long record of safe and effective use when utilized as directed in the treatment of pain. FENTORA™ (fentanyl buccal tablet), is a new formulation of fentanyl in buccal tablet form, intended for transmucosal delivery. FENTORA is a potent opioid analgesic with effects similar to morphine. It has been evaluated in clinical trials at strengths of 100, 200, 400, 600, and 800 mcg for the treatment of breakthrough pain in patients with cancer who are tolerant to opioid therapy. Currently the only other drug marketed for the management of breakthrough pain in patients with cancer is Actiq®, a formulation of fentanyl citrate which is a lozenge dosage form on a handle. Like Actiq, FENTORA will be listed under the Controlled Substances Act as a Schedule II product and labeling for the product will contain a boxed warning.

Opiate drug products have important benefits in alleviating pain but are associated with significant risks of diversion, abuse, and addiction (FDA, 2005). To minimize the risks of misuse, abuse, addiction and diversion of FENTORA and to maximize appropriate use only in opioid tolerant cancer patients, Cephalon has developed the SECURE (Solutions through Education, Communication and Understanding Risk Minimization Excellence) Program. Risks to be Minimized:

As FENTORA contains a potent opiate, fentanyl, the SECURE Program is focused on minimizing three risks associated with:

(1) Use of FENTORA by opioid non-tolerant individuals;
(2) Misuse, abuse and diversion of FENTORA; and;
(3) Unintended (accidental) exposure to FENTORA.

In this RiskMAP, each of these risks is translated into goals and a series of measurable objectives accompanying each goal. To implement the RiskMAP, tools will be employed to mitigate each of the risks. The rationale and specific purpose of each tool is described in this RiskMAP. Its overarching goal is to minimize the three specific risks associated with FENTORA while preserving the product's benefits.

1.1.1 Risk 1: Use of FENTORA by opioid non-tolerant individuals

As is the case with the use of all opioids, individuals using FENTORA who are not tolerant to opioids are at risk for clinically significant and life-threatening adverse events such as respiratory depression. The risk is present at any dose in such individuals and the risk increases with the dose. Therefore, FENTORA must not be used by opioid non-tolerant individuals as the safety and effectiveness of FENTORA in this population has not been established. Patients with cancer considered opioid-tolerant are those who are taking at least 60 mg of oral morphine per day, 25 mcg of transdermal fentanyl per

hour, at least 30 mg of oxycodone daily, at least 8 mg oral hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer. By limiting the use of FENTORA to those already taking opioid products for a sufficient timeframe at sufficient levels, the risk of serious outcomes such as respiratory depression may be minimized.

FENTORA will likely be used primarily in the outpatient setting. To assure that at-risk patients are identified and that FENTORA is used only in opioid tolerant patients with cancer, Cephalon is initiating a risk-minimization program that contains multiple channels of communication and reinforcing educational messages targeted toward physicians who prescribe FENTORA, pharmacists who dispense FENTORA, as well as patients who use the product. These interventions are also intended to reach allied health professionals and caretakers who oversee patients' health.

1.1.2 Risk 2: Misuse, abuse and diversion of FENTORA

The abuse liability of opioids is well known and has been characterized in the medical and lay literature as well as in the media. Opioid misuse and abuse have been known to be a precursor to addiction. The actual rate of addiction to opioids is not known, but has been estimated to be between 4-10% (Savage 1996).

FENTORA is an effective opioid analgesic that delivers pharmacologically significant amounts of fentanyl to the brain. Fentanyl is a known drug of abuse, and the FENTORA dosage form (buccal tablets) has the potential to be abused. Consequently, FENTORA will be labeled, regulated, and listed as a Schedule II opioid, as are all other fentanyl products.

The abuse liability of a product is based on a complex interplay of many factors which include drug characteristics, patient characteristics, as well as societal and other influences. Among these many factors, the onset of action may be a drug characteristic that contributes to increased abuse liability. This view may be supported by the evidence of attempts to reconstitute long-acting opioids into formulations with a rapid release of medication (e.g., crushing Oxycontin tablets, withdrawing fentanyl from a patch for use in a syringe).

Opioids, such as Oxycontin, have experienced 'geographic hot spots' and regional differences in abuse rates, where there is significantly more abuse or misuse and/or diversion than in most other geographic areas. Exact rates of opioid diversion are not known, but diversion is known to have occurred as a result of pharmacy theft/loss, fraudulent prescriptions, individuals obtaining the medication from physicians under false pretenses, patients selling or otherwise diverting drugs, wholesaler loss, manufacturer loss, leftover product not being destroyed, and other factors. Therefore, the integrity of the supply chain is an essential aspect of securing the delivery of FENTORA to patients for appropriate use.

In designing this RiskMAP, Cephalon has focused on 1) ensuring the integrity of its supply chain for FENTORA, 2) tools that can be used to educate broadly, and 3) mechanisms by which cases of diversion or abuse can be detected promptly. In this regard, Cephalon will monitor geographical evidence of abuse through the use of the

RADARS system (see below) to assure that rapid interventions can be applied to areas where there may be a signal of increasing abuse potential.

1.1.3 Risk 3: Unintended (accidental) exposure to FENTORA

The risk of serious consequences from accidental exposure to FENTORA is greater in individuals not-tolerant to opioids. Therefore, the risk of unintended exposure to the drug can be viewed as a component of the first risk described above (i.e., use of FENTORA by opioid non-tolerant individuals). The epidemiology of accidental ingestions suggests that this problem occurs primarily in the pediatric age group. While the tablet formulation and packaging of FENTORA is not expected to be any more intrinsically interesting or appealing to children than tablet formulations in blister packs for other drugs, the serious consequences from accidental exposure to FENTORA make the risk of unintended exposure to the product an important consideration. Therefore, we have identified this as a separate risk requiring a separate set of objectives and tools.

1.1.3.1 Epidemiology of Unintended Exposure

The literature on unintended exposures in the United States indicates that children are at highest risk for accidental ingestion. Of 2.4 million poisonings reported to American Association of Poison Control Centers-Toxic Exposure Surveillance System (AAPCC-TESS) in calendar year 2003, 52% occurred in children aged less than 6 years. Epidemiologic data indicate that the peak incidence of accidental child poisoning is at 15 - 17 months of age, declining rapidly between ages 3 years through 6 years. This observed peak in poisoning incidence coincides with the period of increasing mobility of toddlers and resulting exploration of the environment that is commonly associated with oral exploratory (hand-to-mouth) behavior.

More than half of poison center contacts are due to the exposure of toxic substances to children less than 6 years of age. This same population comprises 3.1% of fatalities (AAPCC-TESS, 2003). This observation suggests that even though childhood exposures are common, the substances most commonly ingested by young children (e.g., cosmetics, household cleaners, and plants) are usually of relatively low inherent toxicity. Similarly, fatalities as a result of pharmaceutical ingestions are observed in a similar manner, i.e., in calendar year 2003, a total of 20 fatal pharmaceutical ingestions in children aged less than 6 years were reported to the TESS poison control centers; four fatal pharmaceutical ingestions in children aged 6 years - 12 years were reported.

There is considerable literature on the prevention of childhood poisoning. It has been documented that a substantial proportion of childhood poisonings can be prevented by keeping medications in child-resistant containers. In contrast, poison warning labels designed for children do not appear to be effective. Additionally, the ability of aversive bittering agents has not been proven to reduce the incidence or severity of childhood poisoning.

1.1.3.2 Implications of Unintended Exposure Epidemiology for FENTORA

The efficacy and safety of FENTORA dosage strengths have been studied in the treatment of breakthrough pain only in adult opioid-tolerant patients. To date there are no

data regarding the safety or efficacy of FENTORA in children. Given the known pharmacology of FENTORA, its onset of action, and the dosage strengths available (up to 800 mcg of fentanyl), it can be anticipated that if a child who is not tolerant to opioids inadvertently is exposed to FENTORA, even in single unit doses, ingestion could result in significant toxicity or death.

Based on the epidemiological data cited above, it appears that the risk of accidental childhood poisoning involving FENTORA is significant. Interventions focused on safe packaging and educational and reminder messages emphasizing safe disposal and storage conditions are important methods of avoiding accidental ingestion by children. Cephalon will be using F1 packaging for FENTORA, which is the most stringent of child-resistant packaging requirements (see Glossary). The packaging will also contain reminder messages to keep the product away from children.

Directed counseling of FENTORA patients will be encouraged by healthcare professionals, including physicians, pharmacists and nurses, involved in the patient's care. These healthcare professionals can reinforce with the patient the need to prevent childrens' access to FENTORA. Patients themselves will be educated on the risk that FENTORA poses to children and can be given guidance on storage and disposal of the medication.

Although adults are less likely to experience unintended exposure to FENTORA than children, this RiskMAP also considers accidental exposure that could occur in adults, such as a result of cognitive impairment or due to medication errors. The RiskMAP takes steps to minimize such risks. For example, when prescribing FENTORA, physicians are informed to assess the ability of their patients to self-administer the medication as directed. When this ability is in question, the patients' caregivers should be counseled by healthcare professionals with guidance given to avoid accidentally exposure.

1.2 Risk-Benefit

1.2.1 Potential Benefits

Breakthrough pain (BTP) in patients with cancer is a well-recognized health problem, and it is important that ~~BTP~~breakthrough pain be managed adequately as part of an overall pain management program. Because of the prevalence and inherent consequences of ~~BTP~~breakthrough pain, it is recommended that patients with chronic pain on regular opioid treatment regimen be provided with supplemental opioid medications for the management of ~~BTP~~breakthrough pain (American Pain Society, 2003). For patients taking around-the-clock opioid therapy, the most commonly used medications for ~~BTP~~breakthrough pain are immediate-release oral opioids. It has been noted, however, that these medications are likely to be inadequate for a substantial proportion of patients (Portenoy et al 1999) because these medications typically take about 30 minutes to begin producing analgesic effects, whereas the onset of peak pain intensity of ~~BTP~~breakthrough pain for most patients occurs within just a few minutes.

As was shown in the pivotal study of cancer patients with breakthrough pain, FENTORA results in rapid onset of analgesia with extensive absorption and a lasting, even improving

effect. The efficacy results show that FENTORA had analgesic effects 15 minutes after tablet placement (the earliest time point assessed) and maintained superiority in analgesic effect compared with placebo treatment through the 60-minute observation period. In addition, patients were twice as likely to require supplemental opioid analgesics for ~~BTP~~breakthrough pain episodes for which placebos were used compared to episodes for which FENTORA was used. The superiority of FENTORA to placebo treatment was demonstrated by all measures of efficacy (pain intensity, pain relief, global medication performance, and use of supplemental rescue medication) and at all time points (15, 30, 45, and 60 minutes after treatment). The effects were both statistically significant and clinically relevant.

While fentanyl has long been recognized as a potent analgesic, there are inherent advantages to the buccal tablet formulation of fentanyl. Fentanyl buccal tablets are uniquely formulated with effervescence ingredients and pH adjusters to facilitate a rapid and extensive absorption of fentanyl through the oral mucosa. Its observed pharmacokinetic profile indicates that approximately 50% of FENTORA is rapidly absorbed and quickly becomes systemically available. These formulation and pharmacokinetic characteristics mean that lower doses are needed by patients for attainment of therapeutically effective plasma concentrations than those required with Actiq, a fentanyl lozenge on a handle (solid dosage form). Specifically, this rapid absorption results in peak plasma concentrations being reached nearly twice as fast as Actiq, allowing for therapeutically effective plasma concentrations to be achieved earlier. These product qualities are advantageous for a condition such as ~~BTP~~breakthrough pain when the time from onset to maximum intensity is short. Because the effervescent formulation is a more efficient delivery system, the tablet strengths of effervescent fentanyl (100 to 800 mcg) are lower than the unit strengths of Actiq (200 to 1600 mcg).

Unlike administration of Actiq, a transmucosal fentanyl lozenge on a handle, administration of a buccal tablet is not only less dependent on the continued "active administration" of the patient, it is also more discreet, automatic and convenient for the patient. The simplicity of administration of a tablet potentially allows for more consistent delivery of fentanyl because it relies on a passive delivery system that is less prone to patient error.

1.2.2 Potential Risks

While FENTORA has been shown to benefit opioid-tolerant patients with breakthrough cancer pain, the product also has potentially serious side effects and risks.

As described above, because it is a potent μ-receptor agonist, there are inherent risks with fentanyl buccal tablets to populations for which the product is not intended, particularly people who are not opioid tolerant. Although respiratory depression, was not seen in clinical studies with FENTORA, the potential for this side effect in people who are not opioid tolerant must be guarded against with interventions that go beyond routine package labeling.

Like other drugs of its class, FENTORA may be habit forming or potentially abused, and as such, physicians should use caution prescribing it to patients who may be at risk for

abuse of the product (e.g., patients with severe ~~BTP~~breakthrough pain & co-morbid history of abuse). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed FENTORA. As with all Schedule II products or fentanyl formulations, all patients receiving FENTORA should be routinely monitored for signs of misuse, abuse, and addiction.

During clinical studies of FENTORA to-date, there have been 4 serious adverse events (SAEs) associated with overdose; one resulting in death. The person who died was a family member of a patient and had a history of substance abuse, and died possibly due to an overdose of his spouse's study medication. With regard to theft of FENTORA, two patients in study 15 and two patients in study 3040 were withdrawn from these studies at the request of the sponsor due to the theft of FENTORA from these patients' homes. In these cases, the patients had family members with a history of drug abuse, and there were questions about whether the family members were involved in the theft.

As with other fentanyl formulations (the transdermal patch or Actiq), the potential exists for abusers to extract fentanyl from FENTORA tablets. The efficiency of the delivery system enables similar plasma levels of fentanyl to be obtained with doses of fentanyl that are lower than those required with Actiq. The tablet strengths for FENTORA (100, 200, 400, 600, and 800 mcg) are half those of the available dose strengths for Actiq (200, 400, 600, 800, 1200, and 1600 mcg). Moreover, the amount of fentanyl in the buccal tablets is also substantially lower than the 10 mg of fentanyl present in the 100-mcg/h transdermal patch. Although the risk of extraction is present for FENTORA, the amount of drug available is lower than with these other formulations.

Based on pharmaceutical development studies, manipulation (e.g., crushing) of FENTORA tablets is not likely to substantially alter the absorption characteristics of the medication when administered buccaly or orally. Although intranasal and intravenous administration of a crushed tablet is possible, the risk of occurrence is not considered to be any greater than for other strong μ-opioids (e.g., oxycodone, hydromorphone, or morphine). At this point, Cephalon does not intend to direct any specific warnings at preventing such procedures (these actions would be more likely among addicts and mere warnings would not be particularly helpful. However, Cephalon will monitor the use of FENTORA and continually evaluate the need for such interventions.

There is also a risk of unintended exposure to FENTORA. The tablet formulation of FENTORA and its packaging is not expected to be intrinsically more interesting or appealing to children than tablet formulations and packaging of other drugs. But the epidemiology of accidental ingestions indicate that they occur primarily in the pediatric age group, and there is a risk of serious or fatal-consequences from accidental exposure to FENTORA, particularly in individuals not opioid tolerant.

Cephalon has developed the SECURE Program to mitigate the three major risks identified above: (a) use by opioid non-tolerant individuals; (b) misuse, abuse, and diversion; and (c) unintended (accidental) exposure to the medication. In the next section, we describe the goals, objectives of this program.

2 RISKMAP GOALS AND OBJECTIVES

Cephalon has identified three goals for the SECURE Program. These goals are expressed as ideal outcomes of the FENTORA RiskMAP. Associated with each of these goals, there are specific and measurable program objectives that are described below.

2.1 Goals

(1) Goal 1: FENTORA should be used only by opioid tolerant patients with cancer~~individuals~~.
(2) Goal 2: Abuse, Misuse and Diversion of FENTORA should not occur.
(3) Goal 3: Unintended (accidental) exposure to FENTORA should not occur.

2.2 Objectives

2.2.1 Goal 1: FENTORA should be used only by opioid tolerant patients with cancer ~~individuals~~

Objectives:

i. Educate physicians that FENTORA should not be used in opioid non-tolerant patients
ii. Educate patients that FENTORA should be used only by individuals with cancer who are opioid tolerant
iii. Educate pharmacists, and other healthcare personnel of the importance of FENTORA being prescribed, distributed, and used only by opioid tolerant patients with cancer.

2.2.2 Goal 2: Abuse, Misuse and Diversion of FENTORA should not occur

Objectives:

i. Ensure adequate controls are instituted, and maintained to prevent the diversion of FENTORA from Cephalon's supply chain.
ii. Ensure adequate education, surveillance, and interventions are instituted and maintained to minimize diversion of FENTORA when the product is no longer within Cephalon's supply chain.
iii. Reduce the potential abuse, misuse, and diversion of FENTORA by (a) providing education to healthcare personnel and to pertinent nationwide demographic communities; (b) performing ongoing surveillance of and reaction to geographical outbreaks of abuse, misuse, and diversion; and, (c) cooperating with and providing assistance to law enforcement in investigations of incidents of abuse or diversion.

2.2.3 Goal 3: Unintended (accidental) exposure to FENTORA should not occur

Objectives:

i. Reduce or eliminate accidental exposure through product packaging.

ii. Educate physicians, pharmacists, and patients about "safe product use" in efforts to reduce or eliminate accidental exposure.

iii. Reduce or eliminate accidental exposure during storage of FENTORA.

2.3 Overall Strategy

In developing the goals, objectives and tools for the SECURE Program, Cephalon also relied upon its experience with implementing its Risk Management Program for Actiq, a closely related product. In addition, principles and methodology of other risk assessment tools, such as Failure Mode Effects Analysis (FMEA), were used to evaluate the potential risks associated with use of FENTORA.

In developing the FMEA, it became apparent that three separate systems were needed to describe the processes related to the three goals. Goal 1 was well described by a "patient use" system that enumerated the process by which the patient was diagnosed, was prescribed the drug, obtained the medication, was monitored for their progress, and was prescribed refills. This process is outlined in Figure 1~~Figure 1~~ below. Goal 2 was well described by the "drug distribution" system that tracked the physical distribution of the drug from manufacturer to distributor, and from pharmacy to patient. This is described in Figure 3~~Figure 3~~ below. Goal 3 was well defined by the "tablet disposition" system that tracked the physical location of individual tablets once the medication was distributed to the patient. This is described in Figure 4~~Figure 4~~ below. For each of the Goals and the related systems, we developed interventions to attain those goals and related objectives. In the sections below we describe the three systems that were developed and the interventions designed to avoid system errors.

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3 OVERALL STRAGEGY FOR PRESCRIBING/DISPENSING/USING FENTORA

At the individual patient level, the ultimate use of FENTORA is predicated upon the general flow of outpatient prescriptions from physician to patient (prescribing) to pharmacist (dispensing) to patient (use) (see Figure 1~~Figure 1~~).

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At each point in this chain, there are a variety of interventions that are devoted to educate and remind physicians, pharmacists, patients and allied health professionals about the contraindicated use of FENTORA in opioid non-tolerant cancer patients (Goal 1), misuse and abuse (Goal 2), and unintended (accidental) exposure (Goal 3).

Figure 1: The Patient Use System – Safe Use Pathway

Physician/Patient Encounter →	Prescribing Decision →	Dispensing of Product →	Monitoring and Surveillance →	Refills

3.1 Physician Education

The first and most critical step in the chain of events leading to the use of FENTORA is the physician-patient interaction where the use of FENTORA is considered. For some patients, this may be to be an ongoing process, where the patient is under continued care of the physician. For other patients, this may be an initial visit where treatment is prescribed. Regardless of the process, it is important that prescribers be aware and knowledgeable of the conditions that would indicate or contraindicate the use of FENTORA.

The boxed warning on the physician labeling provides a clear signal regarding the importance of reading and understanding the message not to use FENTORA in non-opioid tolerant patients. It also assures that information about this contraindication will be included in all promotional pieces. The warning information not only conveys the desired behavior, but the reason for the contraindication (i.e., may cause life-threatening respiratory depression). “Opioid tolerant” (i.e., patients taking at least 60 mg of oral morphine/per day, 25 mcg of transdermal fentanyl/hour, at least 30 my of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or more) is clearly defined.

To assure that prescribers are aware of the importance of not prescribing FENTORA to opioid non-tolerant patients it is important not only to passively convey this warning in labeling but to also provide active interventions. These interventions will be organized in a fashion that will lead physicians through the learning process. Interventions will initially focus on announcing the availability of the new product. Even at this stage, the associated warnings will be communicated. These interventions will be followed with more in depth educational messages provided by both interpersonal and graphic/written means. It should be noted that the warning in the FENTORA labeling is similar to the

warning in the Actiq labeling and other Schedule II opioids. As such, physician education can focus on "associating" the contraindication with information that is already known by most physicians who would potentially prescribe FENTORA. Forming new associations with existing information in memory is an easier educational exercise than creating an entirely new knowledge structure, especially for experts (such as physicians). Physicians are more likely to learn about new drugs by reference to their existing knowledge (i.e., top-down information processing) as opposed to novices that seek to create whole new knowledge structures (i.e., bottom-up information processing) (Alba and Hutchinson, 1987).

The first set of interventions will be direct mail alerts to inform physicians about the availability of this new dosage form. These mailings will include a prominent display of the warning information as well as full product information.

Alerting physicians to the risk information is an important precursor to learning; however, it is helpful to follow-up with more in depth educational and persuasive information. To educate physicians regarding safe use of FENTORA, interpersonal (face-to-face) communication will be provided. Cephalon field representatives will provide direct risk information as part of their detail visit. Using academic centers, professional societies and Pain Centers of Excellence (pain centers identified by Cephalon as having excellent reputations, faculty and resources), additional education will be provided through training and independent Continuing Medical Education (CME) (note: CME programs will be conducted in accordance with FDA and ACCME guidelines). The importance of interpersonal communication is based not only on the need to provide education to prescribers but also to motivate behavioral adherence with the screening process to assure only appropriate patients are prescribed FENTORA. For physicians' desiring more in depth education about FENTORA, Cephalon will provide a product monograph that more fully describes the risks associated with use in opioid non-tolerant individuals. Because physicians in various localities may prefer to learn via different methods, Cephalon will work with the Pain Centers of Excellence to provide teaching opportunities consistent with the needs and resources identified by each Center.

Another tool that will be employed to alert physicians to the risk information associated with FENTORA is the FENTORA professional website. This website will be a portal that physicians can access at any time to learn more about FENTORA.

3.2 Patient Experience at Initial Encounter

From the patients' perspective, physician examination is also likely to be the critical "gatekeeping experience" leading to the prescribing of FENTORA. It is likely that many of the patients that will be prescribed FENTORA will be under the pre-existing treatment of the physician. As such, prescribing physicians should be acutely aware of the patients' experience with the use of opioid therapy. This should avoid communication problems between physicians and other health professionals regarding the patients' previous therapies.

As some patients tend to be "active information seekers" the FENTORA web site will contain warning information regarding the use of FENTORA in opioid non-tolerant

patients written in layman's language. This warning will be consistent with the Medication Guide (see below). Thus, for patients who learn about FENTORA prior to its prescribing and seek additional information through the website, the warning information will be prominently conveyed.

We must also assume that articles in the lay media, news coverage and conversations with friends and family may also make patients aware of FENTORA. Cephalon cannot control the content of these information exchanges (although Cephalon will include all pertinent warning information in press materials). However, for all of the content that Cephalon can control, we will assure that the information is balanced and includes the important warnings consistent with the goal of assuring that only opioid tolerant patients with cancer use FENTORA. Further, we will encourage health care providers to fully communicate this information to patients and we will assure that all patients receiving FENTORA receive sufficient warnings about the use of this product.

For patients who are not active information seekers, their first introduction to FENTORA will be the physician's directions about the product. We believe that with sufficient physician education and reinforcement, that the interaction between physician and patient will include the transfer of information necessary to make an appropriate prescribing decision. To further educate patients about FENTORA and provide patients with more complete information about cancer ~~BTP~~breakthrough pain, side effects, storage and other usage information, Cephalon has prepared a brochure that describes common questions and answers about the use of FENTORA. The brochure will be distributed to prescribers to be provided to patients. We also believe that the physician will provide specific warnings about FENTORA use. For the cases in which this may not occur, redundant interventions are designed as discussed below. To further encourage this verbal interaction, Cephalon has prepared a counseling aid for prescribers that provides questions and answers regarding the safe and effective use of FENTORA.

3.3 Pharmacist Education

A second essential aspect the patient use system is obtaining the prescription from a pharmacy. As a Schedule II prescription, FENTORA orders must be written and signed by the practitioner; they may not be telephoned into the pharmacy except in an emergency. Thus, drug scheduling makes it likely that patients will physically visit the pharmacy to obtain their supply of FENTORA.

To assure that pharmacists are sufficiently educated to screen and counsel patients, Cephalon will provide pharmacists with a similar set of educational interventions as provided to physicians. Pharmacists alerts, direct communication by field representatives and educational interventions will be used to provide this education. As many pharmacists learn about new prescription products through the use of a variety of educational compendia, Cephalon will prepare a letter to the suppliers of educational compendia to assure the inclusion of information about FENTORA.

As the pharmacist must physically dispense the product, the packaging for FENTORA provides a unique opportunity to actively "intercept" the pharmacist during the

dispensing process with a reminder message. Each package of FENTORA will include a special "pharmacist box" (see Figure 2~~Figure 2~~) that will remind pharmacists to:

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a. Make sure that the patient is opioid tolerant

b. Not to substitute the product with other fentanyl products on a mcg per mcg basis

c. Counsel the patient, and

d. Encourage the patient to read the Medication Guide.

Figure 2 FENTORA Outer Carton

In addition to the Pharmacist Box, the familiar inverted triangle will also be placed on the outer carton next to the warning to keep out of the reach for children (note, this warning will be displayed on the two opposite panels of the carton). As with prescribers, Pharmacists will also receive a counseling aid that provides questions and answers regarding safe and effective use of FENTORA.

3.4 Patient Education During Dispensing

The primary method of assuring this communication to patients is the distribution of a Medication Guide (MG). The MG will be enclosed in the FENTORA package. Research with the oral contraceptive patient package insert suggests that patient information is more likely to be dispensed to patients if enclosed in the package as opposed to being provided as a separate sheet (Morris, Mazis and Gordon, 1977). In order to avoid the misperception that the MG is promotional information, the MG will be the only information included in the package and the heading "Medication Guide" will be prominently displayed at the top of each leaflet (in compliance with FDA rules).

As with the physician label, the MG will explain that FENTORA can cause life threatening breathing problems if it is taken by anyone who is not already taking other opioid pain medicines (i.e., not opioid tolerant). This warning is prominently displayed as the first detail provided under the heading, "What is the most important information I should know about FENTORA?" Additional information about appropriate use of the product is provided in later sections of the MG.

The MG provides important information about the safe use of FENTORA, however, it may not provide patients with important contextual and background information that can help patients more fully understand the implications of inappropriate use of this product. Finally, as many pharmacies provide computer-generated counseling sheets along with dispensed prescriptions, Cephalon will correspond with the suppliers of the information system used by pharmacies informing them about FENTORA and its contraindications (e.g., First Data Bank, Health Resources).

3.5 Drug Effect Monitoring and Refills

The MG not only provides information to the patient that can intervene in the decision to initially use the medicine, it also provides information regarding the ongoing use of the drug. The MG states that FENTORA can cause serious breathing problems that can become life-threatening. They are told to call their doctor or get emergency help right away if they:

a. have trouble breathing

b. have extreme drowsiness with slowed breathing,

c. have slow, shallow breathing (little chest movement with breathing), or

d. feel faint, very dizzy, confused, or have unusual symptoms.

The provision of specific symptoms for which patients can monitor is an important aspect of the safe use of FENTORA. Research on risk perception suggests that providing patients with a sense of "control" over product hazards is an important element of risk communication and safe product use (Pidgeon, Kasperson, Slovic, 2003). This information should aid patients in monitoring for the safe use of the product during the time period that they use FENTORA.

Patients will be supplied 28 tablets of FENTORA with the initial prescription. FENTORA users are likely to see their physician on an ongoing basis. However, as a Schedule II drug, the prescription may not be refilled; the patient must see the practitioner again in order to obtain a new prescription. This assures that there will be an ongoing and repeated interaction with physicians and pharmacists and repeated opportunities for counseling. In addition, with each new prescription, a new MG will be dispensed to the patient.

3.6 Strategy and Tools Associated with Goals

Now that we have reviewed the interactions that occur during the "safe use" pathway, we will now look at the strategy and tools associated with each of the goals.

3.6.1 Strategy and Tools Associated with Goal 1: FENTORA should be used only by opioid tolerant patients with cancer ~~individuals~~

A variety of tools will be used to communicate and reinforce the message that FENTORA should be used only by opioid-tolerant patients with cancer ~~individuals~~. The tools have been designed for specific purposes, to be used as part of an organized

communications campaign intended to influence prescribers, pharmacists, and patients. The tools are designed to provide redundant messages through multiple channels to multiple audiences to avoid the possibility that errors will occur through lack of knowledge. Educational interventions intended to assure that there is long term knowledge about the importance to screen for opioid tolerance (including clear definitions of the terminology) is reinforced with reminder cues to assure that this knowledge is recalled at the time of prescribing, dispensing and using.

From the outset, healthcare professionals will be alerted to the risks of this new product through product labeling and promotion. They will be educated about the product's approved indication as well as about the definition of "opioid-tolerant" as described in the package insert. Inclusion of the risk information in the label's boxed warning will assure consistency of the risk warning in a variety of media including all promotional materials.

Tools directed toward prescribers will include introductory letters, visits and assessments by Cephalon field representatives, educational monographs, FENTORA website, and targeted education and outreach programs directed to Pain Centers of Excellence and professional societies.

Tools directed toward pharmacists also will include introductory letters (PharmAlert) and visits by Cephalon field representatives. In addition, counseling messages will be distributed to pharmacies by major publishers of pharmacy counseling software. A reminder checklist is printed on the carton to prompt the pharmacist at the point of dispensing to make sure the patient is opioid tolerant before dispensing FENTORA and to encourage the patient to read the FENTORA MG.

Patient education will not only rely on the counseling of healthcare professionals; it will rely on information specifically designed for patients. The MG describes for the patient, in understandable non-technical language, the serious risks associated with FENTORA. It provides information necessary for the patient to use the product safely and effectively. Patients will also benefit from the use of written counseling aids provided by Cephalon to physicians and pharmacists. These aids will encourage an open dialogue about FENTORA between the healthcare professional and the patient, thereby encouraging active participation of the patient in his/her medical care. The FENTORA website will have a section devoted specifically to patients in user-friendly language.

Table 1~~Table 1~~ summarizes the interventions that will be employed to minimize the risk of FENTORA being used by opioid non-tolerant individuals. It describes each of the tools and the audiences applicable to each of the interventions. It should be noted that the audience column in Table 2~~Table 2~~ corresponds to the specific objectives noted in the RiskMAP. We do not identify specific interventions for nurses or allied health professionals or family, however, many of the interventions discussed below will be available for these audiences.

The surveillance and monitoring activities associated with the proactive interventions described above are located in section 4 and Table 4~~Table 4~~.

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Table 1: Goal 1 Summary Table

Goal 1: FENTORA should be used only by opioid-tolerant individuals					
Goal	**Point(s) of Intervention**	**Primary Audience(s)**	**Tool Category**	**Tools**	**Description**
1	Patient Use	Patients	Targeted Education & Outreach; Reminder System	Blister label	Launch and Ongoing: The blister label (dome side) will contain important warning information ("Only for patients already taking opioids")
1	Dispensing Patient Use	Patients Pharmacists	Targeted Education & Outreach; Reminder system	Carton label	Launch and ongoing: The labeling of the carton contains important warning information ("Only for patients already taking opioids such as fentanyl or morphine;" and "FENTORA contains medicine that could be harmful or fatal to someone who has not been prescribed FENTORA."). A reminder checklist is printed on the carton to prompt the pharmacist to advise the patient that FENTORA should be used only by opioid tolerant individuals and to encourage the patient to read the Medication Guide. The carton label directs the patient and/or caregiver to read the enclosed Medication Guide for important warnings.
1	Prescribing Dispensing Patient Use	Patients Pharmacists Prescribers	Targeted Education & Outreach	Medication Guide	Launch and ongoing: The FENTORA Medication Guide will emphasize the need for the cancer patient to be opioid-tolerant. It will warn the patient of the potentially serious consequences, including death, of using FENTORA if not opioid tolerant. It will be included in the FENTORA packaging and will also be made available to all prescribers and FENTORA stocking pharmacies (via 800#, a product-specific website, and Cephalon sales representatives) for education and dissemination to patients.

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Table 1: Goal 1 Summary Table~~Table 1: Goal 1 Summary Table~~ (continued)

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Goal 1: FENTORA should be used only by opioid-tolerant individuals

Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
1	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Package insert	Launch and ongoing: The package insert will contain a Boxed Warning about the life-threatening risks associated with the use of FENTORA in opioid non-tolerant individuals. It will define opioid tolerance.
1	Prescribing	Prescribers	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch and ongoing: Prescribers will be informed in person of the key messages and elements of the FENTORA RiskMAP, including the potentially life-threatening risk of use of FENTORA by an individual not tolerant to opioids.
1	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Educational introductory letter to healthcare professionals	Launch: Cephalon will develop and disseminate an educational FENTORA introductory letter which will reinforce the use of FENTORA only by opioid-tolerant patients with cancer ~~individuals~~. The letter will be disseminated by direct mail to 10,000 physicians likely to prescribe FENTORA and 3,000 pharmacists likely to stock FENTORA, the top 25 Pain Centers of Excellence.
1	Prescribing	Prescribers	Targeted Education & Outreach	Educational Risk MAP monograph for physicians	Launch: Cephalon will develop and disseminate a FENTORA educational RiskMAP monograph which will reinforce the use of FENTORA only by opioid-tolerant patients with cancer ~~individuals~~. The RiskMAP monograph will be disseminated by direct mail to 10,000 physicians likely to prescribe FENTORA and to the top 25 Pain Centers of Excellence.
1	Dispensing	Pharmacists	Targeted Education & Outreach	PharmAlert	Launch and as needed: Educational material that reinforces the use of FENTORA only in opioid-tolerant patients with cancer~~individuals~~ will be distributed to 40,000 retail pharmacists.

(continued)

Table 1: Goal 1 Summary Table~~Table 1: Goal 1 Summary Table~~ (continued)

Goal 1: FENTORA should be used only by opioid-tolerant individuals					
Goal	**Point(s) of Intervention**	**Primary Audience(s)**	**Tool Category**	**Tools**	**Description**
1	Prescribing	Prescribers	Targeted Education & Outreach	Physician education offered by Pain Centers of Excellence	Launch and ongoing: Cephalon will contact each of the identified top 25 Pain Centers of Excellence to offer further educational opportunities to learn about and inform other physicians about FENTORA, including the risks of use by opioid non-tolerant individuals. The educational platform for these offerings will include symposia and/or teleconferences and will incorporate the key messages of the FENTORA RiskMAP.
1	Dispensing Patient Use	Pharmacists Patients	Targeted Education & Outreach	Counseling messages	Launch and ongoing: Cephalon will provide risk information to First Data Bank and/or other major publishers of pharmacy counseling software to educate the majority of retail pharmacists on the risks associated with the use of FENTORA, including the risk of its use by opioid non-tolerant individuals.
1	Prescribing Dispensing Patient Use	Patients Pharmacists Prescribers	Targeted Education & Outreach	Counseling aids/brochures	Launch and ongoing: In addition to the Medication Guide, Cephalon will develop counseling aids to be used by healthcare professionals when advising and educating patients about FENTORA. These aids will include information about the risk and potentially life-threatening consequences of use of FENTORA by individuals not tolerant to opioids.
1	Prescribing	Prescribers	Targeted Education & Outreach	Physician education (targeted to members of professional societies)	Launch: Professional societies will be contacted to offer educational opportunities to learn about FENTORA and key messages and risks described in the RiskMAP, including the risk of the use of FENTORA by opioid non-tolerant individuals. The educational platform for these offerings will include symposia at the professional society's meeting(s) and/or teleconferences with interested members.

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Table 1: Goal 1 Summary Table~~Table 1: Goal 1 Summary Table~~ (continued)

Goal 1: FENTORA should be used only by opioid-tolerant individuals

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Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
1	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Pharmaceutical compendia	Launch and ongoing: Cephalon will provide FENTORA information (including risk information about its use in opioid non-tolerant individuals) to well-known drug compendia such as the Physicians' Desk Reference (PDR), American Hospital Formulary Service (AHFS), and Drug Facts and Comparisons.
1	Dispensing	Pharmacists	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch and ongoing: Pharmacists likely to dispense FENTORA will be informed in person of the key messages and elements of the FENTORA RiskMAP, including the potentially life-threatening risk of use of FENTORA by individuals not tolerant to opioids. The pharmacists will be alerted to the utility of the Medication Guide
1	Dispensing	Pharmacists	Targeted Education & Outreach	Counseling aid	Launch and ongoing: Educational materials will be disseminated to pharmacists who attend wholesaler trade shows and pharmacy meetings. These materials will provide education that FENTORA should be used only by opioid-tolerant patients with cancer.
1	Prescribing	Prescribers	Targeted Education & Outreach	Risk MAP Speaker training	Launch and ongoing: Cephalon will formally train speakers on aspects of FENTORA consistent with the risk information in the package insert including the key elements and messages of the RiskMAP, specifically the risk of use in opioid non-tolerant patients will be reviewed. Cephalon will also provide speakers with information which they must present, that focus on the risks identified in the RiskMAP. Prior to speaking on behalf of Cephalon, these speakers will verify that they understand the risk associated with use of FENTORA in opioid non-tolerant patients. Evaluations will be provided to verify that the speakers presented the required risk information.

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Table 1: Goal 1 Summary Table~~Table 1: Goal 1 Summary Table~~ (continued)

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Goal 1: FENTORA should be used only by opioid-tolerant individuals					
Goal	**Point(s) of Intervention**	**Primary Audience(s)**	**Tool Category**	**Tool**	**Description**
1	Prescribing Dispensing	Cephalon field representatives	Targeted Education & Outreach	RiskMAP Training for Cephalon field representatives	Launch and ongoing: In addition to routine product-specific training, Cephalon field representatives will receive specific RiskMAP training covering the approved prescribing information for FENTORA, including the use of FENTORA in opioid non-tolerant patients. Upon completion of training, field representatives will be tested on the training and will be required to verify they understand the information included in the FENTORA RiskMAP.
1	Prescribing Dispensing Patient Use	Prescribers Pharmacists Patients	Targeted Education & Outreach	Website	Launch and ongoing: This website will be a tool for healthcare professionals and for patients. It will educate both audiences about the 3 risks associated with FENTORA as identified in the SECURE Program.

3.6.2 Strategy and Tools Associated with Goal 2: Misuse, abuse and diversion of FENTORA should not occur

The risks of misuse, abuse and diversion are inherent with Schedule II opioid drugs. To successfully address this risk in an environment where prescription drug abuse rates have been growing over the past several years requires a combination of efforts including supply chain integrity activities, educational interventions, and ongoing surveillance and monitoring activities. Law enforcement agencies also play a significant role in limiting illicit activities associated with abuse and diversion. Healthcare professionals (e.g., physicians, pharmacists, nurses) who deal with Schedule II opiates should be versed in federal, state, and local legal and regulatory requirements governing their use.

By listing FENTORA under Schedule II of the Controlled Substance Act (CSA), a set of specific controls will be instituted to limit the degree to which the medication is abused and diverted. Federal and state laws and regulations govern the manufacturing, distribution, prescribing, dispensing, storage, and disposal of Schedule II products. Due to this, there are extensive controls, record keeping requirements, and auditing functions in place to minimize the risk of abuse and diversion. For example, prescriptions for Schedule II products must be written in ink, or typewritten and signed by the practitioner. Verbal prescriptions must be confirmed in writing within 72 hours, and may be given only in a genuine emergency. No renewals are permitted. Due to Actiq, Cephalon has specific experience with compliance with the requirements of the CSA and for Scheduled II drugs in particular.

In developing the tools to reduce the risk of misuse, abuse and diversion associated with the use of FENTORA, Cephalon identified several points of intervention in the product's drug distribution system promoting a safe-use pathway (see Figure 3~~Figure 3~~). The early part of this supply chain is most directly under Cephalon's control. These stages will be governed by the Company's internal standard operating procedures (SOPs) and auditing capabilities. Controls are applied from the time Cephalon is in receipt of fentanyl citrate raw material throughout the manufacturing and packaging of the finished product (FENTORA), through distribution to wholesalers.

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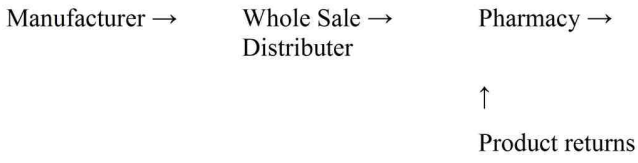
Figure 3: Drug Distribution System– Safe-Use Pathway



At any time departures from the safe-use pathway may occur. This suggests the need for additional efforts at the points of distribution, prescribing, dispensing, patient use, and disposal of the product.

To minimize the risk of diversion of FENTORA, Cephalon will track every shipment of FENTORA from its manufacturing sites to its receipt at the wholesaler. Drug

accountability will be maintained to ensure diversion has not occurred within the company from the time the product departs Cephalon to when it is received by the wholesaler. As part of Cephalon's existing SOP, wholesalers who purchase product from Cephalon will be alerted to the goals of the FENTORA RiskMAP, and prior to shipment, wholesalers will need to verify that they have processes and procedures in place to minimize the risk of diversion when the product is received by the pharmacies.

Through labeling information and physician education interventions, physicians will be informed to use caution when prescribing FENTORA to patients. They will be made aware of circumstances, symptoms, and signs that could contribute to an individual's risk of abuse. Cephalon will support educational programs, such as those provided by Pain Centers of Excellence, to continually refresh physicians' knowledge and awareness of best practices for minimizing drug abuse and diversion. For example, physicians will be informed that persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed FENTORA. Physicians will also be informed that all patients receiving FENTORA should be routinely monitored for signs of misuse, abuse, and addiction. Physicians will be educated about methods used by individuals to obtain Schedule II opiates illicitly (e.g., doctor shopping, feigning illness or pain). Physicians will be educated that for any given patient they are considering prescribing FENTORA, they should balance the risks of product misuse, abuse, and diversion with the medical need to adequately treat pain. It should be noted that the Schedule II classification of FENTORA, and the reminder "CII" placed on all labeling and promotional materials will continually remind physicians and pharmacists of the risks of FENTORA's potential for abuse and diversion.

Similarly, pharmacists will be informed to exercise caution when dispensing FENTORA to patients. Pharmacists, too, should have familiarity with factors that could contribute to an individual's risk of abuse, and should be knowledgeable about methods used by individuals to obtain Schedule II opiates illicitly (e.g., fraudulent prescriptions, pharmacy theft). Cephalon will contribute to this continued education through a variety of tools. Face-to-face and written educational interventions will include sales representatives' discussions, PharmAlert, letters from Cephalon, and information included in pharmaceutical compendium. Cephalon has obtained permission from the DEA to receive returns of Actiq for disposal. We plan to apply for the same permission for FENTORA. This will minimize excess supply and diminish opportunities for pharmacy theft.

Patients will be educated that FENTORA contains a Schedule II opioid pain medication and that they may become addicted to this class of medications. We will inform health care providers to counsel patients that their risk for abuse and addiction may be higher if they have a history of abuse of other medications, street drugs, or alcohol, or if they have a history of mental illness. Patients will be informed that FENTORA contains a federally controlled substance and that to sell or give their medication to others is a violation of the law. Patients should also be advised that they could become targets for those who abuse prescription medications or street drugs (even by household members), and that they should always store FENTORA in a safe and secure place. Many of the tools to be

employed at each of these points of intervention to minimize the risk of abuse and diversion are the same as those designed to educate audiences on the risk of use in non-opioid tolerant patients (Goal 1). These communication tools will include educational messages geared toward Goal 2. To inform physicians of the risks of abuse, misuse and diversion, for example, FENTORA monographs will be distributed and educational programs will be targeted to members of professional societies. Another example of a tool designed to aid the pharmacist as well as other healthcare professionals in this area is the use of well-known pharmaceutical compendia which will highlight the abuse potential of FENTORA. The PharmAlert system will be used to target education and outreach efforts to pharmacists. The Medication Guide is an example of a tool intended for patients that conveys important information about misuse, abuse, and diversion in non-technical, scientifically accurate language.

In addition to these educational tools, distribution controls associated with Schedule II opioids will be a potent factor in limiting the diversion of FENTORA from legitimate medical use. While informational/educational tools may be effective in preventing misuse, inadvertent abuse and, to some extent, protect the product from theft, preventing willful theft and abuse of FENTORA requires a higher level of control and intervention.

Fortunately, there is a great deal of experience (not only by Cephalon, but by other manufacturers of Schedule II products) in dealing with abuse, misuse and diversion problems. As noted earlier, Schedule II abuse is likely to appear in certain geographical "hot-spots." The RADARS "early warning system" has been developed and used by Purdue Pharma to minimize abuse and diversion of Oxycontin. The RADARS system collects and analyzes data from four sources; poison control centers, key informants, law enforcement and methadone programs. Cephalon has purchased a subscription to the RADARS surveillance and monitoring system. The RADARS system provides a method to monitor localities for signals of abuse outbreaks. Once Cephalon receives such a signal from the RADARS System it will initiate an in depth examination. Presently, we are considering forming a "response team" to respond to the problem. (Note: Cephalon will use the monitoring thresholds generated by the RADARS System to denote the presence of signals). Using the RADARS data and knowledge of the distribution of FENTORA, Cephalon will decide on a course of action that is most appropriate for the problem encountered. For example, Cephalon may contact local law enforcement and inform them of the problem, we may dispatch medical liaisons to contact certain physicians, or we may contract with local medical societies to engage in specific education and/or inform wholesalers/distributors to stop shipments to certain pharmacies.

In addition to RADARS, Cephalon will also monitor a variety of additional surveillance databases for evidence of increased abuse, misuse or diversion. Cephalon will actively solicit data from sources such as the Rocky Mountain Poison and Drug Center (RMPDC), the Toxic Exposure Surveillance System (TESS) and the Drug Abuse Warning Network (DAWN). As with the RADARS system, signals generated by any of these databases will generate an examination by Cephalon.

Surveillance and monitoring activities for abuse and diversion are discussed in section 4 and Table 4~~Table 4~~.

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Table 2~~Table 2~~ provides a list of interventions, a description of each of the tools, and the audiences applicable to each of the interventions to minimize the risk of misuse, abuse, and diversion of FENTORA.

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Table 2: Goal 2 Summary Table

Goal 2: Misuse, abuse and diversion of FENTORA should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Cephalon Distribution	Wholesalers/ Distributors/ Pharmacies	Performance linked access	Schedule II manufacturing limitations, record-keeping, accounting	Launch and ongoing: Complying with Schedule II distribution controls and recordkeeping, Cephalon will comply with all requirements of the CSA.
2	Dispensing Patient Use	Patients Pharmacists	Targeted Education & Outreach; Reminder system	Carton label	Launch and ongoing: The labeling of the carton contains several items of information intended to decrease misuse of the product (e.g., "For Buccal Administration. Do not Swallow Tablet"). In addition the carton label advises the patient and/or caregiver to read the enclosed Medication Guide for important warnings and directions. The checklist on the carton reminds the pharmacist to counsel the patient about the use of FENTORA and to encourage the patient to read the FENTORA Medication Guide (which provides important warnings and directions). Similarly, the Schedule II scheduling status of FENTORA is noted prominently on the carton to remind the pharmacist that FENTOR has a potential for abuse.
2	Prescribing Dispensing Patient Use	Patients Pharmacists Prescribers	Targeted Education & Outreach	Medication Guide	Launch and ongoing: The FENTORA Medication Guide provides information to the patient intended to minimize misuse, abuse, and diversion. It includes, for example, a section titled "How should I take "FENTORA." which provides instructions on proper administration of the buccal tablet. As for abuse, it warns that the patient may become physically dependent on opioids and could become addicted to FENTORA. For diversion, it warns patients that FENTORA is a federally controlled substance, that selling the medication or giving it away is against the law, and that the medication should be kept in a safe place to protect it from being stolen. The Medication Guide will be included in the FENTORA packaging and will also be made available to all prescribers and FENTORA stocking pharmacies (via 800#, a product-specific website, and Cephalon sales representatives) for education and dissemination to patients.

(continue)

Table 2: Goal 2 Summary Table (continued)

Goal 2: Misuse, abuse and diversion of FENTORA should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Package insert	Launch and ongoing. The package insert will contain information about opioid misuse, abuse, diversion, and addiction and can serve as a useful reference to healthcare professionals.
2	Prescribing	Prescribers	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch and ongoing: Prescribers will be informed in person of the key messages and elements of the FENTORA RiskMAP, including information on the high potential for FENTORA abuse as well as of its risk of misuse and diversion.
2	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Educational introductory letter to healthcare professionals	Launch: Cephalon will develop and disseminate an educational FENTORA introductory letter which will reinforce key messages of the RiskMAP including the risk for FENTORA misuse, abuse, and diversion. The letter will be disseminated by direct mail to 10,000 physicians likely to prescribe FENTORA, 3,000 retail pharmacists likely to stock FENTORA, and the top 25 Pain Centers of Excellence.
2	Prescribing	Prescribers	Targeted Education & Outreach	Educational Risk MAP monograph for physicians	Launch: Cephalon will develop and disseminate a FENTORA educational Risk MAP monograph which will reinforce messages about the risk of misuse, abuse, and diversion of FENTORA. The monograph will be disseminated by direct mail to 10,000 physicians likely to prescribe FENTORA and to the top 25 Pain Centers of Excellence.
2	Dispensing	Pharmacists	Targeted Education & Outreach	PharmAlert	Launch and as needed: Educational material that reinforces the use of FENTORA is associated with a risk of misuse, abuse, and diversion. This material will be distributed to 40,000 retail pharmacists.
2	Prescribing	Prescribers	Targeted Education & Outreach	Physician education from Pain Centers of Excellence	Launch: Cephalon will contact each of the identified top 25 Pain Centers of Excellence to offer further educational opportunities to learn about and offer learning opportunities to local physicians about FENTORA, including its risks for misuse, abuse, and diversion. The educational platform for these offerings will include symposia and/or teleconferences and will incorporate the key messages of the FENTORA RiskMAP.

(continued)

Table 2: Goal 2 Summary Table (continued)

Goal 2: Misuse, abuse and diversion of FENTORA should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Prescribing Dispensing Patient Use	Prescribers Pharmacists Patients	Targeted Education & Outreach	Counseling aid	Launch and ongoing: Cephalon will develop a counseling aid to be used by healthcare professionals when advising and educating patients about FENTORA. This aid will include information about the risks for misuse, abuse, and diversion.
2	Dispensing	Pharmacists	Targeted Education & Outreach	Counseling aid	Launch and ongoing: Education materials will be disseminated to pharmacists who attend wholesaler trade shows and pharmacy meetings. These materials will provide education that the use of FENTORA is associated with misuse, abuse and diversion.
2	Dispensing Patient Use	Pharmacists Patients	Targeted Education & Outreach	Counseling messages	Launch and ongoing: Cephalon will provide risk information to First Data Bank and/or other major publishers of pharmacy counseling software to educate the majority of retail pharmacists on the risks of misuse, abuse, and diversion associated with the use of FENTORA.
2	Prescribing	Prescribers	Targeted Education & Outreach	Physician education (targeted to members of professional societies)	Launch: Professional societies will be contacted to offer educational opportunities to learn about FENTORA and key messages and risks described in the RiskMAP, including the risk for misuse, abuse, and diversion. The educational platform for these offerings will include symposia at the professional society's meeting(s) and/or teleconferences with interested members.
2	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Pharmaceutical compendia	Launch and ongoing: Cephalon will provide FENTORA information (including risk information about its misuse, abuse and diversion) to well-known drug compendia such as the Physicians' Desk Reference (PDR), American Hospital Formulary Service (AHFS), and Drug Facts and Comparisons.

(continued)

Table 2: Goal 2 Summary Table (continued)

Goal 2: Misuse, abuse and diversion of FENTORA should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Prescribing	Prescribers	Targeted Education & Outreach	RiskMAP Speaker training	Launch and ongoing: Cephalon will formally train speakers on aspects of FENTORA consistent with the risk information in the package insert including the key elements and messages of the RiskMAP, specifically the risk of misuse, abuse and diversion associated with use of FENTORA. Cephalon will also provide speakers with information, which they must present, that focus on the risks identified in the RiskMAP. Prior to speaking on behalf of Cephalon, these speakers will verify that they understand the risk of misuse, abuse and diversion associated with use of FENTORA. Evaluations will be provided to verify that the speakers presented the required risk information.
2	Prescribing	Prescribers and Pharmacists	Targeted Education & Outreach	Physician and Pharmacist education	Ongoing (response to surveillance): Cephalon will implement medical education directed to 'geographic hot spots' that focus on preventing and/or minimizing misuse, abuse, and diversion of prescription drugs. The format of these programs will be tailored to the specific need (e.g., symposium, teleconferences, print materials, etc.)
2	Prescribing Dispensing	Cephalon field representatives	Targeted Education & Outreach	RiskMAP Training for Cephalon field representatives	Launch and ongoing: In addition to FENTORA product-specific training, Cephalon field representatives will receive specific RiskMAP training, including the approved prescribing information for FENTORA and the risk for misuse, abuse and diversion associated with use of FENTORA. Upon completion of training, field representatives will be tested on the training and will be required to verify they understand the information included in the RiskMAP.
2	Prescribing Dispensing	Prescriber Pharmacists	Targeted Education & Outreach	Independent continuing medical education (CME)	Launch and ongoing: Cephalon will support independent education on prescription drug misuse, abuse, and diversion targeted to physicians likely to prescribe FENTORA.

(continued)

Table 2: Goal 2 Summary Table (continued)

Goal 2: Misuse, abuse and diversion of FENTORA should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Prescribing Dispensing Patient Use	Drug Diversion Professionals	Targeted Education & Outreach	Introductory Letter to Drug Diversion Authorities	Launch: Proactive communications to drug diversion control authorities to educate interested parties and alert them to safeguard against the potential diversion of FENTORA.
2	Dispensing	Pharmacists	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch and ongoing: Pharmacists likely to dispense FENTORA will be informed in person of the key messages and elements of the FENTORA RiskMAP, including the risks for misuse, abuse, and diversion for FENTORA. The pharmacists well be alerted to the utility of the Medication Guide.
2	Patient Use	Patients	Targeted Education & Outreach	Product returns and Disposal	Launch and ongoing: Cephalon will accept returns for disposal of unwanted FENTORA. This will be a tool to minimize the amount of excess product available.
2	Prescribing Dispensing Patient Use	Drug Diversion Professionals	Active Monitoring	Reports of Diversion and Abuse	Launch and ongoing: Cephalon will implement an active monitoring system (RADARS) at the time of the launch of FENTORA. Reports form the National Association of Drug Diversion Investigators (NADDI) will be actively monitored and screened for information on FENTORA.
2	Prescribing Dispensing Patient Use	Prescribers Pharmacists Patients	Targeted Education & Outreach	Website	Launch and ongoing: This website will be a tool for healthcare professionals and for patients. It will educate both audiences about the 3 risks associated with FENTORA as identified in the SECURE Program.

3.6.3 Strategy and Tools Associated with Goal 3: Unintended (accidental) exposure to FENTORA should not occur

Like other Schedule II opioids, there is serious concern about accidental exposure to FENTORA. The physical characteristics of the lozenge dosage form make it unlikely that there would be many situations where partially used medication would be found by a child. However, the severity of outcomes for unintended pediatric exposure to FENTORA is similar to that of other Schedule II products. Therefore, the risk of serious harm to a child (or cognitively impaired adult) is a serious concern and constitutes Goal 3. Consequently, Cephalon explored the "tablet disposition" system and defined a safe product use pathway that seeks to minimize the occurrence of unintended or accidental exposure to FENTORA in adults or children (see Figure 4~~Figure 4~~).

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Figure 4: The "Tablet Disposition "System - Safe Product Use Pathway

Physician Prescribes FENTORA →	Physician demonstrates proper opening of blister tablet →	Patient fills script →	Patient use and storage →	Patient disposal

Prior to receipt of the product, patient education should begin with the physician. Cephalon will distribute placebo blister packages to physicians through sales representatives. These blister packages will permit the physician to demonstrate to the patient how to remove a tablet from the package. It will also provide physicians with the opportunity to inform patients not to open the package until the patient is ready to take a dose.

Once the patient obtains a prescription, pharmacist counseling will reinforce the physician's directions. Several tools are directed to stimulate pharmacist counseling. As described earlier, the outer carton for FENTORA contains the important inverted triangle symbol on two panels. This symbol, plus the boxed warning, draws attention and increases the perceived importance to the warning message to keep the product out of the reach of children. This symbol provides emphasis to important safety messages. It is associated with the importance of safe storage, use and disposal in packaging materials directed to patients.

The MG reinforces and explains this message by explaining that accidental use by children constitutes a medical emergency that can cause the death of a child. If accidentally taken by children, parents are told to get emergency help immediately. This message is emphasized by denoting it as a formal warning. It is placed in a box at the top of the MG and it uses a "signal word", "IMPORTANT" to further capture attention and increase perceived relevance. Under usage directions, the MG also informs the patient not to open the blister pack until ready to use the product. This message is reinforced on each blister pack, ~~where~~ by the message, "Use immediately upon opening." This would prevent unprotected tablets from being found by children or other adults.

A physical barrier to access the product is likely the most important tool for achieving Goal 3. The physical characteristics of the product packaging represents an important

tool to prevent accidental pediatric exposure. The FENTORA blister packaging meets the effectiveness specifications using the Child Test procedure for special packaging (16 CFR 1700.20(a)(2)) and meets performance specifications for an "F1" classification (see Glossary). Further, the tablet has been formulated to avoid appealing colors that may attract children. The tablet formulation does not contain any excipients that taste sweet or appealing to children.

In order to reduce unintended exposure to FENTORA tablets that are no longer needed by the patient, Cephalon is in the process of instituting a return policy, as it has done for Actiq, to accept unused tablets returned by patients or their families (e.g., death of a family member who had been taking FENTORA).

Table 2~~Table 2~~ provides a list of interventions, a description of each of the tools, and the audiences applicable to each of the interventions to minimize the risk of accidental exposure to FENTORA.

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Surveillance and monitoring activities for unintended exposure will be discussed in section 4 and Table 4~~Table 4~~.

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Table 3: Goal 3: Unintended (accidental) exposure to FENTORA should not occur

Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Patient use	Patients	Package integrity	Blister	Launch and ongoing: Tablets will be supplied in double foil blister which meet F1 requirements and which have passed tests for child resistance and senior friendliness.
3	Patient use	Patients	Targeted Education & Outreach	Blister label	Launch and ongoing: The blister label warns that FENTORA is to be kept out of the reach of children. It instructs that FENTORA should be used immediately upon opening.
3	Dispensing Patient use	Pharmacists Patients	Targeted Education & Outreach Reminder System	Carton label	Launch and ongoing: The carton labeling contains several items of information intended to decrease the risk of accidental exposure to FENTORA. It warns that FENTORA is to be kept out of the reach of children and that FENTORA contains medicine that could be harmful or fatal to someone who has not been prescribed the medicine. In addition, the carton label advises the patient and/or caregiver to read the enclosed Medication Guide for important warnings and directions. The checklist on the carton reminds the pharmacist to encourage the patient to read the FENTORA Medication Guide (which provides important warnings and directions about accidental exposure)

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Table 3: Goal 3: Unintended (accidental) exposure to FENTORA should not occur~~Table 3: Goal 3: Unintended (accidental) exposure to FENTORA should not occur~~ (continued)

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Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Prescribing Dispensing Patient use	Prescribers Pharmacists Patients	Targeted Education & Outreach	Medication Guide	Launch and ongoing: The FENTORA Medication Guide provides information to the patient intended to decrease the risk of accidental exposure to FENTORA. It warns that FENTORA is to be kept in a safe place away from children, and that accidental use by a child is a medical emergency that can result in death. In the event of accidental use by a child, the Medication Guide provides instructions for contacting a Poison Control Center or the nearest emergency room right away. The Medication Guide will be included in the FENTORA packaging and will also be made available to all prescribers and FENTORA stocking pharmacies (via 800#, a product-specific website, and Cephalon sales representatives) for education and dissemination to patients.
3	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Package insert	Launch and ongoing: The package insert contains a Boxed Warning for healthcare professionals about the risks associated with the accidental exposure to FENTORA.
3	Prescribing	Prescribers	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch and ongoing: Prescribers will be informed in person of the key messages and elements of the FENTORA RiskMAP, including the potentially life-threatening risk of accidental use of FENTORA in children or adults.

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Table 3: Goal 3: Unintended (accidental) exposure to FENTORA should not occur~~Table 3: Goal 3: Unintended (accidental) exposure to FENTORA should not occur~~ (continued)

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Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Dispensing	Pharmacists	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch and ongoing: Pharmacists likely to dispense FENTORA will be informed in person of the key messages and elements of the FENTORA RiskMAP, including the potentially life-threatening risk of accidental use of FENTORA in children or adults. The pharmacists will be alerted to the utility of the Medication Guide.
3	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Educational introductory letter to healthcare professionals	Launch: Cephalon will develop and disseminate an educational FENTORA introductory letter which will reinforce key messages of the RiskMAP including the risk of accidental exposure to FENTORA. The letter will be disseminated by direct mail to 10,000 physicians likely to prescribe FENTORA, 3,000 retail pharmacists likely to prescribe FENTORA, and the top 25 Pain Centers of Excellence.
3	Prescribing	Prescribers	Targeted Education & Outreach	Educational Risk MAP monograph for physicians	Launch: Cephalon will develop and disseminate a FENTORA educational RiskMAP monograph which will reinforce messages about the risk of accidental exposure to FENTORA. The monograph will be disseminated by direct mail to 10,000 physicians likely to prescribe FENTORA and to the top 25 Pain Centers of Excellence.

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Table 3: Goal 3: Unintended (accidental) exposure to FENTORA should not occur~~Table 3: Goal 3: Unintended (accidental) exposure to FENTORA should not occur~~ (continued)

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Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Dispensing	Pharmacists	Targeted Education & Outreach	PharmAlert	Launch and as needed: Educational material that explains the risk of accidental exposure associated with the use of FENTORA.
3	Prescribing	Prescribers	Targeted Education & Outreach	Physician education from Pain Centers of Excellence	Launch and ongoing: Cephalon will contact each of the identified top 25 Pain Centers of Excellence to offer further educational opportunities to learn about FENTORA, including the risks of accidental exposure associated with the use of FENTORA. The educational platform for these offerings will include symposia and/or teleconferences and will incorporate the key messages of the RiskMAP.
3	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Pharmaceutical compendia	Launch and ongoing: Cephalon will provide FENTORA information (including risk information about the risk of accidental exposure to FENTORA) to well-known drug compendia such as the Physicians' Desk Reference (PDR), American Hospital Formulary Service (AHFS), and Drug Facts and Comparisons
3	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Counseling messages	Launch and ongoing: Cephalon will provide risk information to First Data Bank and/or other major publishers of pharmacy counseling software to educate the majority of retail pharmacists in the risks associated with the use of FENTORA, including the risk of accidental exposure associated with its use.

(continued)

Table 3: Goal 3: Unintended (accidental) exposure to FENTORA should not occur~~Table 3: Goal 3: Unintended (accidental) exposure to FENTORA should not occur~~ (continued)

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Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Prescribing Dispensing Patient Use	Prescribers Pharmacists Patients	Targeted Education & Outreach	Counseling aid	Launch and ongoing: In addition to the Medication Guide, Cephalon will develop a counseling aid to be used by healthcare professionals when advising and education patients about FENTORA. This aid will include information about the risk and potentially life-threatening consequences associated with the accidental use of FENTORA.
3	Dispensing	Pharmacists	Targeted Education & Outreach	Counseling aid	Launch and ongoing: Educational materials will be disseminated to pharmacists who attend wholesaler trade shows and pharmacy meetings. These materials will provide education that accidental exposure is associated with the use of FENTORA.
3	Prescribing	Prescribers	Targeted Education & Outreach	RiskMAP Speaker training	Launch and ongoing: Cephalon will formally train speakers on aspects of FENTORA consistent with the risk information in the package insert including the key elements and messages of the RiskMAP, specifically the risk of accidental exposure to FENTORA. Cephalon will also provide speakers with information, which they must present, that focus on the risks identified in the RiskMAP. Prior to speaking on behalf of Cephalon, these speakers will verify they understand the risk of accidental exposure associated with the use of FENTORA. Evaluations will be provided to verify that the speakers presented the required risk information.

(continued)

Table 3: Goal 3: Unintended (accidental) exposure to FENTORA should not occur~~Table 3: Goal 3: Unintended (accidental) exposure to FENTORA should not occur~~ (continued)

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Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Prescribing Dispensing	Cephalon field representatives	Targeted Education & Outreach	RiskMAP Training for Cephalon field representatives training	Launch and ongoing: In addition to routine product-specific training, Cephalon field representatives will receive specific RiskMAP training covering the approved prescribing information for FENTORA, including the risk of unintended (accidental) exposure to FENTORA. Upon completion of training, field representatives will be tested on the training and will be required to verify they understand the information included in the FENTORA RiskMAP.
3	Patient Use	Patients	Targeted Education & Outreach	Product returns and Disposal	Launch and ongoing: Cephalon will accept returns for disposal of unwanted FENTORA. This will be a tool to minimize the amount of excess product available.
3	Prescribing Dispensing Patient Use	Prescribers Pharmacists Patients	Targeted Education & Outreach	Website	Launch and ongoing: This website will be a tool for healthcare professionals and for patients. It will educate both audiences about the 3 risks associated with FENTORA as identified in the SECURE Program.

4 SURVEILLANCE AND MEASURING EFFECTIVENESS OF THE RISKMAP

This RiskMAP is designed to address three principal risks associated with FENTORA: 1) its use by opioid non-tolerant individuals, (2) the risk of misuse, abuse, and diversion, and 3) unintended (accidental) exposure to the product. The effectiveness of the tools identified in this RiskMAP will be evaluated on an ongoing basis.

A principal goal of the RiskMAP is to ensure that physicians, pharmacists, and patients are aware and knowledgeable of these risks and are aware of steps they can take to minimize them. Cephalon will employ a series of independent and unique surveillance and monitoring techniques targeted at prescribers, pharmacists, and patients, respectively, to assess the effectiveness of the targeted education and reminder systems at the points of intervention. The surveillance and monitoring activities associated with the SECURE Program may be found in Table 4~~Table 4~~.

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4.1 Active Surveillance Systems

Active monitoring of national audit data will be used to track specific outcomes related to abuse and misuse. We will use the Toxic Exposure Surveillance System (TESS) (including case abstracts for all accidental pediatric exposures and death reports) and the Drug Abuse Warning Network (DAWN) data ~~-~~to augment Cephalon's routine Pharmacovigilance activities. However, there can be a significant lag period between data capture and subsequent data publication from these surveillance systems.

To compensate for this lag, Cephalon will request authorization to access drug-related emergency department (ED) visit ~~medical examiner~~ data from DAWN LIVE, which is a web-based "real-time" continuous data collection system ~~(data are entered as cases are closed out)~~. Once access is granted, Cephalon will monitor DAWN LIVE on a quarterly basis, or more frequent (if appropriate), for all ED visits related to recent use of FENTORA or fentanyl buccal tablets~~medical examiner and coroner reported deaths~~. This can help identify emerging signals regarding trends or increased rates in FENTORA-related misuse and/or abuse. In particular, data will be analyzed for patterns regarding ~~geographic location,~~ age groups, visit types,~~drug combinations~~ and ~~other~~ possible risk factors. ~~If available,~~ DAWN Live data will also be used to look at Actiq ~~on other opioid products will be used~~ for comparative purposes. Results of this analysis will be integrated with other RiskMAP derived data to assess the need for additional education programs or risk management strategies~~interventions~~.

Cephalon is also employing an active surveillance system (RADARS® System) to provide surveillance and monitoring to detect and characterize misuse, abuse and diversion of FENTORA. (see section 3.6.2 and Table 4~~Table 4~~). The RADARS System calculates rates of prescription opioid abuse on a quarterly basis for each 3-digit zip code in the country. Two rates are generated: one based on populations and one based on unique individuals that have filled a prescription for the drug. The information used in this System is derived from four sources: 1) Poison Centers, 2) Drug Diversion, 3) Key Informant, and 4) Methadone Clinics. Each of these systems provides a unique perspective on prescription drug abuse. The RADARS System is an independent operation under the ownership of the Rocky Mountain Poison and Drug Center (RMPDC), Denver Health and Hospital Authority. The data contained

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in databases created during the development of the system is reviewed by an organized Advisory Board.

Using the RADARS threshold, we have asked RADARS to identify when rates meet or exceed 5/100,000 population per quarter in a 3-digit zip code for Key Informant, Drug Diversion and Methadone data systems. For poison control, Cephalon has specified RADARS to indicate when a rate of 2 or more/100,000 population is identified. The data from the quarterly RADARS reports will be provided to Cephalon for review and inclusion in the Quarterly Report. The Quarterly Report will be provided to the Cephalon Response Team to identify if and what interventions are to be employed based on the observed data.

4.2 ~~Spontaneous~~Post-Marketing Reporting Systems

Cephalon will follow-up on any reports of ADR reports associated with FENTORA and will comply with all reporting requirements described in 21CFR314.80. In addition to these Federal requirements, Cephalon will also submit 15-day Alerts to the FDA for each of the following reports:

1. Serious adverse events (SAEs) that may be associated with abuse, misuse or diversion
2. All spontaneous and possibly related study reports of death
3. All accidental exposures (drug not prescribed regardless of outcome (including asymptomatic reports)
4. All medication error reports regardless of patient outcome.

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~~serious adverse events that may be associated with abuse, misuse, and diversion. These reports will be sent to FDA in an expedited fashion. In addition, all accidental exposures regardless whether symptomatic or asymptomatic will also be expedited to the FDA. This is above and beyond the reporting requirements delineated in 21 CFR 314.80.~~
Reconciliation of the spontaneous reports will be performed to identify redundancy in information. Duplication of information may indicate confirmation of a signal.

4.3 Surveys

A series of surveys will be used to measure knowledge, attitudes and behaviors associated with the FENTORA RiskMAP. We will use three separate surveys targeted at the three principal intended audiences: prescribers, pharmacists and patients.

4.3.1 Physician Surveys

Surveys of physicians will be used to capture pertinent information regarding:

- Physician knowledge of the key risks associated with FENTORA,
- Physician knowledge of the indication (regarding opioid tolerant cancer patients) associated with FENTORA,
- Physician knowledge of the definition of opioid tolerance

- Physician awareness that FENTORA is not equivalent with Actiq on a mcg per mcg basis, and
- Physician behavior regarding usage of titration doses and delivery of patient education when prescribing FENTORA.

The survey will monitor physicians' awareness of the key risks associated with the use of FENTORA and behaviors consistent with mitigating these risks. Compiling, analyzing and tracking the responses to these questions will be important to help understand whether adjustment in interventions and/or key messages will be needed to improve the RiskMAP over time.

The physician surveys will be administered via telephone by an independent third-party research vendor. Instructions to the interviewer administering the surveys will be provided. These indicate that if the pharmacist or physician answer any question (#2 and beyond) not as 'yes' or 'always', they are to be instructed to visit the FENTORA website for full prescribing information. In addition, the research vendor will issue a follow-up letter to these physicians and pharmacists informing them of the importance of selecting and dispensing only to the appropriate opioid tolerant patient to ensure safe use of the product. The letter will be accompanied by a detailed definition of an opioid tolerant patient and the full prescribing information. The survey will be repeated every six months for the first two years of the program. Cephalon internal and external experts ~~(~~will evaluate the results of the survey after each six month interval. Following review of the survey, items such as questions, sample frame, sample size, ~~and~~ time frames in which the survey is pulsed, and number of follow-up letters distributed, will be evaluated and potentially modified.

The sample frame will include all physicians who wrote at least one prescription of FENTORA in the previous six months. Cephalon will utilize a third-party to identify physicians who meet these criteria. This list will be matched up with Cephalon internal detail data to include physician prescribing information with sales call data. This will allow Cephalon to analyze the survey results by two cohorts: physicians who have seen Cephalon representatives in a consistent manner vs. those who have not. The resulting physician list will include the following elements: physician name, contact and reference information, prescribing and detailing figures. The list of physicians will be sent to a third party market research vendor who will manage all parts of the recruitment, execution, and data compilation aspects of the survey. We will require that the vendor report pertinent information regarding characteristics of the recruiting process (i.e., profile those physicians who did not respond or declined the invitation to participate).

We plan a sample frame of 3600 physicians in order to obtain a sample of 110 physician completers of the survey. The margin of error (95% confidence interval) associated with this expected sample size is approximately 9%.

The rationale for this sample size calculation is based on experience surveying Actiq prescribers. Over the past six months, there have been approximately 12,700 prescribers of Actiq (defined as written at least one prescription). Given that Actiq has been marketed for seven years, FENTORA is expected to have a much narrower prescriber base in the early commercialization phase (defined as 12-24 months post launch). It is estimated that 35% of the number of the 12,700 doctors who prescribed Actiq in the past six months will prescribe

FENTORA during its launch and post-launch phase. The impact of this assumption is that a list of approximately 4,400 physicians will be sent to the independent vendor for participation in the survey. Based on previous experience, only 80% of these lists will be usable. Therefore, we project that we will ultimately have a sample frame of approximately 3600 physicians from which to recruit.

When evaluating the ability to obtain a successful number of surveys, we need to evaluate the impact of survey hurdles such as: 1) the attempts to reach physicians; 2) the successful identification of those physicians interested in participating in the survey; 3) the impact of the time required to administer the survey; and 4) the ability to successfully complete the survey process. Surveys of this type have successful recruit rates that range from 30% to 3% of physicians. Based on results from the Actiq surveys, we will use estimates from the lower portion of this estimate. Therefore, we anticipate that approximately 110 physicians will complete the survey. During the launch and early post-launch months, we may not be able to identify this number of respondents who meet the criteria and are willing to complete the survey. In this case, the survey will consist of the maximum number of physicians who meet the survey criteria and are willing to complete the survey. We will monitor this number of participants and assess sample size and accrual after each survey administration.

4.3.2 Pharmacy Surveys

A survey targeting the dispensing pharmacists will also be employed.

The objective of the pharmacist survey will be to evaluate the following:

- Pharmacist knowledge of the key risks associated with the use of FENTORA,
- Pharmacist awareness that FENTORA is not equivalent with Actiq on a mcg per mcg basis,
- Pharmacist behavior regarding dispensation of a Medication Guide with every prescription of FENTORA,
- Pharmacist behavior regarding delivery of key counseling messages

The survey will serve to monitor pharmacists' awareness of the key risks associated with the use of FENTORA and their behaviors associated with mitigating these risks. Compiling, analyzing and tracking the responses to these questions will be important to help understand whether adjustments in interventions and/or key messages will be needed to improve the RiskMAP over time.

The pharmacist surveys will be administered via telephone by an independent third-party research vendor and will be repeated every six months for the first two years of the program. Upon completion of each survey, internal and external experts associated with Cephalon will evaluate the results. Following review of the survey, items such as questions, sample frame, sample size, and time frames in which the survey is pulsed will be evaluated and potentially modified.

The sample frame will be constructed by using a list of pharmacies who ordered FENTORA in the previous three months. This list will be provided internally by Cephalon to a third party research vendor who will manage all parts of the recruitment, execution, and data compilation aspects of the survey. We will require that the vendor report pertinent information regarding

characteristics of the recruiting process (i.e., profiles of those pharmacists who did not respond or declined the invitation to participate).

The vendor will identify individual pharmacists from the list of pharmacies. We plan to screen 6,160 pharmacists in efforts to obtain 40 completed pharmacist surveys. The margin of error (95% confidence interval) associated with this expected sample size if approximately 15%. The sample size will be reassessed at the completion of each survey administration interval and efforts to increase the sample size will be made as feasibly possible.

The rationale for this sample size included review of Cephalon's internal pharmacy stocking report, in which it was estimated that during the 1st quarter of 2006 approximately 8,800 pharmacies (out of a total of approximately 58,000 US pharmacies) purchased Actiq. It is estimated that approximately 35% (3,080) will stock FENTORA during the product early commercialization phase, the first 12-24 months of product marketing.

Cephalon estimates that on average there are two pharmacists employed at each pharmacy. Thus, 6,160 pharmacists would be available for the proposed survey. Past marketing research, however, suggested that about 20% of samples provided to research vendors are not useable due to missing contact information (e.g., missing addresses, phone numbers, etc). Based on this projection, it is estimated that only about 4,928 pharmacists would be survey candidates.

Respondents for this survey will be recruited ahead of time. The typical completion time for a survey is within a two-week time frame. As a result, it is anticipated that only about 35% of prospective respondents (1,725) would be located or contacted for participation in the survey.

Experience suggests recruiting and completion rate of approximately ranging from 30% to 3%. Again, using conservative estimates, we estimate a completion rate for the 1,725 potential respondents that would provide a final sample estimate of approximately 40 respondents. Additionally, since this is a new tool that Cephalon is employing we want to strive to have a sample size that is achievable. As we gain experience in surveying pharmacists as well as longer time on the market with FENTORA, we will reassess the pharmacist survey and make a determination whether or not modifications are warranted.

During the launch and early post-launch months, we may not be able to identify this number of respondents who meet the criteria and are willing to complete the survey. In this case, the survey will consist of the maximum number of pharmacists who meet the survey criteria and are willing to complete the survey. We will monitor this number of participants and assess sample size and accrual after each survey administration.

4.3.3 Patient Surveys

Finally, a patient survey will be employed to evaluate the effectiveness of patient educational tools utilized in the SECURE Program. The patient survey questionnaire was developed using the experience Cephalon gained after years of implementing the Actiq patient survey. This survey will evaluate:

- Patient knowledge of the key risks associated with the use FENTORA,
- Patient knowledge of the indication (regarding opioid tolerant cancer patients) associated with FENTORA,

- Patient knowledge about the directions for use and safe storage of FENTORA, and
- Receipt of, and perceived utility of, the Medication Guide and other counseling tools for FENTORA.

Similar to the physician and pharmacist surveys, the compilation, analysis and tracking of the responses to the questions in this survey will be important to help understand whether the patient education tools or key safety messages in the patient education tools warrant modifications to enhance the benefits of the RiskMAP over time. Cumulative and interval survey responses will be tallied and analyzed for trends.

Using the Actiq patient survey data as a proxy, it was anticipated that during the first year of sales, each pharmacy chain would interview up to 1,000 patients. A review of the pharmacy call-back survey data for Actiq during the period of March 31, 1999 through December 31, 2000, identified 681 patients completed the surveys during this 1.5 year period. At that time, there were 4 participating pharmacy chains conducting the survey. For FENTORA, Cephalon is estimating that approximately 35% of current Actiq prescribers will become FENTORA prescribers within the first year of launch. One pharmacy chain will conduct patient surveys during the launch phase. Thus, it is estimated that approximately 1200 patients will be eligible to participate in the survey. Of the 1200 patients, it is estimated that approximately 40 to 50% of these patients ((N= 480-600) will complete a survey over a one-year period.

As the patient surveys will be administered every six months for the first two years post-launch of FENTORA, we anticipate a sample frame of approximately 300 patients per six-month survey period. The margin of error (at 95% confidence interval) associated with this expected sample size is approximately 5.8%. The ability to obtain the projected number of completed surveys may be impacted by the number of attempts needed to reach the patient, amount of time needed to complete the survey and identification of patients interested in participating in the survey.

During the launch and early post-launch months, we may not be able to identify this number of respondents who meet the criteria and are willing to complete the survey. In this case, the survey will consist of the maximum number of patients who meet the survey criteria and are willing to complete the survey. We will monitor this number of participants and assess sample size and accrual after each survey administration.

4.4 Patient Longitudinal Dispensing Data

Cephalon will also examine purchasing patient longitudinal data as a surveillance tool to help assess the degree to which FENTORA is prescribed to patients who have a recent prescription for another opioid medication. Cephalon will only consider data vendors with leadership in this field of data collection, projection, and analysis. The vendor data will be captured at the patient / prescription transaction level and will identify patients who receive a prescription for FENTORA. The longitudinal data structure will allow Cephalon to determine if an additional opioid medication was prescribed/dispensed in that month or the previous months prior to the FENTORA script. The resulting measure will be a ratio of FENTORA prescriptions that are given to a patient who has a recent opioid prescription over all FENTORA prescriptions. This information will be updated monthly and be part of the quarterly report.

4.5 Other Surveillance Activities

As a follow-up to surveillance and monitoring activities, interventions may be warranted for any one or a combination of the risks described throughout this RiskMAP. For example, if significant abuse or diversion is identified as occurring in a geographic area, Cephalon may employ education initiatives, as well as the use of local media and other communication vehicles, such as community outreach programs, to inform the community about the dangers and laws surrounding prescription opioid abuse.

Healthcare practitioners will be educated proactively and reactively on identifying patients who may be "doctor shopping" and/or have the potential for misuse and abuse of FENTORA. For example, a response after identification of a 'geographic hot spot' may be to follow-up with the prescriber(s) within that vicinity with a letter reminding them of FENTORA's Schedule II scheduling status, risks associated with the drug, and the implications associated with its diversion. Other interventions may include community outreach as a technique to help educate a community that may be at particular risk. Cephalon will cooperate with and assist law enforcement agencies at a federal, state, and local level in cases of abuse or diversion of FENTORA.

As previously mentioned, all data from surveillance and monitoring activities will be entered into a RiskMAP relational database in efforts to conduct analyses not just one a single activity but rather look at the data in aggregate and assess both quantitative and qualitative information. Results will be presented quarterly to the Cephalon Response Team comprised of Cephalon's senior management. The Response Team will be the decision-making mechanism for modifications to interventions within the RiskMAP.

4.6 Evaluation of Target Goals

It is not possible to determine with any degree of confidence an acceptable level of performance for meeting these goals. Rather than set an 'a priori' standard for acceptable compliance, Cephalon proposes to establish a quality assurance procedure. Using the evaluation and surveillance data, Cephalon will actively review each of the goals, objectives, tools and evaluation methods for this RiskMAP. Significant departures from the RiskMAP will be identified as well as the potential causes of such departures and, if needed, changes to the RiskMAP will be made to improve performance. Analytical methods will be used, as feasible, to facilitate the process, (e.g., decision trees, criticality indices). The intent of the assessment is to identify which tools and surveillance activities have been most effective and which ones warrant modification to increase success in achieving the objectives of the RiskMAP. Periodic evaluations will occur to monitor progress of the RiskMAP at meeting its objectives. Areas for improvement will be identified and the RiskMAP may be modified based on these evaluations. Specific measures (included in the evaluations) will be monitored for progress against measured performance. If sufficient progress is not made, RiskMAP modifications will be made.

Cephalon will conduct bi-annual external Advisory Board meetings composed of external experts to review the SECURE program. In this manner, Cephalon will ascertain objective feedback and recommendations on the performance of the FENTORA RiskMAP. This board will be comprised of individuals with expertise in pain management, risk management and

abuse, diversion of Scheduled drugs. The Advisory Board will provide independent review of the RiskMAP and its process evaluations. The Board will report directly to Cephalon and provide advice regarding needed interventions and revisions of the program.

4.7 Time Frames and Progress Report Submission

Data for the RiskMAP will be collected on an ongoing basis by the various mechanisms and functions previously described. To ensure the data are reviewed not in isolation, efforts are being made to develop a RiskMAP relational database which will allow analysis to be conducted across multiple points of intervention.

RiskMAP evaluations will be conducted quarterly for the first two years of marketing, with a report of the evaluations submitted to the FDA.

The data incorporated into these reports will include:

1. Extent of use (denominator estimates)
2. Indicators of inappropriate prescribing (i.e., opioid-naïve), inclusive of patient longitudinal data (see Section 4.4)
3. Summarization of reports involving medication errors and inadvertent pediatric exposures
4. Summarization of adverse events involving opioid naïve patients
5. Rates of suspected misuse, abuse, addiction or diversion reported
6. Results of any investigation or surveys conducted, and
7. Outcomes from any interventions, such as targeted educational interventions and antidiversion programs conducted.

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Subsequent to this time period, assessments of the RiskMAP will be made on an annual basis and Cephalon will provide the FDA with a report of its progress on a quarterly basis from the date of approval and any changes they have made to the program

Table 4: Surveillance and Monitoring Activities

Goal	Purpose	Primary Audience(s)	Tool Category	Tool	Description
1,2,3	Refine understanding of key points of intervention in FMEA analyses	FDA Cephalon	Pharmacovigilance	Spontaneous Adverse Event Reporting System	Expedited reporting of serious adverse events (SAEs) associated with abuse, misuse, or diversion of FENTORA as well as SAEs associated with accidental exposure to FENTORA (including TESS data) or use by opioid non-tolerant individuals. Conduct periodic reviews of reports to discern any pattern(s) in departures from safe-product-use pathways of FENTORA.
1,2,3	Refine understanding of key points of intervention in FMEA analyses	FDA Cephalon	Pharmacovigilance	Literature Review	Regular structured review of scientific literature on (1) misuse, abuse, and diversion of FENTORA, (2) accidental exposures to FENTORA, and (3) SAEs associated with use of FENTORA by opioid non-tolerant individuals to discern any pattern(s) in departures from safe-product-use pathways of FENTORA.
2	Refine understanding of patterns of abuse or diversion of FENTORA™	FDA Cephalon	Pharmacovigilance	Review National Surveys	National surveys on abuse and diversion, such as Drug Abuse Warning Network (DAWN), DAWN LIVE, Monitoring the Future (MTF), National Survey on Drug Use and Health (NSDUH, formerly called NHDSA), will be reviewed to look for any signal or patterns of abuse or diversion associated with FENTORA.
1,2,3	RiskMAP Evaluation	FDA Cephalon	Assessment of comprehension, knowledge, attitudes, and/or desired safety behaviors about drug safety risks	Prescriber surveys	Prescribers will be surveyed to assess (1) their knowledge of the key risks associated with the use of FENTORA, (2) their knowledge of the indication for FENTORA, (3) their patterns of FENTORA prescribing (e.g., opioid vs. non-opioid tolerant), and (4) their assessment of the risk minimization tools (e.g., use of, and reaction to, various Cephalon communications).

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Table 4: Surveillance and Monitoring Activities~~Table 4: Surveillance and Monitoring Activities~~ (continued)

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Goal	Purpose	Primary Audience(s)	Tool Category	Tool	Description
1,2,3	RiskMAP Evaluation	FDA Cephalon	Assessment of comprehension, knowledge, attitudes, and/or desired safety behaviors about drug safety risks	Pharmacist surveys	Pharmacists will be surveyed to assess (1) their knowledge of the key risks associated with the use of FENTORA, (2) their knowledge of the indication for FENTORA, (3) their awareness and use of the carton checklist, Medication Guide, and other information about the product made available by Cephalon field representatives, and (4) their assessment of the value of counseling messages provided by major publishers of pharmacy counseling software.
1,2,3	RiskMAP Evaluation	FDA Cephalon	Assessment of comprehension, knowledge, attitudes, and/or desired safety behaviors about drug safety risks	Patient surveys	Patients will be surveyed to assess (1) their knowledge of the key risks associated with the use of FENTORA, (2) their knowledge of the indication for FENTORA, (3) their knowledge about the directions for use of FENTORA, and (4) their receipt of, and perceived utility of, the Medication Guide and other counseling tools for FENTORA.
1,2,3	RiskMAP Evaluation	FDA Cephalon	Process measures that reflect desirable safety behavior & Outcome measures	Patient Longitudinal data	Cephalon will evaluate, via feasibility studies, whether the purchase of patient longitudinal data as a surveillance tool will provide meaningful information on clinical outcomes associated with the use of FENTORA.
1,2,3	Internal Auditing	Cephalon	Validation of internal process	FENTORA speaker bureau training	Cephalon will verify that FENTORA speakers have been trained on and understand the 3 principal risks identified in the RiskMAP.
1,2,3	External Auditing	Cephalon	Validation of external process	Validation of speaker bureau communication of risks	Cephalon field personnel will verify that FENTORA speakers present the information that focuses on the risks identified in the RiskMAP at each FENTORA promotional education program.

GLOSSARY OF TERMS

Abuse: Drug abuse (limited to medicinal products only) is defined as "a persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects (Volume IX of Pharmacovigilance; The Rules of Governing Medicinal Products in the EU).

Accidental Pediatric Exposure: All accidental pediatric (children <17 years of age) exposures including misguided uses or use facilitated by a non-healthcare professional, excluding intentional recreational use by an adolescent.

Diversion: The willful transfer of a drug from legitimate supply (manufacture, distribution, or storage in hospitals, pharmacies, physicians' offices) and/or patients for whom the drug has been prescribed to unauthorized users and/or for illegal sale.

F1 packaging: Packaging that meets the effectiveness specifications using the Child Test procedure for special packaging (16 CFR 1700.20(a)(2)). The "F value" is the number of individual units (e.g., tablets) to which access is obtained by a child under these testing conditions. For FENTORA tablets, access to a single 100 mcg tablet by a child could produce serious personal injury or serious illness. Under these conditions, F1 means that during such testing should a child be able to enter the package and gain access to one or more placebo test tablets, the package will fail for that particular child.

Failure Mode Effects Analysis (FMEA): A prospective procedure in which each potential failure mode in every subitem of an item is analyzed to determine its effect on other subitems and on the required function of the item.

Launch: The 6-month time period immediately following commercialization of a product, where commercialization means shipping a product to a wholesaler for subsequent distribution and sale.

Misuse: Patient intentionally disregards prescriber's instructions regarding use of medication, such as taking it for other than the intended use, taking other than the prescribed amount, taking it too frequently or for too long. Misuse may also include illicit or recreational use that does not meet definition for abuse.

Root-Cause Analysis: A process for identifying the basic or causal factor(s) that underlie variation in performance, including the occurrence or possible occurrence of a sentinel event.

Safe product use pathway: A set of explicit instructions and control measures that describe the safe use of the product at appropriate intervention points including at the supply chain, at the point of prescribing, at the point of dispensing, during consumer storage and at the disposal of product.

Supply chain: Begins with Cephalon's receipt of fentanyl citrate through the manufacturing and packaging of FENTORA.

REFERENCES

American Pain Society. Principles of analgesic use in the treatment of acute pain and cancer pain. Glenview, IL: American Pain Society; 2003.

Joseph W, Alba J. Wesley Hutchinson Dimensions of Consumer Expertise Journal of Consumer Research 1987;13(4):411-54.

Morris LA, Mazis M, Gordon E. A survey of the effects of oral contraceptive patient information. JAMA 1977;238:2504-8.

Pidgeon N, Kasperson RE, Slovic P (Eds). The Social Amplification of Risk, Cambridge University Press, Cambridge England 2003.

Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. Pain 1999;81(1-2):129-34.

Savage S. Long-term opioid therapy: assessment of consequences and risks. J Pain Symptom Manage 1996;11(5):274-86.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). Guidance for Industry: Development and Use of Risk Minimization Action Plans; March 2005.

APPENDIX A TOOLS EMPLOYED IN THE FENTORA RISKMAP

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
1	Blister	Launch and ongoing: Tablets will be supplied in double-foil blister which meet F1 requirements and which have passed tests for child resistance and senior friendliness. This tool is designed to minimize the risk of accidental exposure to FENTORA.	Patients	3	L,O	√
2	Blister label	Launch and ongoing: The blister label contains warning information that FENTORA should be kept of the reach of children and that is only for patients already taking opioids; it also contains instructions for use.	Patients	1,3	L,O	√
3	Carton label	Launch and ongoing: The labeling of the carton will contain warning information, be color coded by strength, and will contain a reminder checklist to prompt the pharmacist to counsel the patient about the 3 principal risks associated with use of FENTORA. The carton label also directs the patient and/or caregiver to read the Medication Guide for important warnings.	Patients Pharmacists	1,2,3	L,O	√

(continued)

APPENDIX A TOOLS EMPLOYED IN THE FENTORA RISKMAP (continued)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
4	Medication guide	Launch and ongoing: The FENTORA Medication Guide will emphasize the 3 principal risks associated with the use of FENTORA. Specifically it warns the patient of the potentially serious consequences, including death, that may occur when using FENTORA in opioid non-tolerant patients; it warns that the patient may become physically dependent on opioids and could become addicted to FENTORA; and lastly it warns that FENTORA is to be kept out of the reach of children and that FENTORA contains medicine that could be harmful or fatal to someone who has not been prescribed the medicine. It will go directly to patients via packaging the carton and will be made available to all prescribers and FENTORA-stocking pharmacies (via 800#, product-specific website and Cephalon sales representatives) for education and dissemination to patients.	Patients Pharmacists Prescribers	1,2,3	L,O	√
5	Package insert	Launch and ongoing: The package insert will contain a Boxed Warning about the life-threatening risks associated with the use of FENTORA in opioid non-tolerant patients; misuse, abuse and diversion; and accidental exposure to the medication.	Pharmacists Prescribers	1,2,3	L,O	√
6	Direct Risk communication by Cephalon field representatives	Launch and ongoing: Prescribers will be informed in person of the key messages and elements of the FENTORA RiskMAP, including the potentially life-threatening risk of use by an opioid non-tolerant individual, the high potential for FENTORA abuse as well as the risk of misuse and diversion, and the potentially life-threatening risk of accidental use of FENTORA in children or adults.	Prescribers	1,2,3	L,O	√

(continued)

APPENDIX A TOOLS EMPLOYED IN THE FENTORA RISKMAP (continued)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
7	Direct Risk communication by Cephalon field representatives	Launch and ongoing: Pharmacists likely to dispense FENTORA will be informed in person of the key messages and elements of the FENTORA Risk MAP, including the potentially life-threatening risk of use by an opioid non-tolerant individual, the high potential for FENTORA abuse as well as the risk of misuse and diversion, and the potentially life-threatening risk of accidental use of FENTORA in children or adults.	Pharmacists	1,2,3	L	√
8	Educational Introductory Letter to Healthcare Professionals	Launch: Cephalon will develop and disseminate an educational FENTORA introductory letter reinforcing the 3 principal messages of the RiskMAP. Specifically these messages will address that FENTORA is to be used only by opioid-tolerant patients with cancer ~~individuals~~; a risk of misuse, abuse and diversion is associated with FENTORA; and there is a risk of accidental exposure associated with the use of FENTORA. At the time of launch, the letter will be disseminated via direct mail to 10,000 identified healthcare practitioner targets, 3,000 retail pharmacists likely to stock FENTORA, and the top 25 Pain Centers of Excellence.	Prescribers Pharmacists	1,2,3	L	√
9	Educational RiskMAP monograph for physicians	Launch: Cephalon will develop and disseminate a FENTORA educational RiskMAP monograph which will reinforce the 3 principal messages of the RiskMAP. Specifically these messages will address that FENTORA is to be used only by opioid-tolerant individuals; a risk of misuse, abuse and diversion is associated with FENTORA; and there is a risk of accidental exposure associated with the use of FENTORA. The monograph will be disseminated at launch via direct mail to 10,000 identified healthcare practitioners and the top 25 Pain Centers of Excellence.	Prescribers	1,2,3	L	√

(continued)

APPENDIX A TOOLS EMPLOYED IN THE FENTORA RISKMAP (continued)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
10	PharmAlert	Launch and as needed: Educational material that reinforces the 3 principal messages of the RiskMAP. Specifically these messages will address that FENTORA is to be used only by opioid-tolerant patients with cancer ~~individuals~~; a risk of misuse, abuse and diversion is associated with FENTORA; and there is a risk of accidental exposure associated with the use of FENTORA. These will be distributed to 40,000 retail pharmacists.	Pharmacists	1,2,3	L	√
11	Physician education directed to Pain Centers of Excellence	Launch and ongoing: Cephalon will contact each of the identified top 25 Pain Centers of Excellence to offer further educational opportunities to learn about FENTORA, including the 3 principal risks identified in the RiskMAP. Specifically risk of use by opioid non-tolerant individuals, the risks for misuse, abuse and diversion, and the risk of accidental exposure to FENTORA will be addressed. The educational platform for these offerings will include symposia and/or teleconferences.	Prescribers	1,2,3	L	√
12	Pharmaceutical compendia	Launch and ongoing: Cephalon will provide FENTORA information, including the 3 principal risks identified in the RiskMAP, to several well-known compendia such as Physicians' Desk Reference (PDR), American Hospital Formulary Service (AHFS), and Drug Facts and Comparisons.	Prescribers Pharmacists	1,2,3	L,O	

(continued)

APPENDIX A TOOLS EMPLOYED IN THE FENTORA RISKMAP (continued)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
13	Counseling messages	Launch and ongoing: Cephalon will provide risk information to First Data Bank and/or other major publishers of pharmacy counseling software to educate the majority of retail pharmacists on the 3 principal risks associated with use of FENTORA. Specifically these messages will address that FENTORA is to be used only by opioid-tolerant patients with cancer ~~individuals~~; a risk of misuse, abuse and diversion is associated with FENTORA; and there is a risk of accidental exposure associated with the use of FENTORA.	Prescribers Pharmacists	1,2,3	L,O	√
14	Counseling aid	Launch and ongoing: In addition to the Medication Guide, Cephalon will develop a counseling aid to be used by healthcare professionals when advising and educating patients about FENTORA. This aid will include information about the 3 principal risks associated with use of FENTORA. Specifically the aid will include information addressing that FENTORA is to be used only by opioid-tolerant patients with cancer ~~individuals~~; a risk of misuse, abuse and diversion is associated with FENTORA; and there is a risk of accidental exposure associated with the use of FENTORA.	Patients Pharmacists Prescribers	1,2,3	L,O	√

(continued)

APPENDIX A TOOLS EMPLOYED IN THE FENTORA RISKMAP (continued)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
15	Counseling aid	Launch and ongoing: Educational materials will be disseminated to pharmacists who attend wholesaler trade shows and pharmacy meetings. These materials will provide education on the 3 principal risks identified in the RiskMAP. Specifically these materials will include information addressing that FENTORA is to be used only by opioid-tolerant patients with cancer ~~individuals~~; a risk of misuse, abuse and diversion is associated with FENTORA; and there is a risk of accidental exposure associated with the use of FENTORA.	Pharmacists	1,2,3	L,O	√
16	RiskMAP Speaker training	Launch and ongoing: Cephalon will formally train speakers on aspects of FENTORA consistent with the risk information in the package insert, including the key elements and messages of the RiskMAP. Cephalon will also provide speakers with information which they must present, that focus on the risks identified in the RiskMAP. Prior to speaking on behalf of Cephalon, these speakers will verify that they understand the 3 principal risks associated with the use of FENTORA. Evaluations provided will monitor whether speakers presented the required risk information.	Prescribers	1,2,3	L,O	√
17	RiskMAP Training for Cephalon field representatives	Launch and ongoing: In addition to product-specific training, Cephalon field representatives will receive -RiskMAP- specific training Upon completion of the training, field representatives will be tested on the training and will be required to verify their understanding of the information, including the information on the 3 principal risks identified in the RiskMAP.	Cephalon field representatives	1,2,3	L,O	√

(continued)

APPENDIX A TOOLS EMPLOYED IN THE FENTORA RISKMAP (continued)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
18	Independent continuing medical education (CME)	Launch: Cephalon will support independent education on prescription drug misuse, abuse, and diversion targeted to physicians likely to prescribe FENTORA.	Prescribers Pharmacists	2	L	
19	Introductory Letter to Drug Diversion Authorities	Launch: Proactive communications to drug diversion control authorities to educate interested parties and alter them to safeguard against the potential diversion of FENTORA.	Drug diversion professionals	2	L	
20	Product returns and disposal	Launch and ongoing: Cephalon will accept returns for disposal of unwanted FENTORA. This will be a tool to minimize the amount of excess product available.	Patients	2,3	L,O	√
21	Physician and Pharmacist education	Ongoing (response to surveillance): Cephalon will implement medical education directed to 'geographic hot spots' that focus on preventing and/or minimizing misuse, abuse, and diversion of prescription drugs. The format of these programs will be tailored to the specific need (eg, symposium, teleconferences, print materials, etc.)	Prescribers Pharmacists	2	O	√
22	Reports of diversion and abuse	Launch and ongoing: Cephalon will attempt to implement an active monitoring system (eg, RADARS) at the time of the launch of FENTORA. Reports from the National Association of Drug Diversion Investigators (NADDI) will be actively monitored and screened for information on FENTORA.	Drug Diversion Professionals	2	L,O	

(continued)

APPENDIX A TOOLS EMPLOYED IN THE FENTORA RISKMAP (continued)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
23	Physician education (targeted to members of professional societies)	Launch: Professional societies will be contacted to offer educational opportunities to learn about FENTORA and key messages and risks described in the RiskMAP, including the risk for misuse, abuse, and diversion. The educational platform for these offerings will include symposia at the professional society's meeting(s) and/or teleconferences with interested members.	Prescribers	2	L	√
24	Website	Launch and ongoing: This website will be a tool for healthcare professionals and for patients. It will educate both audiences about the 3 risks associated with FENTORA as identified in the SECURE Program.	Prescribers Pharmacists Patients	1,2,3	L,O	√

FENTORA™ Risk Minimization Action Program

Xst Quarterly Report

(Month Day, Year through Month Day, Year)

FENTORA™ Risk Minimization Action Plan Quarterly Report
The SECURE Program

1.0 REGULATORY OVERVIEW [Regulatory Affairs]

Authoring Note:
Provide background including the purpose of the FENTORA riskMAP, the goals and objectives of the RiskMAP, clear delineation of what was collected during the reporting period and hence what will be reported on for the particular reporting period, and any pertinent correspondene between sponsor and FDA regarding the RiskMAP during the reporting period.

2.0 SURVEILLANCE AND MEASURING EFFECTIVENESS OF THE RISKMAP (Note: Section headings in subsequent section 2.0 correlate with section headings to Section 4.0 in the RiskMAP) [Regulatory Affairs]

This RiskMAP was designed to address three principal risks associated with FENTORA: 1) its use by opioid non-tolerant individuals, (2) the risk of misuse, abuse, and diversion, and 3) unintended (accidental) exposure to the product.

A principal goal of the RiskMAP is to ensure that physicians, pharmacists, and patients are aware and knowledgeable of these risks and are aware of steps they can take to minimize them. Cephalon has employed a series of independent and unique surveillance and monitoring techniques targeted at prescribers, pharmacists, and patients, respectively, to assess the effectiveness of the targeted education and reminder systems at the points of intervention.

2.1 Active Surveillance Systems [Global Product Safety]

Active monitoring of national audit data was used to track specific outcomes related to abuse via the Toxic Exposure Surveillance System (TESS), the Drug Abuse Warning Network (DAWN) and DAWN LIVE.

2.1.1 RADARS report [Regulatory Affairs]

Cephalon has employed an active surveillance system (RADARS® System) to provide surveillance and monitoring to detect and characterize misuse, abuse and suspected diversion of FENTORA. The RADARS System calculates rates of prescription opioid abuse on a quarterly basis for each 3-digit zip code in the country. Two rates are generated: one based on populations and one based on unique individuals that have filled a prescription for the drug. The information used in this System is derived from four sources: 1) Poison Centers, 2) Suspected drug diversion, 3) Key Informant, and 4) Methadone Clinics. Each of these systems provides a unique perspective on prescription drug abuse. The RADARS System is an independent operation under the ownership of the Rocky Mountain Poison and Drug Center (RMPDC), Denver Health and Hospital Authority. Using the RADARS threshold, we asked RADARS to identify when rates meet or exceed 5/100,000 population per quarter in a 3-digit zip code for Key Informant, Suspected drug diversion and Methadone data systems. For poison control, Cephalon has specified RADARS to indicate when a rate of 2 or more/100,000 population is identified.

A summary of the data obtained from RADARS is provided below, and a complete RADARS report is located in Appendix XX of this report (FULL RADARS REPORT-ALREADY PROVIDED)

RADARS executive summary

2.2 Post Marketing Reporting Systems [Global Product Safety]

Cephalon has followed-up on any reports of serious adverse events that may be associated with abuse, misuse, and suspected diversion. These reports were sent to FDA in an expedited fashion. In addition, all accidental exposures regardless whether symptomatic or asymptomatic were expedited to the FDA. Medication error reports, regarless of patient outcome, were collected and also reported to FDA in an expedited manner. Reconciliation of the spontaneous reports was performed to identify redundancy in information.

The following table summarizes all reports meeting the FENTORA RiskMAP criteria that were received during this reporting period for FENTORA.

Table X. Total FENTORA Product Experience Reports

Quarter ending Day Month Year

Month, Year	Total No. of RISKMAP Cases	Any report with an outcome of death	Any report in a child or adolescent (ages 0-16), whether or not the exposure was intended or unintended, and regardless of outcome	Any medication error reports regardless of patient outcome (including accidental exposure)
Month				
Month				
Month				

Authoring Note: A discussion should be included incorporating Cephalon's understanding of the information provided in the product experience reports, whether or not any futher intervention was warranted, and whether or not the case was conclusive or still under investigation.

Table X. FENTORA Reports Submitted as 15-day Alerts under the RISKMAP
Quarter Ending Day Month Year

Report Type	Cephalon MCN	Submission Date
Death, Pediatric Exposure, or Medication Error (including accidental exposure)	**US0XXXXX**	

FENTORA reports received during the reporting period and expedited under the RISKMAP are summarized by reporting category below.

ADRs Expedited under the FENTORA Risk Management Program

Any report with an outcome of death

There were x reports with an outcome of death in the Xth Quarter Year. These are summarized in the table below.

Table X Reports With an Outcome of Death Received Xst Quarter Year

MCN #	Report Date	Age of child	Gender	Dose strength	Symptoms reported	Health care facility (HCF) treatment	Outcome
US0XXXXX	Day-Month-Year		Female or Male				

Authoring Note: Please include narrative around the cases presented in the table as well as a summary statement(s) with regard to Cephaon's conclusions based on this data..

Any report in a child or adolescent (ages 0-16), whether or not the exposure was intended or unintended, and regardless of outcome

Table X. Any report in a child or adolescent (ages 0-16), whether or not the exposure was intended or unintended, and regardless of outcome

There were x reports in children or adolescents (ages 0-16), whether or not the exposure was intended or unintended, and regardless of outcome. These are summarized in the table below.

MCN #	Report Date	Age of child	Gender	Dose strength	Symptoms reported	Health care facility (HCF) treatment	Outcome
US0XXXXX	25-Apr-Year	23 mo	Female	400mcg	Asymptomatic	None – observed at home	No effect

There were x reports of medication error reports regardless of patient outcome (including accidental exposure) in the Xth Quarter Year. These are summarized in the table below.

Table X Reports of medication error reports regardless of patient outcome (including accidental exposure) Xst Quarter Year

MCN #	Report Date	Age of child	Gender	Dose strength	Symptoms reported	Health care facility (HCF) treatment	Outcome
US0XXXXX	Day-Month-Year		Female or Male				

Authoring Note: Please include individual narratives around the cases presented in the table as well as a summary statement(s) with regard to Cephalon's conclusions based on this data. If interventions were employed, indicate such.

4.2 Surveys [Market Research/ Global Product Safety]

The reslts of the physician, pharmacist, and patient call-back surveys are included in Sections 4.2.1, 4.2.2, and 4.2.3 of this report, respectively. These surveys were used to measure knowledge, attitudes and behaviors associated with the FENTORA RiskMAP. We used three separate surveys targeted at the three principal intended audiences: prescribers, pharmacists and patients.

4.2.1 Physician Surveys [Market Research]

See example for 4.2.2 for example

4.2.2 Pharmacy Surveys [Market Research]

Authoring Note: For Quarters 1 and 3 state the following: "Physician survey analyses are completed twice yearly. An analysis will be provided in the next quarterly report."

For Quarters 2 and 4 state the following: "A survey targeting the dispensing pharmacists was also employed." Describe any pertinent background information, such as any changes that were made to the survey in the previous report and the reason. Describe the objectives for this reporting period, such as the following: The objective of the pharmacist survey for this reporting period was to evaluate the following:

- *Pharmacist knowledge of the key risks associated with the use of FENTORA*
- *Pharmacist awareness that FENTORA is not equivalent with Actiq on a mcg per mcg basis*
- *Pharmacist behavior regarding dispensation of a Medication Guide with every prescription of FENTORA,*
- *Pharmacist behavior regarding delivery of key counseling messages*

Explain the number of physicians screened and participated, such as the following: "XX physicians were screened for participation in the physician survey during this reporting period. Of these XX physicians, YY physicians were eligible and successfully completed the survey."

The complete summary data are provided in **Appendix X**. An analysis of the data is presented below.

Evaluate the data opposite the stated objectives and provide an analysis. For reports subsequent to the initial report also discuss trends. For example:

Based upon the survey responses an evaluation of the pharmacists' knowledge of the key risks revealed the following:

- *In the first or second half of year, X% of physicians were knowledgeable that FENTORA cannot be used by opioid non-tolerant patients.. This represents an X% increase/decrease from the previous quarter (result for survey question 2b).*

- *In the first or second half of year, X% of physicians were knowledgeable that FENTORA can be misused, abused, or diverted. This represents an X% increase/decrease from the previous quarter (result for survey question 2b).*
- *In the first or second half of year, X% of physicians were knowledgeable that FENTORA is especially at risk for unintended or accidental exposure (#%). This represents an X% increase/decrease from the previous quarter (result for survey question 2c).*

An analysis of the pharmacists' awareness that FENTORA is not equivalent with Actiq on a mcg per mcg basis revealed the following:

- *In the first or second half of year, X% of physicians were knowledgeable that FENTORA cannot be substituted for Actiq on a mcg per mcg basis. This represents an X% increase/decrease from the previous quarter (result for survey question 2c). .*

An analysis of pharmacists' behavior regarding dispensation of a Medication Guide with every prescription of FENTORA revealed the following:

- *In the first or second half of year, X% of physicians reported dispensing a Medication Guide with every prescription of FENTORA (result for survey question 3).*

Analysis of pharmacists' behavior regarding delivery of key counseling messages revealed the following (result for survey questions 4 a-c):

- *#% reported that they always counsel patients on keeping FENTORA in its original (blister) packaging until needed. #% reported that they sometimes counsel patients on keeping FENTORA in its original (blister) packaging until needed. #% reported that they never counseling patients on keeping FENTORA in its original (blister) packaging until needed.*
- *#% reported that they always counsel patients on keeping FENTORA in a safe place out of the reach of children. #% reported that they sometimes counsel patients on keeping in a safe place out of the reach of children. #% reported that they never counseling patients on keeping FENTORA in a safe place out of the reach of children.*
- *#% reported that they always counsel patients on keeping FENTORA in a safe place to protect from theft. #% reported that they sometimes counsel patients on keeping FENTORA in a safe place to protect from theft. #% reported that they never counseling patients on keeping FENTORA in a safe place to protect from theft..*

It should be noted that If a pharmacist answered other than yes or always, Cephalon intervened via having the survey interviewer instruct the pharmacist to visit the website associated with FENTORA for full prescribing information. Additionally ,in these cases the survey interviewer initiated a follow-up letter to inform the pharmacist of the importance of selecting and dispensing only to appropriate opioid-tolerant patients and of safe use of FENTORA. As a result, in this reporting period, # letters were issued.

Include any additional analysis and proposed changes to the survey.

4.2.2 Patient Surveys [Global Product Safety]

See 4.2.2 for example

4.3 Patient Longitudinal Dispensing Data [Global Product Safety/ Market Research]

Authoring Note: Provide summarized patient longitudinal data and analysis here to assess the degree to which FENTORA was prescribed to patients who had a recent precription for another opioid medication during the reporting period.The data obtained provides a ratio of FENTORA prescriptions given to a patient who has a recent opioid prescription over all FENTORA prescriptions. In reports subsequent to 1st RMP, discuss changes in this ratio (if applicable).

4.4 Other Surveillance Activities [Regulatory Affairs]

Authoring Note: This section is intended to include follow-up surveillance and monitoring activities in which interventions were employed and tracked in Cephalon's database. Examples of interventions shall include but are not limited to:

1. *employment of a Cephalon community outreach educational initative in response to reports of significant abuse or suspected diversion in a particular geographic area*
2. *Instituting an educational program for healthcare practitioners to help them proactively and reactively identify patients who may be "doctor shopping" and/or have the potential for misuse and abuse of FENTORA*
3. *In response to identification of a 'geographic hot spot', Cephalon may follow-up with the prescriber(s) within that vicinity with a phone call/letter/visit reminding them of FENTORA's Schedule II status, risks associated with the drug, and the implications associated with its suspected dirversion*
4. *Other interventions may include community outreach as a technique to help educate a community that may be at particular risk.*
5. *Mention ways in which Cephalon has cooperated with and assist law enforcement agencies at a federal, state, and local level in cases of abuse or suspected diversion of FENTORA. Discuss any intervention and the outcome in this section.*

4.5 Evaluation of Target Goals

Cephalon conducts bi-annual external Advisory Board meetings composed of external experts to review the SECURE program. In this manner, Cephalon has ascertained objective feedback and recommendations on the performance of the FENTORA RiskMAP. This board is comprised of individuals with expertise in pain management, risk management and abuse, suspected diversion of Scheduled drugs. The Advisory Board provides independent review of the RiskMAP and its process evaluations. The Board reports directly to Cephalon and provides advice regarding needed interventions and revisions of the program

Authoring Note: Provide the final report from the Cephalon Advisory Board on Risk Minimization in this section or mention that analysis will be provided in the next quarterly report. Considerations for the Advisory Board have been advised on the following considerations: The Board should keep in mind that it is not possible to determine with any degree of confidence an acceptable level of performance for meeting these goals. Rather, they should set an 'a priori' standard for acceptable compliance.. Using the evaluation and surveillance data, they should actively review each of the goals, objectives, tools and evaluation methods for this RiskMAP. The Board should identify any significant departures from the RiskMAP as well as the potential causes of such departures and, if needed, propose changes to the RiskMAP will be made to improve performance. Use analytical methods, as feasible, to facilitate the process, (e.g., decision trees, criticality indices), the Board should identify which tools and surveillance activities have been most effective and which ones warrant modification to increase success in achieving the objectives of the RiskMAP. The Board should also identify areas for improvement will be identified and be modified based on these evaluations. ANY PROPOSED INTEGRATED SAFETY TABLES (COMPARING RADARS, TESS, DAWN)