

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

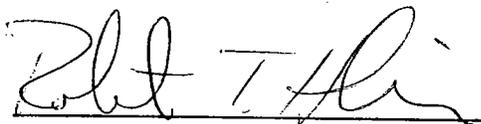
21-947

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

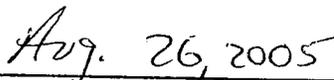
Patent Certification

Pursuant to 21 C.F.R. §314.50 (i)(1)(ii), applicant makes the following certification:

In the opinion and to the best knowledge of Cephalon, Inc. there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.



Robert Hrubiec, Ph.D., J.D.
Vice President, Intellectual Property &
Chief Patent Counsel
Cephalon, Inc.



Date

EXCLUSIVITY SUMMARY

NDA # 21-947

SUPPL #

HFD # 170

Trade Name Fentora

Generic Name fentanyl buccal tablet

Applicant Name Cephalon, Inc.

Approval Date, If Known September 25, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Yes, for the fentanyl MOIETY-as the active ingredient in Duragesic (N 19-813)--which fulfilled a PWR and was granted pediatric exclusivity. This PRODUCT does not have a PWR in place and the firm is not requesting pediatric exclusivity at this time for this drug product.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-338 Duragesic
NDA# 20-747 Actiq
NDA# 16-619 Sublimaze

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study 099-14

[The Division only required ONE adequate and well-controlled trial for this product due to the Division's long term experience with the moiety and the similarity to the RLD (Actiq).]

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study 099-14

[The Division only required ONE adequate and well-controlled trial for this product due to the Division's long experience with the moiety and the similarity to the RLD (Actiq).]

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #_65,447	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

Investigation #1
!
! YES NO
! Explain: ! Explain:

Investigation #2
!
! YES NO
! Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Kim Compton, Project Manager with Rob Shibuya, Medical Officer
Title: Project Manager and Medical Officer
Date: 6-23-06, updated 9-21-06

Name of Office/Division Director signing form: Bob Rappaport
Title: Director, Division of Anesthesia, Analgesia and Rheumatology Products

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Bob Rappaport
9/25/2006 04:29:03 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-947 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: July 25, 2006 (AZ) Action Date: September 25, 2006

HFD-170 Trade and generic names/dosage form: Fentora (fentanyl buccal tablet)

Applicant: Cephalon, Inc. Therapeutic Class: Opioid (Narcotic)

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): one

Indication #1: the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is exempt for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

■ Other:

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 0 _____ Tanner Stage _____
Max _____ kg _____ mo. 11 _____ yr. 16 _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): 9-25-11

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

[See appended electronic signature page]

Regulatory Project Manager

cc: NDA 21-947
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT (HFD-960) (901-594-7337)

(revised 12-22-03)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kimberly Compton
9/25/2006 04:21:11 PM

Cephalon, Inc.

NDA 21-947

fentanyl effervescent buccal tablet

CONFIDENTIAL

Debarment Certification

Debarment Certification

Cephalon, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Penny S. Levin, MS

Penny S. Levin, MS
Associate Director, Regulatory Affairs
Cephalon, Inc.

July 12, 2005

Date

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-947	Efficacy Supplement Type SE-	Supplement Number
Drug: Fentora (fentanyl buccal tablet)		Applicant: Cephalon, Inc.
RPM: Kim Compton		HFD-170 Phone # 301-796-1191
<p>Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input checked="" type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): N 20-747, Actiq (oral transmucosal fentanyl citrate)
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		4S
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		
		6-30-06 (cycle 1-AE) 9-25-06 (cycle 2-AP)
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid UF ID number 3006142
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? () Yes () No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? () Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	Summary is attached (signed 9-25-06)
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	X (filing) 11-3-05, and (addendum) 6-23-06, (Wrap-Up on Consultant Responses) 9-25-06

❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	AE – 6-29-06
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X (see AP letter)
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	X (1 st cycle original)
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	DDMAC—5/25/06 DSRCS – 6-16-06 (Med Guide Rvw) DMETS—4/12/06 and 6-27-06 and 8/17/06 (includes Proprietary Name Rvws)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X (agreed on 6-28-06)
• Applicant proposed	X (1 st cycle original)
• Reviews	(Information incorporated into labeling reviews listed above)
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	12/5/03
• Pre-NDA meeting (indicate date)	4/6/05
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	X (Div Dir AE memo) – 6-29-06 X (Div Dir AP memo)- 9-25-06
❖ Clinical review(s) (indicate date for each review)	X – 6-28-06 (cycle 1, Review and Addendum), 9-15-06 (cycle 2, review/chronology of cycle)
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See Clinical Rvw
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	X (ODS) –4/27/06 (cycle 1), 8/29/06 (cycle 2) X (OCC)- copies of outgoing consults on RMP to OCC (plus CSS rvws as listed below) X (Dep Dir Memo on CSS responses) –9-22-06
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X (9-25-06)
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	X- 5-2-06 (cycle 1)
❖ Biopharmaceutical review(s) (indicate date for each review)	X- 3-16-06, and 6-7-06 (cycle 1)
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	X – 5/9/06 (Executive Summary), 5/17/06, and 6/6/06 (cycle 1), and 9/1/06 and 9/15/06 (cycle 2)
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X (4-28-06)
• Bioequivalence studies	N/A
❖ CMC review(s) (indicate date for each review)	X – 6-16-06 and 6-28-06 (cycle 1)
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	X – 6-16-06 (cycle 1)
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: 6-26-06 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested (X) Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	X – 6-22-06 (cycle 1)
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	
❖ CAC/ECAC report	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products
Bldg 22, Rm 3105 10903 New Hampshire Ave Silver Spring, MD
Tel: (301) 796-2280

**Project Manager's Memo of FDA Consultant Groups Responses for Complete
Response to Approvable Letter, and Documentation of Changes Included in Final
Response from Applicant**

NDA #:	21-947
Drug Name (generic) :	FENTORA (fentanyl buccal tablets)
Sponsor:	Cephalon
Indication:	Management of breakthrough pain in opioid-tolerant cancer patients
Type of Submission:	Amendment to complete response to approvable letter
Dates of Submission:	19 September 2006
Review Date:	20 September 2006
Material Summarized: and final	Final reports of consultants (OSE, DDMAC, and CSS) response by applicant (submission dated 9/19/06)
Project Manager:	Kim Compton
Medical Officer:	Robert Shibuya, M.D.

Background

FENTORA is a reformulation of oral transmucosal fentanyl citrate (OTFC). The applicant is seeking an indication of the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying cancer pain.

The initial NDA (21-947) was submitted on 31 August 2005. The Division took an Approvable action on this application on 29 June 2006. There were no questions of efficacy or safety and agreement on the labeling (package insert, Medication Guide and carton and container labels) was reached with the input and concurrence of pertinent internal parties [the Office of Surveillance and Epidemiology (OSE), Controlled Substance Staff (CSS), and Division of Drug Marketing, Advertising, and Communication (DDMAC)] and the applicant.

The one issue that precluded the approval of NDA 21-947 was that Cephalon was not able to submit a finalized, complete Risk Minimization Action Plan (RiskMAP) before the PDUFA date. The Division took an Approvable action with the understanding that the applicant would finalize the RiskMAP in a timely fashion and resubmit it. The Division agreed that the resubmission would be considered a Class I resubmission with a 2-month PDUFA goal date.

In a submission dated 25 July 2006, Cephalon provided a Complete Response to the Division's Approvable Letter. The resubmission and requests for consultation were sent to OSE, CSS, DDMAC, and Office of Chief Counsel (OCC).

This memo will serve to summarize final responses from those consultants and to document changes made by the applicant in response to requests from the Agency after 14 September 2006. This memo documents only changes made by the applicant in their last submission to the NDA in this cycle.

For a discussion of Agency requests and applicant responses in this review cycle prior to 14 September 2006, please refer to Dr. Robert Shibuya's (Medical Officer), comprehensive review of the chronology of this entire review cycle up until 14 September 2006, which includes discussion of Agency requests as outlined in Agency Discipline Review letters of 29 August and 7 September 2006, and TCs between the Agency and applicant on 31 August and 13 September 2006, as well as a discussion of the applicant's responses to these requests. Refer to Dr. Shibuya's review for a discussion of these items and all other issues in this review cycle. For a discussion of the requests in the Agency Information Request Letter of 30 August 2006, and the applicant's responses please see the review by Dr. Sharon Hertz (TL/Deputy Director).

Section I.--Requests made by Agency after 14 September 2006:

In an email request on 18 September 2006, the firm was asked to revise section 4.1 of their RiskMAP as follows (see separate DFS memo for documentation of this request):

Although FDA agreed that Cephalon would review the data for signal detection over 3 consecutive quarters for the first year (and quarterly thereafter), the Agency asked that the sponsor share their data on a quarterly basis and that we may ask for early intervention if an important increase is noted.

In the firm's response, dated 19 September 2006, they have complied with this request and modified section 4.1 of the RiskMAP accordingly to reflect this change.

Section II.--Summary of Consultant Responses:

1. CSS-

Following review of the applicant's draft submission, emailed by the applicant on 14 September 2006, and forwarded to the team on 15 September 2006 (intended to be officially submitted if acceptable to the Agency), Silvia Calderon of CSS, indicated that the applicant's "minutes" reflected the agreements made in the 13 September 2006 discussions with the applicant. (Please see copy of email below

and refer to the Medical Officer's review for listing of agreements discussed in the 13 September 2006 TC.)

From: Calderon, Silvia N
Sent: Friday, September 15, 2006 12:31 PM
To: Compton, Kimberly
Cc: Leiderman, Deborah; Zeldes, Geoffrey
Subject: RE: FENTORA - updated RiskMAP and revised tools per teleconference of September 13, 2006
Hi Kim,
The attached minutes reflect the agreements made at the September 14, 2006 telecon.
Silvia

From: Compton, Kimberly
Sent: Friday, September 15, 2006 10:30 AM
To: Calderon, Silvia N; Zeldes, Geoffrey; Holquist, Carol A; Dempsey, Mary; Clark, Nancy; Willy, Mary E; Karwoski, Claudia B; Arnwine, Kristina; Akhavan-Toyserkani, Gita; Lee, Lauren; Leiderman, Deborah; Moody, Corinne P
Subject: FW: FENTORA - updated RiskMAP and revised tools per teleconference of September 13, 2006

Hello all,

Attached is the firm's responses (Cephalon) on Fentora issues we raised with them in our DR/IR ltrs and TC on Wed.

Please let me know if ASAP if OK and they will send in a formal submission of this. (Our action date is in just over one week so we need to get things resolved quickly now.)

Thanks,
Kim

Taken with the other CSS reviews in DFS for this NDA, the Division now considers the review of this application by CSS to be complete with all issues CSS raised regarding this NDA to have been addressed.

2. OSE-

Following review of the applicant's draft submission, emailed by the applicant on 14 September 2006, and forwarded to the team on 15 September 2006 (intended to be officially submitted if acceptable to the Agency), Claudia Karowski, indicated that OSE had one additional item they would like the applicant to address regarding section 4.1 of the proposed RiskMAP (for a detail of that

request and the applicant's response, please see Section I above.) A copy of the OSE email is found below.

From: Karwoski, Claudia B
Sent: Monday, September 18, 2006 7:04 AM
To: Willy, Mary E; Compton, Kimberly; Calderon, Silvia N; Zeldes, Geoffrey; Holquist, Carol A; Dempsey, Mary; Clark, Nancy; Arnwine, Kristina; Akhavan-Toyserkani, Gita; Lee, Lauren; Leiderman, Deborah; Moody, Corinne P
Subject: RE: FENTORA - updated RiskMAP and revised tools per teleconference of September 13, 2006
Hi all,

I have received only one comment from Mary W with regard to #2

2. FDA requested that we assess signal detection by looking at 2 consecutive quarters instead of 3 consecutive quarters as proposed.

After discussion with the Agency, agreement was reached that Cephalon would review the data over 3 consecutive quarters for the first year post-approval and then review the data from quarter to quarter for signal detection in subsequent years. The RiskMAP Section 4.1 has been modified to reflect this change and is included with this submission.

FDA Response: Although we agree that Cephalon would review the data for signal detection over 3 consecutive quarters for the first year (and quarterly thereafter), we asked that the sponsor share their data on a quarterly basis and that we may ask for early intervention if an important increase is noted.

- If there are no other comments, we will forward this to Kim this morning.

Claudia

No other comments on the applicant's response were received from OSE. This comment was shared with the applicant and responded to (please see Section I of this memo.)

Therefore, taken along with the other reviews in DFS for this application from OSE, the Division now considers OSE's review of this NDA complete and all issues raised by OSE regarding this NDA addressed.

3. DDMAC-

Following review of the applicant's draft submission, emailed by the applicant on 14 September 2006, and forwarded to the team on 15 September 2006 (intended

to be officially submitted if acceptable to the Agency), Michelle Safarik of DDMAC, indicated that DDMAC had reviewed the response provided by the applicant and found it acceptable (per email attached below).

From: Safarik, Michelle
Sent: Friday, September 15, 2006 10:50 AM
To: Compton, Kimberly
Cc: Hu, Elaine J; Markos, Constantine
Subject: RE: FENTORA - updated RiskMAP and revised tools per teleconference of September 13, 2006
Hi Kim,

I have reviewed Cephalon's revisions to the revised proposed RMP-associated materials and have no further comments at this time.

Thanks and have a great weekend!

Michelle

-----Original Message-----

From: Compton, Kimberly
Sent: Thursday, September 14, 2006 6:59 PM
To: Safarik, Michelle; Markos, Constantine
Subject: FW: FENTORA - updated RiskMAP and revised tools per teleconference of September 13, 2006

Responses on fentora from Cephalon...please let me know if OK and they will send in a formal submission of this.

Thanks,
Kim

Therefore, taken along with the other input and reviews in DFS for this application from DDMAC, the Division now considers DDMAC's review of this NDA complete and all issues raised by DDMAC regarding this NDA addressed.

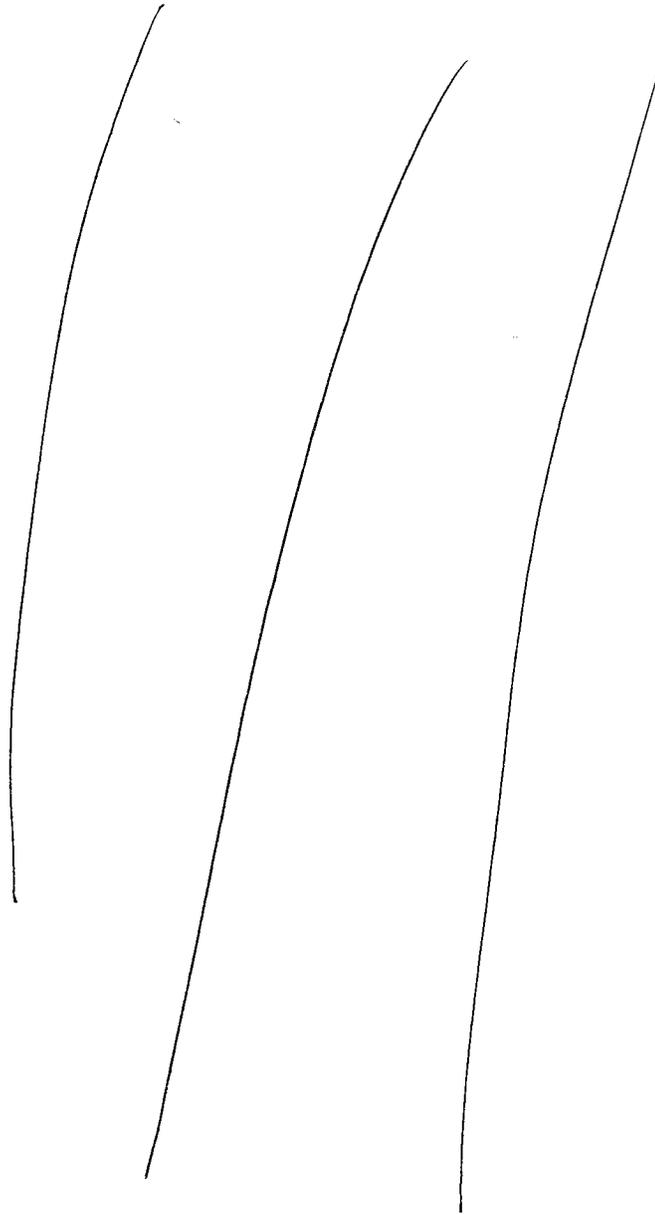
4. OCC-

Following review of the materials in cycle 1, and of the Complete Response to Approvable Letter (submission dated 25 July 2006) materials, OCC requested a TC with the Division on 28 August 2006. At that time Heidi Gertner and Lynn Mehler of OCC shared their comments on the RiskMAP and draft AP letter with the Division and the Division forwarded the RiskMAP comments to the applicant in the IR letter dated 30 August 2006.

OCC indicated during that TC that if the applicant addressed the issues raised by OCC, then OCC did not need to further review the materials for the NDA. OCC

also indicated that the draft AP letter was acceptable and to update them if it was changed closer to the action date.

In an email on 20 September 2006, Lynn Mehler indicated that following internal discussion, OCC agreed that the draft AP letter and RiskMAP summary were still acceptable and that the Division could take an AP action when ready unless any significant new information or changes arose. (See copy of email below for documentation.)



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 Draft Labeling

 ✓ Deliberative Process

Therefore, taken along with the other input for this application from OCC, the Division now considers OCC's review of this NDA complete and all issues raised by OCC regarding this NDA addressed.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Kimberly Compton
9/25/2006 04:12:55 PM
CSO

Sara Stradley
9/25/2006 04:21:11 PM
CSO

From: Compton, Kimberly
Sent: Monday, September 18, 2006 11:01 AM
To: Levin, Penny; 'Marchione, Carol'
Cc: Compton, Kimberly
Subject: Agency response to your 9-14-06 submission

Hi Penny and Carol,

We have looked over your draft response submission you emailed on 9-14-06 and we have the following comment.

2. FDA requested that we assess signal detection by looking at 2 consecutive quarters instead of 3 consecutive quarters as proposed.

After discussion with the Agency, agreement was reached that Cephalon would review the data over 3 consecutive quarters for the first year post-approval and then review the data from quarter to quarter for signal detection in subsequent years. The RiskMAP Section 4.1 has been modified to reflect this change and is included with this submission.

FDA Response: Although FDA agreed that Cephalon would review the data for signal detection over 3 consecutive quarters for the first year (and quarterly thereafter), the Agency asked that the sponsor share their data on a quarterly basis and that we may ask for early intervention if an important increase is noted.

Please revise this section accordingly and officially submit your response to include this revision. Please contact me with any questions.

Thanks,
Kim

Kimberly Compton

Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products (HFD-170)
301-796-1191

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/s/

Kimberly Compton
9/18/2006 03:52:54 PM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: September 15, 2006

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology Products
(HFD-170)

Through: Deborah B. Leiderman, M.D., M.A. Director
Controlled Substance Staff (HFD-009)

From: Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

Subject: NDA 21-947 for fentanyl citrate effervescent buccal tablets (100, 200, 400, 600, 800 mcg) Risk Minimization Action Plan.
Indication: management of breakthrough pain in opioid tolerant patients with cancer.
Date of communications from Sponsor: September 7, 2006; September 12, 2006 and telecon on September 13, 2006
PDUFA Goal Date: September 25, 2006
Sponsor: Cephalon, Inc.

This memorandum comments on Cephalon's revised Risk Minimization Plan (RiskMAP) for **fentanyl citrate effervescent buccal tablets (100, 200, 400, 600, 800 mcg)**. Please refer to prior CSS consultations on NDA 21-947 (DFS, NDA 21-947, Executive Summary dated May 9, 2006; Review dated May 17, 2006; RMP Recommendations dated June 6, 2006, and September 1, 2006).

In the most recent communications from Cephalon dated September 7 and September 12, 2006 and follow-up telecon on September 13, 2006, Cephalon addresses the Division, CSS and OSE's recommendations for changes to the label, the Medication Guide and promotional materials. In these submissions Cephalon also provides information regarding the frequency and type of reporting commitments, specifies rate calculations and proposes signal thresholds for capturing increases of misuse, abuse, diversion, deaths and accidental exposures.

Comparing the most recent proposed label for Fentora (September 13, 2006) with the recently revised label for Fentora (dated September 6, 2006), subtle but potentially significant differences in the wording of the Indication of the products were noted.

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/s/

Silvia Calderon
9/15/2006 01:22:01 PM
CHEMIST

Deborah Leiderman
9/15/2006 01:38:32 PM
MEDICAL OFFICER

3 Page(s) Withheld

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_____ 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 _____ in the proposed marketing brochures.

The brochures _____

_____ 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

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

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: September 1, 2006

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology Products
(HFD-170)

Through: Deborah B. Leiderman, M.D., M.A. Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

From: Geoffrey Zeldes, M.D., Pharm.D., Medical Officer
Controlled Substance Staff (HFD-009)

Subject: NDA 21-947 for fentanyl citrate effervescent buccal tablets (100, 200, 400, 600, 800 mcg) Risk Minimization Action Plan.
Indication: management of breakthrough pain in opioid tolerant patients with cancer.
Date of Submission: July 25, 2006
PDUFA Goal Date: September 13, 2006
Sponsor: Cephalon, Inc.

This memorandum provides CSS' comments on Cephalon's revised Risk Minimization Plan (RiskMAP) for **fentanyl citrate effervescent buccal tablets (100, 200, 400, 600, 800 mcg)**. Please refer to prior CSS consultations on NDA 21-947 (DFS, NDA 21-947, Executive Summary dated May 9, 2006; Review dated May 17, 2006; RMP Recommendations dated June 6, 2006; Sponsor's submission dated June 16, 2006 and Medical Officer's review dated June 27, 2006). CSS has identified the following deficiencies in the proposed labeling and RiskMAP for Fentora.

I- Labeling Issues

CSS proposes labeling changes in the package insert and the MedGuide.

In the package insert, CSS proposes changes regarding:

- the description of the effervescent technology and its association with a faster dissolution and absorption
- the amount of tablets to be used during titration and maintenance, and

- an editorial change to better reflect the risks associated with the use of fentanyl intravenously.

In addition CSS requests information regarding the type of advice that the Sponsor will provide through the toll free number listed in the label.

In the MedGuide, CSS proposes strengthening the warnings against sharing the medication and the risk of respiratory depression and death associated with the misuse and abuse of Fentora.

- Package Insert

CSS's proposed changes are listed below.

1) Effervescent Technology

Under the "Description" section, 3rd 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.

In the June 23, 2006 telecom, the Sponsor agreed not to use the term "effervescent" in describing the formulation. The Sponsor also agreed not to make reference to the _____ 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.

Promotional claims related to the _____ 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 _____ 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 the Sponsor in their June 16, 2006 submission. The

medication may harm or even kill the person for whom it has not been prescribed”, should be more prominent and deserves a separate paragraph.

- 2) 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.
- 3) Respiratory depression should be explained clearly in lay language.
- 4) 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.
- 5) All educational materials provided by the Sponsor should include warnings not to share Fentora or use it to treat other types of pain, such as pain not associated with cancer.

II- RiskMAP

CSS requests from the Sponsor the following.

- 1) 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.
- 4) Commitment from the Sponsor to submit expedited reports for the following:
 - All reports of death as the outcome,
 - All pediatric (0-16 years of age) exposure reports, regardless of intention and outcome,
 - All serious adverse events associated with medication errors, misuse, abuse and addiction.
- 3) 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.
- 4) Clearly propose interventions and specify quantitative thresholds for signals that will prompt those interventions and revisions to the RiskMAP during the post-marketing surveillance period.
- 5) Clarification of the role and responsibilities of the Cephalon External Advisory Board as well as its interaction with the FDA
- 6) 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.

- 7) Cephalon proposes to use DAWN Live! as a source of medical examiners' 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).
- 8) Cephalon proposes to use DAWN Live! to monitor emergency department 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).
- 9) The Sponsor should use 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.
- 10) Sponsor should provide information on how it is planning to capture fatalities associated with the use of their product.
- 11) Educational materials for both the physician and patient should be revised and the Sponsor should honor commitments made at the June 23, 2006 telecom.
- 12) Overall, the educational pieces should incorporate a stronger message to convey the risks of overdose associated with the product.

III- Proposed Website

- 1) More emphasis on risks of overdosing or sharing this medication.
 - 2) Remove ~~_____~~
 - 3) It has been noted that the Fentora health care providers' web site ~~_____~~
- / / /

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/s/

Geoffrey Zeldes
9/1/2006 01:33:45 PM
MEDICAL OFFICER

Silvia Calderon
9/1/2006 01:51:04 PM
CHEMIST



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 _____

- 2. Remove any presentation of information that _____

- 3. Reference is made _____ throughout the RiskMAP. To avoid any terminology that might promote off-label use of Fentora, replace _____ 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



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 _____



The aforementioned statements and graphics in addition to other references _____ appear throughout the Fentora product information _____

_____ Remove all references from the product information.

4. Use of Abbreviations

The abbreviations BTP (breakthrough pain), _____) 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.

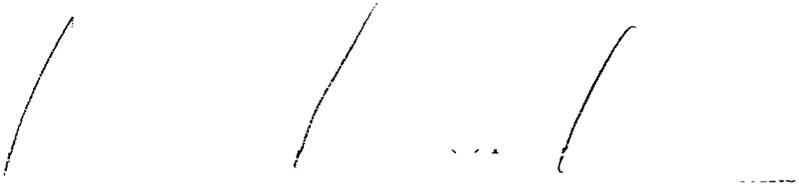
The FDA in conjunction with the Institute for Safe Medical Practice (ISMP) launched a campaign on June 14, 2006 to reduce medication mistakes caused by unclear medical

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

5.



6.



7. Tablet Color

The [redacted] has pictures of all white tablets while the website presents pictures of [redacted]. Revise pictures to the correct color scheme.

8. Correct Administration

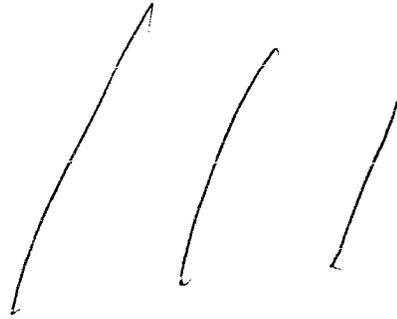
a. Fentora is to be placed above a rear molar tooth between the upper cheek and gum. However, the picture below from the website [redacted]

[redacted] 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 [redacted]





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

- e. Pharmacist and Physician Survey Instruments – The instruction to the interviewer administering the survey states

[Handwritten scribbles and lines, possibly representing redacted or illegible text]

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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this page is the manifestation of the electronic signature.**

/s/

Sara Stradley

8/29/2006 06:46:55 PM

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: August 29, 2006

TO: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Office of Surveillance and Epidemiology

FROM: OSE Fentora RiskMAP Review Team

DRUG: Fentora (Fentanyl Buccal Tablets)

NDA#: 21-947

SPONSOR: Cephalon, Inc.

SUBJECT: Review of Final Fentora RiskMAP, submitted July 25, 2006

PID #: 2006-166

INTRODUCTION

The purpose of this memorandum is to provide the Office of Surveillance and Epidemiology's (OSE) view on the final RiskMAP for Fentora, submitted to FDA on July 25, 2006. Fentora is a potent rapid onset oral opioid analgesic proposed for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain. Its use is contraindicated for management of acute or post-operative pain. The Sponsor received an approvable letter from FDA on June 29, 2006, indicating that a submission of the final RiskMAP was required in order to obtain FDA approval of Fentora.

In this document, we reviewed our original recommendations and the Sponsor's revisions to determine if they were adequate. We additionally reviewed the new materials submitted by the Sponsor including the labeling, packaging, education materials, and surveys.

3 SUMMARY OF THE SPONSOR'S FINAL RISK MINIMIZATION ACTION PLAN (RISKMAP)

The Sponsor's has developed a RiskMAP entitled the SECURE (Solutions through Education, Communication and Understanding Risk Minimization Excellence) Program. The goals of the program are:

- Fentora should be used only by opioid tolerant individuals
- Abuse, misuse and diversion of Fentora should not occur
- Unintended (accidental) exposure to Fentora should not occur

We describe below the basic tool categories and specific tools of the RiskMAP. Our comments on the final RiskMAP are included in Section 5 (pages 8-14) of this review.

3.1 TARGETED EDUCATION AND OUTREACH³

The Sponsor plans to utilize the following education and outreach tools:

- Package Insert (prescribers and pharmacists) – includes a boxed warning about the life-threatening risks associated with the use of Fentora in opioid non-tolerant individuals.
- / / / /
- Carton label (patients and pharmacists)
 - includes the warnings - “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”
 - includes a reminder checklist for the pharmacist to advise the patient that Fentora should be used only by opioid tolerant individuals and to encourage the patient to read the MG.
- Medication Guide (patients, pharmacists, and prescribers) – consistent with product labeling and will be included in the Fentora packaging and made available to all prescribers.
- Direct Risk Communication by Cephalon field representatives (prescribers and pharmacists) – in person visit by Cephalon field reps to prescribers and pharmacies
- Educational introductory letter (prescribers and pharmacists) – will be disseminated by direct mail to 10,000 physicians likely to prescribe Fentora and 3000 pharmacists
- / / / /
- PharmAlert (pharmacists) – this is a one page announcement of product availability that includes the box warning and directs readers to the company

³ The intended audience of the Targeted Education and Outreach tools is in parenthesis.

website for more information on the product and the RiskMAP. It will be distributed to 40,000 retail pharmacists.

- Physician education offered by Pain Centers of Excellence (prescribers) – the Sponsor will contact each of the identified top 25 Pain Centers of Excellence to offer further educational opportunities to learn about Fentora. The platform for these offering will include symposia and/or teleconferences and will incorporate key messages of the RiskMAP.
- Counseling messages (pharmacists and patients) - risk information will be provided to First Data Bank and/or other major publishers of pharmacy counseling software.
- Counseling aids/brochures (patients, pharmacists, and prescribers) – these are to be used by HCPs when advising and educating patients about Fentora.
- Physician education (prescribers) - professional societies will be contacted to offer educational opportunities to learn about Fentora. The platform for these offering will include symposia and/or teleconferences and will incorporate key messages of the RiskMAP.
- Pharmaceutical compendia (prescribers and pharmacists) – Cephalon will provide Fentora information to drug compendia including the Physician’s Desk Reference, American Hospital Formulary Service (AHFS), and Drug Facts and Comparisons.
- RiskMAP Speaker Training (prescribers) – Cephalon will formally train speakers on aspects of Fentora, the risks, and the RiskMAP.
- RiskMAP training (Cephalon field representatives) – training on the RiskMAP will also be provided to Cephalon Field Reps.
- Website (prescribers, pharmacists, and patients) – will be for all audiences and will include general product information as well as information about the RiskMAP.

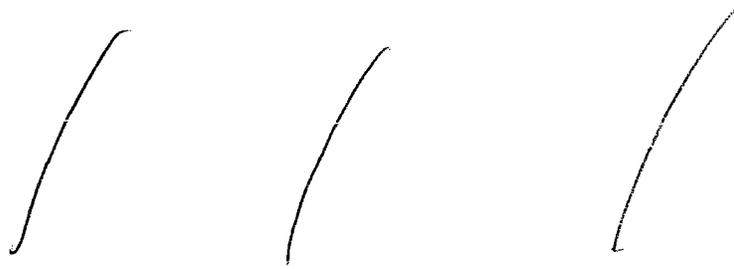
Most of the educational and outreach tools described above (aside from the FDA approved packaging and labeling) to prescribers and pharmacists include general product information or are promotional in nature. We do note however, that the key risk messages (use only in opioid tolerant patients, risk of abuse and misuse, as well as risk to children with accidental ingestion) are generally consistent with the information in the product label and medication guide. Specific comments on these tools are included in Section 5 of this review.

3.2 REMINDER TOOLS

The Sponsor plans to utilize the following reminder tools:

- Carton label - serves as an education tool and as a reminder to pharmacists. It includes:
 - the warnings - “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 for the pharmacist to advise the patient that Fentora should be used only by opioid tolerant individuals and to

- Methadone Clinics



4.2 SPONTANEOUS REPORTS

In addition to the post-marketing reporting requirements under CFR 314.80, the Sponsor plans to submit the following types of reports to the Agency in an expedited fashion:

- Any reports of serious adverse events that may be associated with abuse, misuse and diversion
- All accidental exposures regardless of whether they are symptomatic or asymptomatic

In a Discipline Review (DR) letter sent to the Sponsor on May 19, 2006, the Agency requested that the sponsor submit the following types of reports in an expedited fashion:

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

In response to the DR letter, the Sponsor submitted an amendment stating that they would commit to submitting the referenced reports as 15 day Alerts; however, this commitment is not reflected in this final RiskMAP submission.

4.3 SURVEYS

The Sponsor plans to measure knowledge, attitudes, and behaviors associated with the Fentora RiskMAP utilizing three separate surveys targeted at the three intended audiences: prescribers (physicians), pharmacists, and patients.

- Physician Surveys – physician surveys will be conducted via telephone by an independent third party research vendor. It will be repeated every 6 months for the first two years of the program and results will be evaluated after each 6 month interval. The sample frame will include all physicians who wrote at least one prescription for Fentora in the previous six months. The Sponsor will analyze the survey results by two cohorts: those who have seen Cephalon representatives in a

consistent manner and those who have not. The Sponsor plans a sample frame in order to obtain a sample of 110 physician completers of the survey.

- Pharmacist Surveys - pharmacist surveys will be conducted via telephone by an independent third party research vendor. It will be repeated every 6 months for the first two years of the program and results will be evaluated. The sample frame will include a list of pharmacies who ordered Fentora in the previous 3 months. They plan to screen 6,160 pharmacists in efforts to obtain 40 completed surveys. Respondents will be recruited ahead of time.
- Patient Surveys – patient surveys will be conducted every 6 months for the first two years post launch. The Sponsor anticipates a sample frame of 300 patients. Surveys will be conducted in a similar fashion as was done with Actiq via participating chain pharmacy call-back to patients dispensed Fentora. One pharmacy chain will conduct patient surveys during the launch phase.

4.4 PATIENT LONGITUDINAL DISPENSING DATA

The Sponsor states that they will examine purchasing longitudinal data as a surveillance tool to assess the degree to which Fentora is prescribed to patient who have a recent prescription for another opioid medication. The Sponsor plans to determine if another opioid medication was prescribed in that month or previous months prior to the Fentora prescription. The resulting measure will be a ratio of Fentora prescriptions that are given to a patient who has had recent opioid prescription over all Fentora prescriptions. The information will be updated monthly and part of the quarterly report.

4.5 OTHER SURVEILLANCE ACTIVITIES

The Sponsor mentions that interventions may be warranted as follow-up to surveillance and monitoring activities. These interventions are generally described as education or community outreach.

4.6 TARGET GOALS

The Sponsor did not set a standard for acceptable compliance for meeting the RiskMAP goals but stated that they will conduct bi-annual external Advisory Board meetings composed of external experts to review the RiskMAP.

4.7 TIME FRAMES AND PROGRESS REPORT SUBMISSION

The Sponsor plans to enter all data from surveillance and monitoring activities into a RiskMAP relational database. The Sponsor plans to evaluate the RiskMAP quarterly for the first two years with a report of the evaluation submitted to FDA. Subsequent evaluations will be made on an annual basis.

Comments on Education and Outreach Tools

1. Use of

~~_____~~
~~_____~~
~~_____~~
~~_____~~

Recommendation: All references to _____ should be removed from the product information.

~~_____~~
~~_____~~

2. Use of Abbreviations

The abbreviations BTP (breakthrough pain) 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 increase the potential for confusion. The FDA in conjunction with the ISMP launched a campaign on June 14, 2006 to reduce medication mistakes caused by unclear medical abbreviations.

Recommendation: In order to comply ISMP's campaign, we request all uses of the abbreviations "BTP," _____, " be removed from all Fentora product information.

3.



4. (



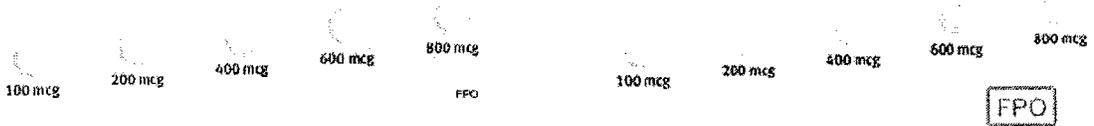


Recommendation: Remove these statements from all Fentora product information.

5. Tablet Color

The ' _____ ' has pictures of all white tablets meanwhile the website presents pictures of _____

Recommendation: Pictures need to be revised to the correct color scheme.



Core Sales Aid

Website

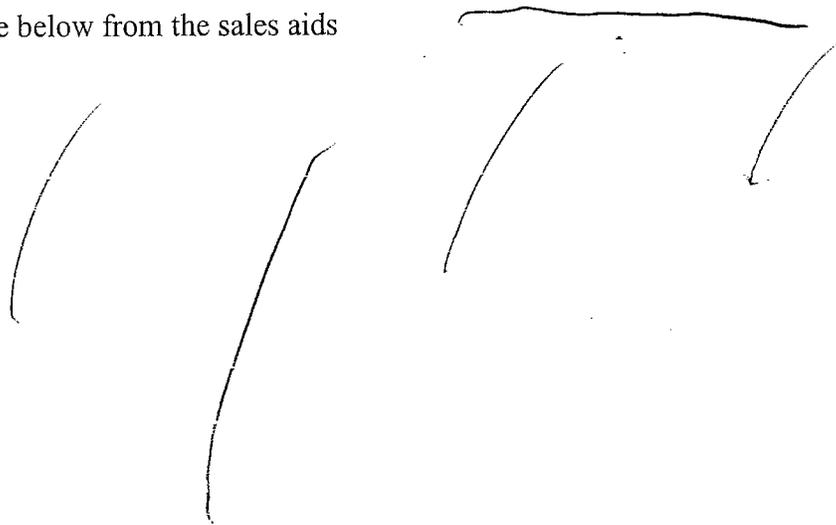
6. Correct Administration

- a. Fentora is to be placed above a rear molar tooth between the upper cheek and gum. However, the picture below from the website _____ Patients often heavily rely on pictures with regard to correct administration of drug products.

Recommendation: Revise this picture to reflect correct administration of the tablet.



- b. The picture below from the sales aids _____



are not representative because participation of hospitals and the completeness of data vary.

Recommendations:

- ***DAWN Live! should function more as an early warning surveillance system of possible cases of drug misuse abuse and problems with the drug. If the sponsor were to gain access to DAWN Live!, we recommend the sponsor gain access to all their 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, the Sponsor should work to understand the source of this increased risk and work with the FDA to develop more effective risk management strategies.***
- ***Little information was provided on how the sponsor plans to use data from TESS. We encourage the Sponsor to _____***

2. Surveys

- a. General Survey Methodology - In several places in the submission (between pages 40-43), the Sponsor indicates that they will evaluate and potentially modify the methodology: questions, sample frame, sample size, and time frames.

Recommendation: The Sponsor should notify FDA 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, ' _____ of _____

Recommendation: Revise to say, _____

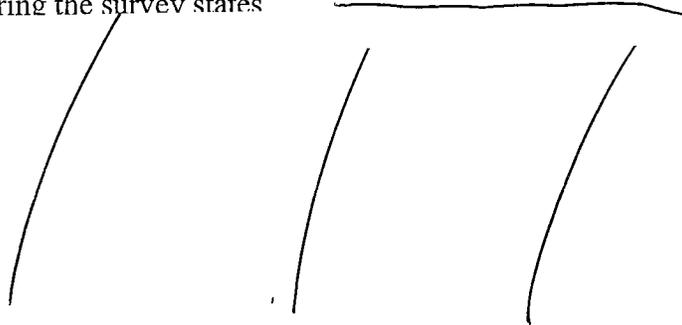
- c. Pharmacist _____ Survey Methodology - On p42 of the submission, the Sponsor indicates that "respondents for this survey will be recruited ahead of time." We question the need for this recruitment step.

Recommendation: For purposes of reaching adequate sample size, it would decrease drop-out if the Sponsor completed the interview as soon as the pharmacist _____ 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.

Recommendation: The sample should be determined regardless of whether the physician has seen a sales rep. _____

- e. Pharmacist and Physician Survey Instruments – The instruction to the interviewer administering the survey states “



6 CONCLUSIONS

The OSE has reviewed the submitted final RiskMAP for Fentora and has found it to be acceptable with the modifications recommended above.

**APPEARS THIS WAY
ON ORIGINAL**

ODS Fentora RiskMAP Review Team

Gita Akhavan-Toyserkani, Pharm.D., Safety Evaluator, DDRE

Kristina C. Arnwine, PharmD, Safety Evaluator, DMETS
Nancy Clark, Pharm.D., Project Manager, DSRCS
Mary Dempsey, Project Management Officer, OSE IO
Jodi Duckhorn, MA, Patient Information Team Leader, DSRCS
Cathy Dormitzer, Ph.D., Epidemiologist, DDRE
Carol Holquist, R.Ph., Director, DMETS
Lauren Lee, Pharm.D., Safety Evaluator Team Leader, DDRE
Claudia Karwoski, PharmD, Scientific Coordinator, OSE IO
Toni Piazza-Hepp, Pharm.D., Deputy Director, DSRCS
Denise Toyer, PharmD, Deputy Director, DMETS
Mary Willy, Ph.D., Senior Drug Risk Management Analyst, OSE-IO (detail)

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/s/

Mary Dempsey
8/29/2006 03:22:55 PM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
8/29/2006 03:50:09 PM
MEDICAL OFFICER

MEMORANDUM**Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
WO 22, Mailstop 4447, HFD-420
Center for Drug Evaluation and Research**

To: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia and Rheumatology Products
HFD-170

Through: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: August 1, 2006

Subject: OSE Review 05-0283-3, Fentora (Fentanyl Buccal Tablets) 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg; NDA 21-947

This memorandum is in response to a July 25, 2006 request from your Division for a re-review of the proprietary name, Fentora. Revised container labels, carton and insert labeling were submitted for review and comment. The sponsor's July 25, 2006 resubmission of their risk management plan will be reviewed under separate cover.

The sponsor, Cephalon, Inc., initially submitted the proposed name _____ which was found to be _____ by the Division of Drug Marketing, Advertising, and Communication (DDMAC). The review division concurred with DDMAC's assessment and DMETS did not conduct a safety review of the proposed name _____. Subsequently, the sponsor submitted the proposed name _____ which was found unacceptable by DMETS in ODS Consult 05-0283 dated April 12, 2006. As a result, the sponsor submitted the proposed name Fentora which was initially found acceptable in OSE Consult 05-283-1 dated June 27, 2006. Since the initial review of Fentora, DMETS has not identified any additional names with the potential for sound-alike and/or look-alike confusion with Fentora.

DMETS previously reviewed the labels and labeling of this NDA in the ODS review 05-0283 dated April 12, 2006. DMETS acknowledges that the sponsor has addressed most of our recommendations. However, DMETS has identified the following areas of improvement, which might minimize potential user error.

1. Blister Label

l l l l

2. Carton Labeling

- a. Revise the "DO NOT SWALLOW TABLET WHOLE," statement to read, ' _____ to help ensure correct administration of Fentora tablets.
- b. Include ' _____ prior to the statement "See insert for dosage and administration," so that it reads, " _____ See package insert."
- c. Revise the net quantity to read _____ to more accurately reflect the packaging configuration.

3. Package Insert Labeling

Disposal of Fentora Section – Include explicit instructions with regard to how to dispose of Fentora tablets once they are no longer needed (e.g., flush down the toilet) in order to decrease the potential for accidental exposure to unintended patients.

In summary, DMETS has no objections to the use of the proprietary name, Fentora. Additionally, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the name, Fentora, acceptable from a promotional perspective. Please submit revised drafts of container labels, carton, package insert, and patient package insert labeling when available for review and comment. Risk management recommendations will be forwarded under separate cover. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Diane Smith at 301-796-0538.

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/s/

Kristina Arnwine
8/17/2006 11:46:48 AM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
8/17/2006 11:59:40 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
8/17/2006 01:27:57 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/17/2006 02:24:03 PM
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-947

Cephalon, Inc
c/o CIMA Labs
41 Moores Road
Frazer, PA 19355

Attention: Carol S. Marchione
Senior Director, Regulatory Affairs

Dear Ms. Marchione:

We acknowledge receipt on July 25, 2006, of your July 25, 2006, resubmission to your new drug application for FENTORA (fentanyl buccal tablets).

We consider this a complete, class 1 response to our June 29, 2006, action letter. Therefore, the user fee goal date is September 25, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a waiver of pediatric studies for ages 0 to less than 6 years and a deferral of pediatric studies for 6 to 18 years for this application. Once the application has been filed, we will notify you whether we have waived and/or deferred the pediatric study requirement for the specified age groups for this application.

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Kimberly Compton
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CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO22, Mail Stop Room 4447)**

DATE RECEIVED: June 6, 2006	DESIRED COMPLETION DATE: July 6, 2006	OSE REVIEW #: 05-0283-1
DATE OF DOCUMENT: May 26, 2006	PDUFA DATE: June 28, 2006	

TO: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-170

THROUGH: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support

FROM: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME:
Fentora
(Fentanyl Citrate Buccal Tablet)
100 mcg, 200 mcg, 400 mcg, 600 mg, and 800 mcg

NDA#: 21-947

NDA SPONSOR: Cephalon, Inc.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Fentora. This is considered a final decision. If the approval of the NDA is delayed beyond 90 days from the signature date of this document, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.
2. DDMAC finds the proprietary name, Fentora, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
White Oak Bldg 22, Mail Stop Room 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 22, 2006

NDA#: 21-947

NAME OF DRUG: Fentora (Fentanyl Citrate Buccal Tablet)
100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg

NDA HOLDER: Cephalon, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170), for assessment of the proprietary name, Fentora, regarding potential name confusion with other proprietary or established drug names.

The sponsor, Cephalon, Inc., initially submitted the proposed name _____ which was found to be _____ by the Division of Drug Marketing, Advertising, and Communication (DDMAC). The review division concurred with DDMAC's assessment and subsequently, _____ was not reviewed by DMETS for potential look-alike and/or sound-alike confusion. Subsequently, the sponsor submitted the proposed name _____ which was found unacceptable by DMETS in ODS Consult 05-0283 dated April 12, 2006. As a result, the sponsor submitted the proposed names Fentora (primary) and _____ (secondary) for review by DMETS. Due to time constraints and in an effort to meet the PDUFA goal date of June 28, 2006, DMETS was not able to fully assess the secondary name _____. Thus, the proposed proprietary name, Fentora, is the subject of this review.

PRODUCT INFORMATION

Fentora is a potent opioid analgesic intended for buccal mucosal administration. Fentora is indicated for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain. The starting dose of Fentora is 100 mcg which is then titrated to an effective dose. A dose of Fentora may be repeated once during a single episode of breakthrough pain if pain is not adequately relieved 30 minutes after the initial dose. Fentora is supplied as 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg effervescent buccal tablets, which dissolve in the mouth when placed behind the rear molar teeth, rather than in water, are packaged in blister cards containing four tablets. Each carton contains seven blister cards.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Fentora to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Fentora. Potential concerns regarding drug marketing and promotion related to the proposed name(s) were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the name, Fentora, acceptable from a promotional perspective.
2. The Expert Panel identified six proprietary names that were thought to have the potential for confusion with Fentora. These products are listed in table 1 (see page 4, along with the dosage forms available and usual dosage.)

**APPEARS THIS WAY
ON ORIGINAL**

¹ MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA)

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name			Other*
Fentora		by mouth as needed	
Vytorin	Ezetimibe/Simvastatin Tablets 10 mg/10 mg, 10mg/20 mg, 10 mg/40mg, and 10mg/80 mg	10 mg/10 mg to 10 mg/80 mg by mouth once daily	SA
Pentasa	Mesalamine Capsules, controlled-release 250 mg and 500 mg	1 gram by mouth 4 times daily for a total dose of 4 grams for up to 8 weeks	LA
Antara	Fenofibrate Capsules 43 mg and 130 mg	43 mg to 130 mg by mouth once daily	SA/LA
Femara	Letrozole Tablets 2.5 mg	2.5 mg once daily	SA/LA
Fentuss	Guaifenesin/Hydrocodone Syrup 100 mg/5 mg per 5 mL	1 teaspoon to 3 teaspoons by mouth every 4 to 6 hours as needed	LA
Sufenta	Sufentanil Citrate Injection 50 mcg	1 mcg/kg to 3 mcg/kg	LA
Ventolin HFA	Albuterol Sulfate Aerosol 17 grams – 90 mcg per actuation	Inhale 2 puffs by mouth every 4 to 6 hours	SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Fentora with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 119 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Fentora (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> <p><i>Fentora</i> <i>100mg</i> <i>#120</i> <i>1 tablet QID</i></p>	<p>“The third prescription is for Fentora 100 mg, #120. 1 tablet qid.”</p>
<p>Inpatient RX:</p> <p><i>Fentolin 100mg QID</i></p>	

2. Results:

Two respondents in the inpatient written study misinterpreted the name as Fentolin. Fentolin may look and sound similar to the currently marketed U.S. product, Ventolin. See appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Fentora, the primary concerns related to look-alike and/or sound-like confusion with Vytarin, Pentasa, Antara, Femara, Fentuss, and Sufenta. Similarly, through independent review, one additional drug name, Ventolin HFA, was also determined to have potential for confusion with Fentora. Furthermore, two respondents in the inpatient written study misinterpreted the name as Fentolin, which may sound and look similar to the currently marketed product Ventolin HFA. However, when further comparing this name pair they lack convincing look-alike/sound-alike similarities in addition to having numerous differentiating product characteristics such as the product strength, indication for use, frequency of administration, route of administration, and dosage form. Thus Ventolin HFA will not be discussed further in this review.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Fentora.

1. Pentasa was identified as name that is similar in appearance to Fentora. Pentasa is a gastrointestinal agent indicated for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis. Depending on how the names are scripted, the beginnings of each name (Fent vs. Pent) can look similar, which is the primary contribution to the look-alike similarities between the names. Additionally, the endings of each name (-ora vs. -asa) can look similar as well (see page 6). Furthermore, both names contain an upstroke with the letter ‘t’ which also contributes to the look-alike similarities of each name.

fentora *pentasa*

With regard to product characteristics both Fentora and Pentasa are solid oral dosage forms (buccal tablet vs. capsule). Although there is no set dosing schedule for Fentora (as needed for breakthrough pain)

Pentasa is taken four times daily. However, Fentora and Pentasa do not overlap with regard to product strength, as Fentora is available in 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg tablets and Pentasa is available as 250 mg and 500 mg tablets. Additionally, the usual dose of Fentora ranges from 100 mcg to 800 mcg and the usual dose of Pentasa is 1 gram. Overall, despite some orthographic similarities, the differing product strengths and usual doses minimizes the potential for confusion between Fentora and Pentasa.

2. Vytarin was identified as a name that sounds similar to Fentora. Vytarin is an antihyperlipidemic combination product indicated for the treatment of primary hypercholesterolemia and homozygous familial hypercholesterolemia (HoFH).

The second and third syllables of each name sound similar (TOR-ah vs. TOR-in) which is the primary contribution to the sound-alike similarities between the names. However, the first syllable of each name differs phonetically (Fen vs. Vy), which helps to distinguish the names from each other. Although both Fentora and Vytarin are oral tablets, the two products do not overlap with regard to any other product characteristics. Fentora is dosed as needed, However, Vytarin has a scheduled dose of once daily. Furthermore, Fentora and Vytarin do not share commonalities with regard to product strength (100 mg, 200 mcg, 400 mg, 600 mcg, and 800 mcg vs. 10 mg/10 mg, 10mg/20 mg, 10 mg/40mg, and 10mg/80 mg) or usual dose (100 mcg to 800 mcg vs. 10 mg/10 mg to 10 mg/80 mg). Additionally, since Fentora is a schedule II narcotic, there is low likelihood that it will be ordered verbally, thereby helping to decrease the potential for verbal confusion. Overall, the differing product characteristics in addition to the context of prescribing for Fentora decrease the potential for confusion between Fentora and Vytarin.

3. Antara was identified as a name that sounds and looks similar to Fentora. Antara is a fibric acid derivative indicated for adjunctive therapy in the treatment of hypercholesterolemia and hypertriglyceridemia. The second and third syllables of each name may sound similar when pronounced (TOR-ah vs. TAR-ah). However, the first syllable of each name (Fen vs. An) differs, which may help to distinguish the two names from each other. The last four ending letters in each name (tora vs. tara) can look similar when scripted. However, the beginning portion of each name (Fen vs. An) appears to be distinguishable when scripted.

fentora *Antara*

With regard to product characteristics, both Fentora and Antara are solid oral dosage forms (tablets vs. capsules). However, the products do not overlap with regard to any other product characteristics. Fentora is dosed as needed. However, Antara has a scheduled dose of once daily. Fentora and Antara do not share common product strengths as Fentora is available in 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg tablets and Antara is available in 43 mg and 130 mg capsules. In addition, the two products have differing usual doses (100 mcg to 800 mcg vs. 43 mg to 130 mg). Furthermore, since Fentora is a schedule II narcotic there is a low likelihood that it will be ordered verbally, thereby helping to decrease the potential for verbal confusion. Overall, despite some orthographic

and phonetic similarities, the differing product characteristics in addition to the context of prescribing for Fentora decrease the potential for confusion between this name pair.

4. Femara was identified as a name that sounds and looks similar to Fentora. Femara is an aromatase inhibitor indicated for use as an adjuvant treatment of early breast cancer and for first-line treatment of locally advanced or metastatic breast cancer. The beginnings of each name look and sound similar (Fen vs. Fem) which is the principal contribution to the similarities between the names. Additionally, the endings of each name (ora vs. ara) can look and sound similar as well. However, the letter 't' in Fentora gives an upstroke characteristic to the name, which may help to distinguish the two names orthographically and phonetically.



With regard to product characteristics, both Fentora and Femara are oral tablets used to treat cancer patients allowing for potential overlapping patient and prescriber populations. However, there are different product characteristics which may minimize the potential for confusion. Fentora is dosed 100 mcg to 800 mcg as needed, _____ Conversely, Femara has a scheduled dose 2.5 mg once daily. Additionally, the two products do not share common product strengths (100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg vs. 2.5 mg). Furthermore, since Fentora is a schedule II narcotic there is a low likelihood that it will be ordered verbally, thereby helping to decrease the potential for verbal confusion. Thus, despite potential for overlapping patient and prescriber populations, the differing product characteristics such as the differing usual doses and product strengths in addition to the context of prescribing for Fentora decrease the potential for confusion between Fentora and Femara.

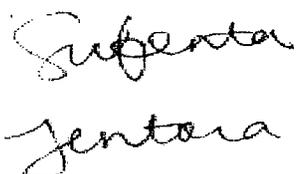
5. Fentuss was identified as a name that looks similar to Fentora. Fentuss is an oral antitussive indicated for the temporary relief of non-productive cough. Both names begin with the letters 'Fent' which is the primary contributor to the look-alike characteristics of each name. Depending on how they are scripted, it is possible for the endings of each name (tora vs. tuss) to look similar as well (see below).



With regard to product characteristics, both Fentora and Fentuss can be taken _____ daily (as needed _____ vs. every 4 to 6 hours as needed). Additionally, both products are taken by mouth. However, Fentora is supplied in tablets and Fentuss is a syrup, thus causing the prescribed dosing units to differ (mg or tablets vs. mL or teaspoons). Furthermore, the two products do not share common usual doses (100 mcg to 800 mcg vs. 1 teaspoonful to 3 teaspoonsful). Fentora and Fentuss also differ with regard to product strength (100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg vs. 100 mg/5 mg per 5 mL). However, since Fentuss is supplied as 100 mg of guaifenesin and 5 mg of hydrocodone per 5 mL, it is possible for prescribers to specify only the desired amount of guaifenesin, and omit the hydrocodone dose, and a product still be dispensed without further clarification from the prescriber. For example, the prescriber may order "Fentuss 100 mg four times daily as needed," which may look similar to "Fentora 100 mcg four times daily as needed." Upon

further examination, DMETS has learned that Fentuss has not been sold in the United States since 2001, which may help to decrease the potential for confusion between this name pair. Thus, despite some orthographic similarities, the differing product strengths decrease the potential for confusion between Fentora and Fentuss.

6. Sufenta was identified as a name that looks similar to Fentora. Sufenta is an opioid analgesic indicated for use as an analgesic adjunct for the maintenance of balanced general anesthesia in patients who are intubated and ventilated, as a primary anesthetic agent for the induction and maintenance of anesthesia, and as an analgesic for epidural administration combined with low-dose bupivacaine during labor and vaginal delivery. The first letter in each name (F vs. S) can look similar depending on how it is scripted. Additionally, both names contain the letters "fent" which may cause practitioners to confuse the two names. However, the letters are presented in different positions in each name which may help to differentiate the two names (see below).



Both Fentora and Sufenta are indicated for the relief of pain and both products are dosed in micrograms. Additionally, since the dose of Sufenta is weight based it is possible for Fentora and Sufenta to have overlapping doses (100 mcg to 800 mcg vs. 1 mcg/kg to 30 mcg/kg). However, the different dosage form and route of administration of each product (oral tablet vs. injection) may lessen the potential for confusion between this name pair. Due to the fact that Sufenta is an injection, it will most likely be limited to an inpatient setting, unlike Fentora which is likely to be used primarily in outpatient settings. Additionally, the two products do not overlap with regard to product strength (100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg vs. 50 mcg). In summary, despite the potential for overlapping doses, the orthographic differences in conjunction with the differing dosage forms, product strengths and contexts of use decrease the potential for confusion between Fentora and Sufenta.

Inpatient Written	Outpatient Written	Verbal
Fentara	Fentana	Centoria
Fentdia	Fentane	Centura
Fentdia	Fentara	Efentera
Fentoia	Fentara	Fentora
Fentolia	Fentara	Fentora
Fentolia	Fentara	Phentora
Fentolia	Fentara	Phentora
Fentolin	Fentara	Sentora
Fentolin	Fentara	Sentora
Fentora	Fentara	Sentora ? Fentora
Fentora	Fentara	Ventura
Fentora	Fentara	
Fentora	Fentasa	
	Fentora	
	Fintana	
	Fintora	
	Tenara	

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/s/

Kristina Arnwine
6/27/2006 04:24:50 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
6/27/2006 04:25:50 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/27/2006 04:33:18 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/27/2006 04:36:27 PM
DRUG SAFETY OFFICE REVIEWER

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Kimberly Compton
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CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 16, 2006

TO: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products

VIA: Kim Compton, Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Solomon Iyasu, M.D., M.P.H., Acting Director
Division of Surveillance, Research, and Communication Support

SUBJECT: ODS/DSRCS Review of Medication Guide for fentanyl citrate buccal tablet, NDA 21-947

Background and Summary

The sponsor submitted an NDA for fentanyl citrate buccal tablet, NDA 21-947 on August 31, 2005. The Patient Information Subcommittee met March 21, 2006, and agreed that a Medication Guide should be available to patients for products such as this that requires opioid tolerance for use.

Comments and Recommendations

1. We have revised the _____ to a Medication Guide (per CFR section 208) and used the recent review division changes to _____ as the source document for revisions. See the attached for our recommendations. We have simplified the wording where possible, made it consistent with _____ and removed unnecessary information.

2. The sponsor listed an _____

_____ / _____ / _____ / _____ / _____
For this reason, we recommend not listing the

Please let us know if you have any questions. We can provide a clean copy of the revised document in Word if requested by the review division.

_____ **Medication Guide**

c

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/s/

Jeanine Best
6/16/2006 03:08:50 PM
DRUG SAFETY OFFICE REVIEWER

Solomon Iyasu
6/16/2006 03:24:05 PM
MEDICAL OFFICER

From: Compton, Kimberly
Sent: Wednesday, June 07, 2006 4:54 PM
To: 'Levin, Penny'; Marchione, Carol
Cc: Diaz, Simon
Subject: FW: N 21-947-- Proposal regarding tablet colors
HI Penny,

I am running out the door (early for a change) but just got the OK on this info on coloring (tablets and lbg/blisters) and wanted to send to you to share with your team. If discussion is needed, we can pursue tomorrow.

Thanks,
Kim

After considering all the concerns and comments, we think that the following measures should address the safety issue surrounding the tablet colors:

1. The chosen color combination for the tablet strengths should be retained since the stability studies carried out on the colored tablets supports an expiration dating of 24 months.
2. Tablets should be debossed with the first letter of each strength (e.g. 1, 2, 4, 6, 8). Data has been provided indicating that debossing does not impact product quality or performance or stability.
3. The blister/carton colors should be revised to match the tablet colors
4. The blister/carton labels should display the debossed description prominently.

With this arrangement, there should not be any need for any post-approval activity with regard to color changes etc.

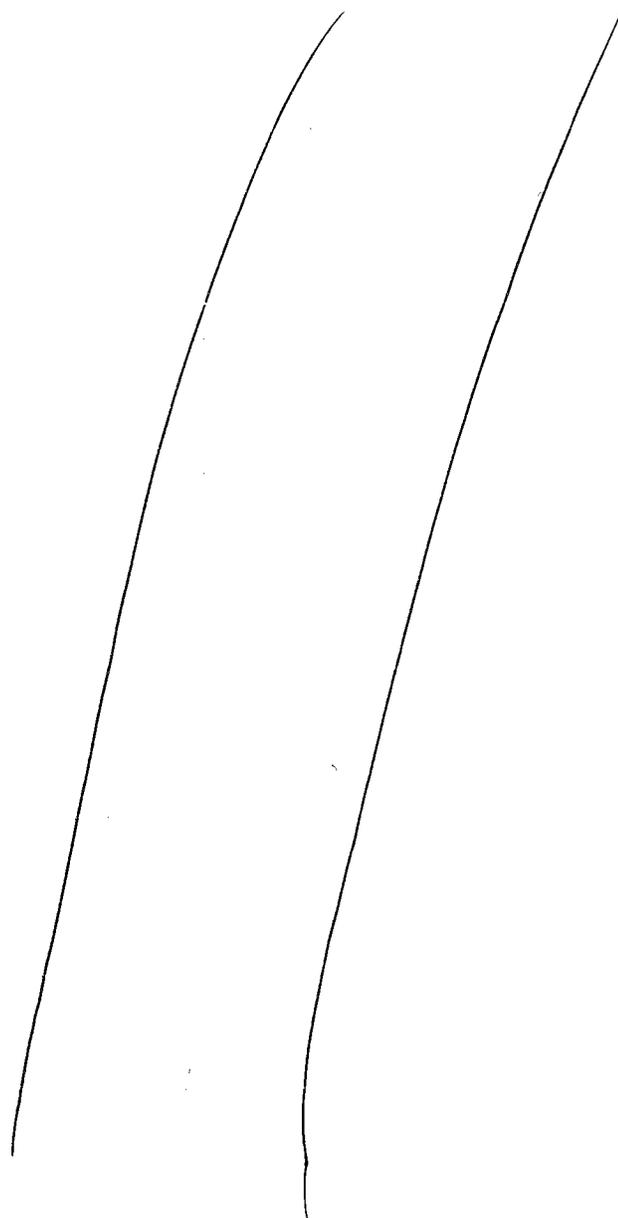
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/s/

Kimberly Compton
6/8/2006 06:42:34 PM
CSO

- 1.) As a means of understanding representativeness, provide non-response rates for the surveys and some information about those who decline participation in these surveys.
- 2.) A key risk not addressed in any of the surveys is accidental exposure to drug (any exposure, not just specific to pediatric exposure).

b. Patient Survey



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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 6, 2006

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology
Products (HFD-170)

From: Silvia Calderon, Ph.D., Team Leader
Deborah Leiderman, M.D., Director
Controlled Substance Staff (HFD-009)

Subject: Consultation NDA 21-947 for Fentanyl Effervescent Buccal Tablets (100, 200, 400, 600, 800 mcg). Recommendations regarding the proposed RMP.
Date of Submission: August 31, 2005
Sponsor: Cephalon, Inc.

This memorandum is a follow up to the internal RMP meeting of June 1, which included ODS staff, Division staff and CSS, and responds to a request regarding specific recommendations to the Fentanyl Effervescent Buccal Tablets (FEBT).

RECOMMENDATIONS FOR THE FEBT RMP:

- 1- CSS's prior recommendations stand (DFS, NDA 21-947, Executive Summary, May 9, 2006 and Review, May 17, 2006).
- 2- Agreement exists among the CDER offices regarding the significant risks associated with the use of FEBT, particularly at the higher doses. FEBT poses risks as great as and in some respects greater than Cephalon's Actiq which was approved with an extensive RMP under Sub Part H. As a starting point all elements of the Actiq RMP should be implemented at a minimum.
- 3- In prior reviews, CSS proposed restricted distribution of FEBT to assure prescribing by qualifying physicians and dispensing of the product to appropriate patients and to those patients who will follow the conditions of use. Restricted access tools used in other RMPs include: product dispensed by a central pharmacy, patient and physicians registries, or dispensation of the product only to patients with evidence of safe and appropriate use of the product.
- 4- The prescribing of FEBT should be limited to the indication of cancer-related pain in appropriate opioid tolerant patients maintained on longer acting potent opioids. Prescribing should be limited to oncologists and to physicians who are actively treating patients with malignancy related pain, who are knowledgeable of and skilled in the use of high dose, high potency opioids to treat cancer pain.

- 5- The Actiq label calls for the following titration plan: "ACTIQ should be individually titrated to a dose that provides adequate analgesia and minimizes side effects. If signs of excessive opioid effects appear before the unit is consumed, the dosage unit should be removed from the patient's mouth immediately, disposed of properly, and subsequent doses should be decreased." Since the FEBT formulation does not allow for interruption of the dosing, during titration phase, patients, family members and caregivers should be instructed on how to recognize signs of respiratory depression and specifically be instructed of potential side effects of the medication.
- 6- Limit quantity dispensed for patient and household member safety:
During the titration phase it is recommended that physicians prescribe an initial supply of six 100 mcg units. At each new dose of FEBT during titration, it is recommended that only six units of the next higher dose be prescribed. A limited supply of the medication during titration will allow re-evaluation of the patient and a chance for the physician to query the patient on his or her understanding of the safe and appropriate use of the medication.
- 7- Once a stable dose is selected following titration, no more than a two week supply of FEBT should be prescribed. In patients and homes at high risk (e.g. children or adolescents, extended family etc), consider even smaller quantities. Provide child secure container.
- 8- Include on the shelf carton a checklist for the pharmacist. This checklist should remind the pharmacists to make sure the patient is already taking opioids chronically, to counsel the patient about child safety, to encourage the patient to read the Medication Guide, and to counsel the patient about the safe use of FEBT and potential side effects.
- 9- Educational Programs directed to all audiences should include these key messages, in addition to the Sponsor's proposed key messages:
 - *Definition of the appropriate treatment population and proper patient selection.* FEBT SHOULD ONLY BE USED BY OPIOID TOLERANT PATIENTS. The Sponsor's proposed black boxed warning should clearly convey this message. In addition this message should be located underneath the Brand Name.
 - *Risks and Safety messages.* Physicians and patients must understand and accept responsibility for appropriate use of FEBT. The risks of overdose--unintentional or otherwise--should be properly addressed and explained.
 - *Risks of abuse, diversion, and theft.* Physicians and patients need to know that the high concentration of fentanyl in FEBT makes this product a target for theft and diversion. The black boxed warning should clearly warn patients about the dangers of accidental ingestion, non-medical use, overdose and risk of abuse of the product. Specifically, the black boxed warning should state the Schedule II status of the medication and the high abuse potential.
- 10- Develop specific education programs for the prescriber to ensure that the product is used only in opioid tolerant patients utilizing very strict criteria. These programs should also alert the prescriber to inquire about home settings and whether children could potentially be exposed to the product.

- 11- Patients and family members must be warned about the risk of respiratory depression, unconsciousness and death if a child inadvertently swallows this medication. Specific educational programs would include instructions on monitoring for respiratory depression and how to perform rescue breathing.
- 12- An educational kit should be planned for issue to patients with the first dispensing of product. The contents of the kit need to be described in the RMP. A method of surveying patients who have received this kit must be devised to measure the effectiveness of this strategy.
- 13- Sales representative training for this drug must be described. All promotional and educational materials should be submitted for prior review.
- 14- The Sponsor should be instructed to submit any reports related to pediatric and adolescent exposures regardless of the outcome or intent, off label use, misuse, and diversion to the FDA. Reporting frequency to the FDA needs to be defined.
- 15- The RMP should include specifics on how the Sponsor plans to monitor who is actually prescribing this product, how these restrictions will be enforced, and what will happen if other providers (e.g. dentists) start prescribing this drug. Tamper resistant mandatory prescription pads should be distributed for this product. CSS acknowledges that distribution of the product through a central pharmacy, as well as a patient registry might not be feasible considering the indication of the product.
- 16- Address the issues of accidental overdose in patients and unintended users. Specific plans need to be developed to actively monitor for these cases. DAWN "live" may be a useful tool to monitor for ED abuse related cases. The Sponsor should plan to monitor and submit reports from medical examiners, toxicology and poison control centers.
- 17- Periodically contact State Control Authorities and State Boards of Pharmacies to track and minimize abuse and diversion within respective states. Submit reports of abuse and diversion obtained in this way to the FDA as part of the RMP quarterly reports.
- 18- Develop a plan to survey patients (through pharmacy network and/or HMO/health insurance data) about receiving the proposed product to collect information about use, opioid tolerance, welcome kit and other RMP measures.
- 19- Consider limited roll out and active surveillance with quarterly reporting for first 2 years. Re assess after 1 yr.

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/s/

Silvia Calderon
6/6/2006 04:48:06 PM
CHEMIST

Deborah Leiderman
6/6/2006 04:56:23 PM
MEDICAL OFFICER



NDA 21-947

DISCIPLINE REVIEW LETTER

Cephalon, Inc
c/o CIMA Labs
41 Moores Road
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 fentanyl effervescent buccal tablets.

The Office of Drug Safety (ODS) review of your proposed RiskMAP is complete and we have identified the following deficiencies.

Bioavailability

1. We are concerned that this product may be mistaken for candy due to the size and color of the tablets. We also note the product which will cause the tablet to have a sweet taste. Because these tablets may be more attractive to children, it is imperative that all precautions be taken to ensure the product is kept out of the reach of children.

Revise the carton labeling so that a warning statement appears boxed and in bold type. It should be written in consumer-friendly language for easier comprehension.

2. The fentanyl buccal tablet is approximately two times as potent as the oral transmucosal system (Actiq). The warning included in the PRECAUTIONS section of the package insert concerning product equivalency is not adequate to ensure the understanding of these key differences.
 - a. Include a statement in the **BOXED WARNING** concerning the differences in product bioavailability.
 - b. Include a **BOXED WARNING** on the carton labeling which conveys that the products cannot be substituted. This statement should also refer health care professionals to the **DOSAGE AND ADMINISTRATION** section of the labeling for instruction on proper conversion between these product formulations.

- c. Test key safety messages in practicing health care professionals to determine the wording that will best convey this key message.

Educational Material

3. Your Health Care Provider Education should include the following:
 - a. A plan to ensure that practitioners understand that the oral fentanyl products are not equivalent on a mcg to mcg basis.
 - b. An explanation that fully describes conversion between products.
 - c. Clarification that this product is not intended for use in opioid naïve patients
 - d. A plan to ensure that practitioners understand and counsel patients on the proper administration of this drug (e.g., correct placement of the tablet in the mouth; instructions not to chew or swallow the tablet).
4. Your Patient Education should include the following:
 - a. Plans to educate patients to understand that these two oral fentanyl products are not the same and cannot be interchanged on a mcg per mcg basis or used concomitantly.
 - b. Plans to educate patients to understand the proper administration of this drug (e.g., correct placement of the tablet in the mouth; instructions not to chew or swallow the tablet)

Survey Methodology

5. Submit a more detailed description of your survey methodology, which includes (but is not limited to) answers to the following questions.
 - a. Who will receive the survey, how will the sample be determined, and what are the selection criteria?
 - b. What controls will they use to minimize bias?
 - c. What controls will they use to compensate for the limitations associated with their methodology?
 - d. How many physicians/pharmacists/patients will be surveyed?
 - e. How will the survey be administered?
 - f. What questions will be posed on the survey instrument?

6. You indicate in the RiskMAP that your surveys will be conducted every 6 months for two years, and that you will reevaluate the RiskMAP for possible modification.

Clarify if this reconsideration of the RiskMAP will occur with each 6 month evaluation, or at the end of the two year survey period. Also clarify how this information will be conveyed to FDA.

Claims

7. You proposed to use claims data to monitor prescribing patterns. We recommend the claims data provide adequate information on patients' opioid tolerance.

Literature Review

8. Include in your literature review a review of case reports and studies that specifically address safety concerns.

National Survey Review

9. You propose utilizing national surveys to find signals or patterns of abuse and diversion of your product. Your proposal has the following limitations:
 - a. You propose using the Drug Abuse Warning Network (DAWN) to track adverse events and propose comparing it to other fentanyl products. Pharmaceutical firms have access to DAWN *Live!* via an online query system and may receive information on an as needed basis. You have not provided information on how often you plan to access this information, nor what benchmarks will be used to detect a safety signal. Comparing your fentanyl product requires utilization on all comparators to be included in these comparisons.
 - b. Monitoring the Future (MTF) data which collects data on secondary school students, college students, and young adults currently does not collect information on fentanyl use.
 - c. The National Household Survey on Drug Use and Health also does not collect data on fentanyl use at this time.
10. Consider using the monitoring media surveillance, Key Informant Network, and Law Enforcement Drug Diversion Units as part of the pharmacovigilance plan.
11. Evaluate drug use trends in the following manner:
 - a. Use of sales and prescription data to monitor for disproportionate increases by geographic area
 - b. You plan to educate practitioners on how to deal with patients who may be doctor shopping; provide details of how doctor shoppers would be identified.

12. Create a 24-hour toll-free telephone number to provide medical information, receive adverse event information and address product complaints.

Post-Marketing Reporting

13. Submit the following as Post-marketing 15-day Alert Reports:
 - 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 outcome.
 - c. Any medication error reports regardless of patient outcome
14. Include a special section in the descriptive portion of your quarterly Periodic Reports describing the status of any efforts and data relating to your risk management plan. This section should include (but not be limited to) available data on the following:
 - a. Extent of use (denominator estimates)
 - b. Indicators of off-label use or inappropriate prescribing (i.e. opioid-naive)
 - 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.
15. Provide additional details and/or clarification on the following. Your response to these items is not required to continue our evaluation of your NDA.
 - a. Clarify what are the “25 Pain Centers of Excellence,” and how they will contribute to the dissemination of educational information.
 - b. Clarify whether educational materials targeted to health care professionals will convey the importance of counseling/educating patients on the appropriate and safe use of the product.
 - c. Clarify what is meant by “support independent continuing medical education.”

- d. Clarify how patients will learn that you accept returns for the disposal of unwanted drug (to minimize availability of excess product), e.g., information included in the Medication Guide, etc.
- e. Describe more fully what the "PharmAlert" tool for pharmacists consists of and how it will be distributed.
- f. Provide a description of how speakers will be chosen and how they will be trained.
- g. Describe the method(s) planned for returning drug product to you (e.g., prepaid special mailer provided to patients/hospitals upon request, etc.) and ensuring that diversion will be minimized during the return process.

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
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