CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022569Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 29, 2011
To:	Bob Rappaport, M.D., Director Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Through:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK)
From:	**Scientific Lead,** Doris Auth, Pharm.D., Risk Management Analyst **DRISK Review Team** Megan Moncur, M.S., Team Leader Kate Heinrich, M.A., Health Education Reviewer Brian Gordon, M.A., Social Science Reviewer Sharon Mills, BSN, RN, CCRP, Sr. Patient Labeling Reviewer **Division of Drug Marketing, Advertising and Communications (DDMAC)** Mathilda Fienkeng, Regulatory Review Officer (RRO) Twyla Thompson, RRO **Office of Compliance (OC)** Marcia Britt Williams, PhD; Director Regulatory
Subject:	Final Risk Evaluation and Mitigation Strategy (REMS) Review for Lazanda (Fentanyl) nasal spray
Drug Name (Established Name):	Lazanda, fentanyl citrate nasal spray
Dosage and Route:	Nasal spray 100mcg, 400mcg
Therapeutic Class:	Opioid
Application Type/Number:	NDA 22-569
Applicant:	Archimedes

1. INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that the Division of Risk Management (DRISK) review and evaluate the proposed Risk Evaluation and Mitigation Strategy (REMS) for Lazanda (Fentanyl) nasal spray.

1.1 Product Overview

Lazanda is a reformulation of fentanyl, a potent opioid analgesic, for administration via the nasal mucosa, and a member of a group of Schedule II controlled substances that the Agency has collectively termed transmucosal immediate release fentanyl (TIRF) products. Following nasal inhalation, appropriate doses of Lazanda should result in a reportable decrease in pain intensity within 15-30 minutes of administration. The proposed indication for Lazanda is for the management of breakthrough pain in patients with cancer, (b) (4), who are already receiving and who are tolerant to opiod therapy (b) (4)

Actiq, Fentora, Onsolis and Abstral are approved TIRF products, also indicated for the management of breakthrough pain in cancer patients who are already receiving and tolerant to opiod therapy. These formulations deliver fentanyl rapidly via the oral mucosa. Drug delivery in this manner eliminates first pass metabolism that occurs with oral formulations and results in increased bioavailability. Lazanda is the first of the transmucosal products to be delivered via the nasal mucosa. When Lazanda comes in contact with calcium ions in the nasal mucosa, the pectin in the solution forms a gel, which allows systemic absorption of fentanyl to occur.

The rate and maximum plasma concentrations vary considerably between the available TIRF products, as well as Lazanda, therefore, they are not interchangeable. Life-threatening respiratory depression may occur at any dose in the following situations: in patients who are not opiod tolerant, if accidentally consumed by a child or for anyone for whom they were not prescribed, or if used for the treatment of acute or postoperative pain. It is because of these risks that a REMS is required for the transmucosal immediate-release fentanyl products.

1.2 Regulatory and Review History for Lazanda

Lazanda (formerly referred to as (b) (4)) was submitted August 31, 2009 (NDA 22-569; Seq No. 000) and received a Complete Response (CR) letter on June 30, 2010. Issues cited in the CR included safety of container closure system, accuracy of dose counting mechanism, amount of residual volume of fentanyl solution following use, and the need for an assay for Burkholderia cepacia in the drug product, as well as in the purified water (b) (4)

Lazanda has been part of ongoing and interrelated discussions within the Agency that included the review teams for other TIRF products, and often involved Senior Management (see REMS Review dated 05/13/2010, Author: Akhavan Toyserkani, GA; and REMS Review dated June 29, 2010; Author: Moncur, M).

Following are highlights of key regualtory actions and communications for Lazanda, following the June 2010 CR:

30 September 2010: (Seq No. 0023) Class 2 Resubmission

28 October 2010: Meeting with all TIRF product sponsors (innovator and generic), to inform them that, in order to minimize the burden on healthcare providers and patients, a single-shared REMS should be implemented for the TIRF products (Meeting Minutes: memo dated 01/03/2011; Author: Adeolu, Abolade A).

12 November 2010: Pre-Approval REMS Notification letter; describing the elements of the TIRF single-shared REMS that could be standardized and implemented for each TIRF product individualy, and ultimately across all TIRF products collectively, as a single-shared REMS.

22 December 2010: (Seq N0. 0029) Submission of revised Lazanda REMS, revised to conform to the TIRF REMS standardized template.

31 January 2011: (Seq No. 0032) Submission; full set of website screenshots provided

15 February 2011: Teleconference with sponsor; communicated the need to harmonize the individual programs to facilitate the implementation of a single, shared system across all TIRF products.

03 March 2011: Teleconference with sponsor; communicated the need to develop additional REMS materials.

04 March 2011: Interim Comment Set #1 (1st set of comments on the December 2010 TIRF REMS submission) & Interim Comment Set #1.1 (Ed materials only)

20 March 2011: Interim Comment Set #2

28 March 2011: Review Extension-Major Amendment, PDUFA 30 June 2011 Extension to allow sponsor to conduct comprehension study of the instructions in the Medication Guide on how to prepare, use and dispose of Lazanda.

06 May 2011: Interim Comment Set #3 (e-mail)

15 June 2011: Interim Comment Set #4 (e-mail)

21 June 2011: Teleconference with sponsor

23 June 2011: Interim Comment Set #5 (e-mail)

27 June 2011: Submission final REMS for review (Seq No. 0040)

28 June 2011: Interim Comment Set #6 (e-mail)

29 June 2011: Submission of final agreed-upon REMS (Seq No. 0041)

1.3 Regulatory History for other TIRF Products

In October 2010, the Agency determined that in order to minimize the burden to healthcare providers and patients, the TIRFs should engage in a single-shared REMS system. Archimedes and the other TIRF innovator and generic sponsors received REMS Notification Letters (in October and November of 2010), describing the elements of the single-shared REMS system that could be implemented across all TIRF products, and

were instructed to revise their proposed REMS to conform to this program. Because the single-shared system will require substantial time to develop, each TIRF sponsor was instructed to develop and implement individual TIRF REMS, within six months of receiving the notification letter.

The TIRF REMS includes the following components: Medication Guide, Elements to Assure Safe Use (prescriber certification, pharmacy certification, and documentation of safe use conditions), an Implementation System, and a Timetable for Submission of Assessments.

An overview of the other TIRF products follows.

Actiq (oral transmucosal fentanyl citrate lozenge, Cephalon) was initially approved in November 1998 with a Risk Managent Plan (RMP). Actiq was identified as a product deemed to have a REMS under section 909(b) of FDAAA. **Fentora** (fentanyl effervescent buccal tablet, Cephalon) was approved in September 2006 and is commercially available under a RiskMAP. Shortly after approval, the Agency received reports of serious adverse reactions, including death due to prescribing in patients who were not opiod tolerant, and to inappropriate substitution with Actiq. The sponsor (Cephalon) was notified that a REMS would be required to ensure the benefits outweigh the risks of the drug. Cephalon, the sponsor for both Actiq and Fentora, has submitted a single REMS that includes both products. The Actiq/Fentora TIRF REMS is currently under review by the Agency.

Onsolis (fentanyl bioerodible mucoadhesive system, Meda) was approved in July 2009 with a REMS which included a Medication Guide, Communication Plan, Elements to Assure Safe Use, an Implementation System, and a timetable for submission of assessment of the REMS. The approved REMS requires prescriber and patient enrollment, verification of safe use conditions by a Call Center prior to dispensing, and distribution of Onsolis through a specialty pharmacy. The TIRF REMS for Onsolis is currently under review.

Abstral (fentanyl citrate sublingual orally disintegrating tablets, ProStrakan) was approved January 2011, and was the first TIRF product to be approved in with a REMS that conforms with the elements outlined in the October/November REMS Notification Letters.

There are approved generic versions of Actiq and Fentora.

2. METHODS

2.1 Analysis Techniques

The REMS proposal was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA) and consistency with the REMS notification letter dated November 12, 2010 and the Abstral REMS (fentanyl citrate, NDA 22-510) approved on January 7, 2011.

2.2 Data and Information Sources Reviewed

- Lazanda REMS submitted December 22, 2010; revised to conform to the TIRF REMS standardized template (Seq No. 0029)
    - REMS Amendment submitted January 31, 2011 (Seq No. 0032)
    - REMS Amendment received March 7, 2011 (e-mail)
    - REMS Amendment received May 18, 2011 (e-mail)
    - REMS Amendment received June 21, 2011 (e-mail)
    - REMS Amendments received June 22, 2011 (2 e-mails)
    - REMS Amendment submitted June 26, 2011 (Seq No. 0040)
    - REMS Amendment submitted June 29, 2011; final agreed-upon REMS (Seq No. 0041)

2.3 Data and Information Sources Referenced

- DRISK Memo. Reviewer: Akhavan Toyserkani, GA, dated May 13, 2010
- DRISK REMS Review. Reviewer: Moncur M, dated June 29, 2010
- DRISK REMS Review for Abstral. Reviewer:LaCivita C, dated December 22, 2010
- Lazanda Prescribing Information, submitted on September 30, 2010 submission, and revised on March 9, 2011.
- Chemistry Review of LAZANDA. Reviewer: Pinto, J, dated February 22, 2011
- Clinical Review of LAZANDA. Reviewer: Yip, L, dated 2 March 2011.
- Cross-Discipline Team Leader Review for LAZANDA. Reviewer: Shibuya RB, dated March 7, 2011.
- Controlled Substance Staff Review of LAZANDA. Reviewer: Gong JP, dated March 22, 2011.

3. PROPOSED LAZANDA RISK EVALUATION AND MITIGATION STRATEGY

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4. DISCUSSION AND RECOMMENDATIONS

An individual REMS will be implemented by Archimedes until a single-shared TIRF REMS system has been approved. The proposed LAZANDA REMS, submitted June 29, 2011, includes all the elements put forth in the Agency's TIRF REMS for a single-shared system, and addresses all comments conveyed to the sponsor, to date (as described in Section 1.2 of this document). The REMS elements include a Medication Guide, Elements to Assure Safe Use, an Implementation System, and a Timetable for Submission of Assessments.

The DRISK Review Team finds the proposed REMS for LAZANDA, as submitted June 29, 2011 (and appended to this review) to be acceptable.

16.1.1 REMS FOR NDA 022569: VERSION 9

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

DRISK INTERIM REMS REVIEW

REMS Comment Set # 1

Date: March 04, 2011

To: Bob Rappaport, M.D., Director
Division of Anesthesia and Analgesia Products (DAAP)

Through: Claudia Karwoski, Pharm.D., Director
Division of Risk Management (DRISK)

From: **Scientific Lead,**
Doris Auth, Pharm.D., Risk Management Analyst

DRISK Review Team
Megan Moncur, M.S., Acting Team Leader
Kate Heinrich, M.A., Health Education Reviewer
Brian Gordon, M.A., Social Science Reviewer

Subject: Interim REMS Review Comments for Lazanda

Drug Name (Established Name): Lazanda, fentanyl citrate nasal spray

Therapeutic Class: Opioid

Application Type/Number: NDA 22-569

Applicant: Archimedes

COMMENTS FOR DAAP

The following comments and questions are DRISK's preliminary review of the proposed Lazanda REMS. Please request that the applicant respond to these comments as soon as possible to facilitate further review. As we continue our review, we will provide additional comments.

Appended to this review is the REMS proposal including our track changes (see **Attachment A**). The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

COMMENTS AND QUESTIONS FOR THE SPONSOR:

We refer to the meeting held on October 28, 2010 and to the REMS notification letter for Lazanda dated November 12, 2010. We further refer to the teleconference on February 15, 2011, during which we communicated harmonizing the individual programs to facilitate the implementation of a single, shared system across all TIRF products. We also refer to the teleconference on March 03, 2011, in which we communicated the need for creation of additional REMS materials.

We acknowledge receipt of your proposed REMS for Lazanda included in your submissions dated December 22, 2010, and January 31, 2011. In the Lazanda REMS, you have proposed changes that do not conform with the standardized materials. You have not provided adequate justification for these changes, and in the interest of standardization, we are requesting that you conform the REMS to the template as we requested originally. The attached redline reflects the changes that are needed to conform to the template.

The comments below are based on the preliminary review of the Lazanda REMS and supporting materials. We hope you can provide replies quickly so that we can provide you final input on the REMS, REMS Materials and Supporting Document.

1. The REMS document has been revised to conform with the standardized materials. Please see **Attachment A** for a redlined version of the REMS document. NOTE: FDA has added text to the footer of this document, for document control purposes. This footer (red text) should be deleted in your final document.

2. As discussed in the February 15, 2011 teleconference, your proposed education program and knowledge assessment will require modifications. We will be providing you with specific comments under a separate cover.

3. As discussed in the March 03, 2011 teleconference, Dear Healthcare Provider Letter and Dear Pharmacist Letter distribution has been added to the REMS (under ETASU A and ETASU B, respectively). Refer to the Abstral REMS program 'Dear Healthcare Provider Letter,' 'Dear Outpatient Pharmacy Letter,' and 'Dear Inpatient Pharmacy letter,' create and submit these letters for the Lazanda REMS.

4. As discussed in the March 03, 2011 teleconference, REMS Program Overview materials are needed to inform enrollees about REMS program requirements and operations. Refer to the Abstral REMS program's "Prescriber Program Overview," "Overview for Outpatient Pharmacies," "Overview for Inpatient Pharmacies," and "Overview for Patients & Caregivers," and create and submit these materials for the Lazanda REMS program.

5. As discussed in the February 15, 2011 teleconference, please remove the (b) (4)

6. We recommend that you be mindful of any additional datafields that are being discussed for the single-shared system, and include them in your current program, to facilitate transitioning to the single, shared system.

7. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.

8. Submit the REMS and the REMS Supporting Document as two separate WORD documents.

9. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in WORD.

Attachment A

Lazanda REMS

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/s/

MEGAN M MONCUR
03/04/2011

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation II
Division of Anesthesia and Analgesia Products

NDA/BLA #s:	022569
Products:	Fentanyl citrate nasal spray
APPLICANT:	Archimedes Development Limited
FROM:	Bob A. Rappaport, M.D., Director, Division of Anesthesia and Analgesia Products
DATE:	June 16, 2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for fentanyl citrate nasal spray to ensure that the benefits of the drug outweigh the risks of overdose, abuse, addiction, and serious complications due to medication errors. In reaching this determination we considered the following:

A. The estimated number of patients in the United States with breakthrough cancer pain is between 1 to 2 million. This estimate is based upon the number of patients with cancer in the US (American Cancer Society), the proportion of cancer patients with moderate to severe pain[1], and the proportion of cancer patients with breakthrough pain.[2]

B. The patients for this product are cancer patients with pain that cannot be adequately controlled using around-the-clock oral or transdermal opioids alone. Many of these patients have multiple concurrent complications of their underlying disease and therapy.

C. The expected benefit of the drug to patients is that the delivery system is different from the existing oral transmucosal fentanyl products. This product is the first of these products to be formulated as a nasal spray.

D. The expected duration of treatment with the drug will be from days for the sickest patients who are preterminal, to months for patients with less tumor burden and longer prognoses for survival.

E. The most serious of the known adverse events that are related to the use of fentanyl-containing products include death, respiratory depression and CNS depression which occur primarily if the product is not used properly. In addition to the aforementioned risks, fentanyl nasal spray, as other fentanyl-containing products, can have a potential to increase intracranial pressure and induce bradyarrythmias.

F. Fentanyl citrate nasal spray is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for fentanyl citrate nasal spray. FDA has determined that fentanyl citrate nasal spray poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of fentanyl citrate nasal spray. FDA has determined that fentanyl citrate nasal spray is a product for which patient labeling could help prevent serious adverse effects and that has serious risks relative to benefits of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use fentanyl citrate nasal spray.

The elements of the REMS will be a Medication Guide, a communication plan, elements to assure safe use including prescribers training and certification under FDCA 505-1(f)(3)(A), pharmacies certification under FDCA 505-1(f)(3)(B), dispensing fentanyl nasal spray to patients with evidence or other documentation of safe use conditions under FDCA 505-1(f)(3)(D), an implementation system, and a timetable for submission of assessments of the REMS.

Bob A. Rappaport, M.D.
Director, Division of Anesthesia and Analgesia Products

[1] Marieke HJ, van den Beuken-van Everdingen MHJ, deRijke JM, Kessels SG, Schouten HC, van Kleef M, Patijn. High prevalence of pain in patients with cancer in a large population-based study in The Netherlands. Pain 2007;132:312-320.

[2] Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. Pain 1999;81:129-134.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	FENTANYL NASAL SPRAY

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/s/

MATTHEW W SULLIVAN
06/30/2010

BOB A RAPPAPORT
06/30/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 29, 2010
To:	Bob Rappaport. M.D., Director Division of Anesthesia and Analgesia Products (DAAP)
Thru:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK)
From:	**Scientific Lead:** Megan Moncur, MS, Risk Management Analyst, DRISK **Reviewers:** **DRISK** Marcia Britt, PhD, Regulatory Health Specialist Brian Gordon, MA, Social Science Reviewer Latonia M. Ford, RN, BSN, MBA, Patient Product Information Reviewer Gita A. Toyserkani, Pharm. D., MBA, Acting Team Leader **Office of Compliance/Division of Risk Management & Surveillance** Agnes Plante BSN, RN Consumer Safety Officer
Subject:	Review of Proposed Risk Evaluation and Mitigation Strategy (REMS) for (b) (4), Fentanyl Citrate Nasal Spray
Drug Name(s):	(b) (4) (final name pending); (fentanyl citrate) Nasal Spray
Application Number:	NDA 22-569
Applicant/sponsor:	Archimedes Development LTD
OSE RCM #:	2009-1860

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EXECUTIVE SUMMARY

This memo is in response to a request from the Division of Anesthesia and Analgesia Products (DAAP) to the Division of Risk Management (DRISK) to review the proposed Risk Evaluation and Mitigations Strategy (REMS) for (b) (4), (fentanyl citrate) nasal spray, and provides documentation of the status of the Applicant's proposal at the time of the Agency's Complete Response (CR) action letter.

(b) (4) (fentanyl citrate) Nasal Spray is an opioid analgesic proposed for the management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy (b) (4) To address the risk of overdose, abuse, addiction, and serious complications due to medication errors, FDA informed Archimedes in pre-NDA meeting communications (September 2008) that a Risk Evaluation and Mitigation Strategy (REMS) would be required.

Archimedes included a proposed REMS in their initial submission (received 31 August 2009). The proposed REMS includes a Medication Guide, Communication Plan, Elements to Assure Safe Use (certification of prescriber, pharmacy, documentation of safe use conditions, patient monitoring, and a patient registry), an Implementation System, and a Timetable for Submission of Assessments (every six months for the first year, then annually).

Due to outstanding issues, mainly having to do with Chemistry, Manufacturing, and Controls (CMC) deficiencies, DAAP plans to issue a CR letter; therefore, DRISK defers further review and comments on the proposed Medication Guide, Instructions for Use, and on the amended proposed REMS until the sponsor resubmits a satisfactory response to the CR action letter.

1 BACKGROUND

1.1 INTRODUCTION

This memo is in response to a request from the DAAP to the DRISK to review the proposed REMS for (b) (4) (fentanyl citrate) nasal spray, and provides documentation of the status of the Applicant's proposal at the time of the Agency's CR action letter.

(b) (4) is a reformulation of fentanyl, a potent opioid analgesic, for administration via the nasal mucosa. Archimedes, the Applicant, has formulated fentanyl in an aqueous solution that includes pectin. The drug product is a (b) (4) solution that is capable of being used in a multiple-use spray device. The drug is administered into the nose as a spray[1]. Each spray delivers 100 mcL of solution containing either 100 mcg or 400 mcg fentanyl base.

[1] Dr. R. Shibuya's CDTL Review (30 April 2010)

The proposed indication is the management of breakthrough pain in opioid-tolerant patients with cancer. Actiq, (fentanyl citrate) oral transmucosal lozenge, approved in 1998, Fentora (fentanyl buccal tablet), approved in 2006, and Onsolis (fentanyl buccal soluble film), approved in 2009, have the same indication. The risks of these products, which include misuse, abuse, addiction, and overdose, have been recognized and anticipated since the initial approval of Actiq. One of the main safety concerns with these products is use in opioid non-tolerant patients because of life-threatening respiratory depression in patients who are not on a chronic opioid therapy.

(b) (4) was tested in a single, adequate and well-controlled study using the 505(b)(2) approval mechanism, referencing Actiq. While the safety assessment of (b) (4) is confounded (patients were very ill with many concomitant medications and high background opioid use), no unexpected safety signals were observed in the clinical development program.

DAAP is recommending a CR for this application to address several deficiencies including an inadequate container-closure system for the device portion of this the product, an inadequate method for disposal of the priming sprays, and a significant amount of residual fentanyl solution remaining after use.

A REMS for (b) (4) was included in the initial submission (received August 31, 2009). The proposed REMS includes a Medication Guide, Communication Plan, Elements to Assure Safe Use (certification of prescriber, pharmacy, documentation of safe use conditions, patient monitoring, and a patient registry), an Implementation System, and a Timetable for Submission of Assessments (every six months for the first year, then annually). Interim comments on the proposed REMS have been provided to the Sponsor. The Sponsor has responded adequately to the FDA interim comments to date and has submitted an amendment to the proposed REMS on May 19, 2010. DRISK's final assessment of the proposed REMS is being deferred; pending the Applicant's submission of a complete response to the Agency's action letter.

1.2 REGULATORY HISTORY

A summary of the key regulatory history relevant to the proposed (b) (4) REMS is included below:

September 2008: In pre-NDA meeting communications, Archimedes was informed that (b) (4) would require a REMS, and that it must be submitted at the time of initial NDA submission. The Applicant was referred to the Anesthetic and Life Support Drugs Advisory Committee Meeting convened on May 6, 2008 (Actiq and Fentora were discussed) for guidance on specific risk management strategies. FDA indicated that a complete review of the application would be necessary to determine which REMS components would be required.

August 31, 2009: Initial submission, including a proposed REMS. The REMS included a Medication Guide, Communication Plan, Elements to Assure Safe Use, Implementation System, and Timetable for Submission of Assessments (see Section 3, below)

January 27, 2010: Interim Review (IR) REMS Comment Set #1 sent to the sponsor. Comments on the REMS and REMS Supporting Document included a request for materials, and clarification of (b) (4)

February 17, 2010: (S-010; eCTD Seq# 0009) Applicant responded to FDA's IR Comment Set#1 and submitted requested materials.

March 31, 2010: IR REMS Comment Set #2 sent to sponsor; included a preliminary list of questions and comments for the Applicant to be discussed at an impending teleconference. Comments included a request for clarification of responses in the Applicant's February 17, 2010 submission, as well as clarification of (b) (4) (b) (4)

April 14, 2010: Applicant e-mailed response to IR Comment Set #2 (currently not in DARRTS)

April 16, 2010: Teleconference between FDA (DAAP, DRISK) and Archimedes (and REMS partners Analgesic Solutions and Covance). *Note:* Shortly before the teleconference, the Applicant also provided a proposal for a real-time demonstration of the REMS; however, FDA deferred comment until they had adequate time for the proposal's review.

May 13, 2010: DRISK REMS Review for Oral Transmucosal Fentanyl Citrate (OTFC) and Fentanyl Citrate Nasal Spray (FCNS) products; internally distributed documentation of the main concerns identified in the proposed REMS for these products.

May 19, 2010: (S-018; eCTD Seq# 0017) Archimedes' resubmission including an amended REMS and REMS Supporting Document, and a draft report of their REMS Pilot Study.

1.3 OTHER REGULATORY HISTORY

(b) (4) has been part of ongoing and interrelated discussions within the Agency that included the review teams for other fentanyl products, and often involved Senior Management. In addition to (b) (4), the Agency is currently reviewing the REMS proposals for three other fentanyl products for breakthrough cancer pain: Abstral (NDA 22-510), Actiq (NDA 20-747), and Fentora (NDA 21-947) (see REMS Review, dated May 13, 2010). Although there are many similarities between the proposed REMS programs, the key difference lies in the responsibility to enroll and counsel the patient.

The Actiq and Fentora REMS model focuses this responsibility at the pharmacy-level, while the (b) (4) and Abstral models focus the responsibility at the prescriber-level. In a meeting on May 25, 2010, Senior Management informed Cephalon (the sponsor for Actiq and Fentora) that their proposed model, in which the pharmacy plays the most active role, was an acceptable model to pursue.

Also of note, on June 24, 2010, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for (b) (4) (PecFent), recommending the granting of a marketing authorization. The European Commission's decision on marketing authorization is normally issued 67 days from CHMP's adoption of an opinion.

2 METHODS AND MATERIALS

2.1 DATA AND INFORMATION SOURCES

The following materials were reviewed from the Applicant's electronic NDA 22-569 submissions, Agency reviews, and comments communicated to the Applicant. The materials are listed by the date of the document or event.

- Memo to File; Agency responses to pre-NDA meeting package questions, dated September 18, 2008 (IND 70, 854)
- Proposed REMS & REMS Supporting Document , received August 31, 2009 (initial eCTD Seq# 0000)
- Proposed Prescribing Information and Medication Guide, dated August 13, 2009, received August 31, 2009 (initial eCTD Seq# 0000)
- DRISK IR Comment Set #1, dated January 27, 2010
- Applicant Response to DRISK IR Comment Set #1, received February 17, 2010: (S-010; eCTD Seq# 0009)
- DRISK IR Comment Set #2, dated March 31, 2010
- Applicant Response to DRISK IR Comment Set #2, received April 14, 2010 (e-mailed to DAAP)
- Teleconference between FDA and Applicant, April 16, 2010
- DRISK REMS Review (multiple fentanyl products), dated May 13, 2010
- Applicant Response to issues raised during April 14, 2010 Teleconference and revised proposed REMS and REMS Supporting Document, submitted May 19, 2010: (S-018; eCTD Seq# 0017)

2.2 ANALYSIS TECHNIQUES

The (b) (4) REMS proposal was reviewed for responsiveness to Agency comments communicated to the Applicant and for conformance with the Food and Drug Administration Amendments Act of 2007.

3 RESULTS OF REVISED PROPOSED REMS REVIEW

The amended proposed (b) (4) REMS was submitted on May 19, 2010. Additional revisions will be required, pending the Applicant's submission of a complete response to the Agency's action letter.

(b) (4)

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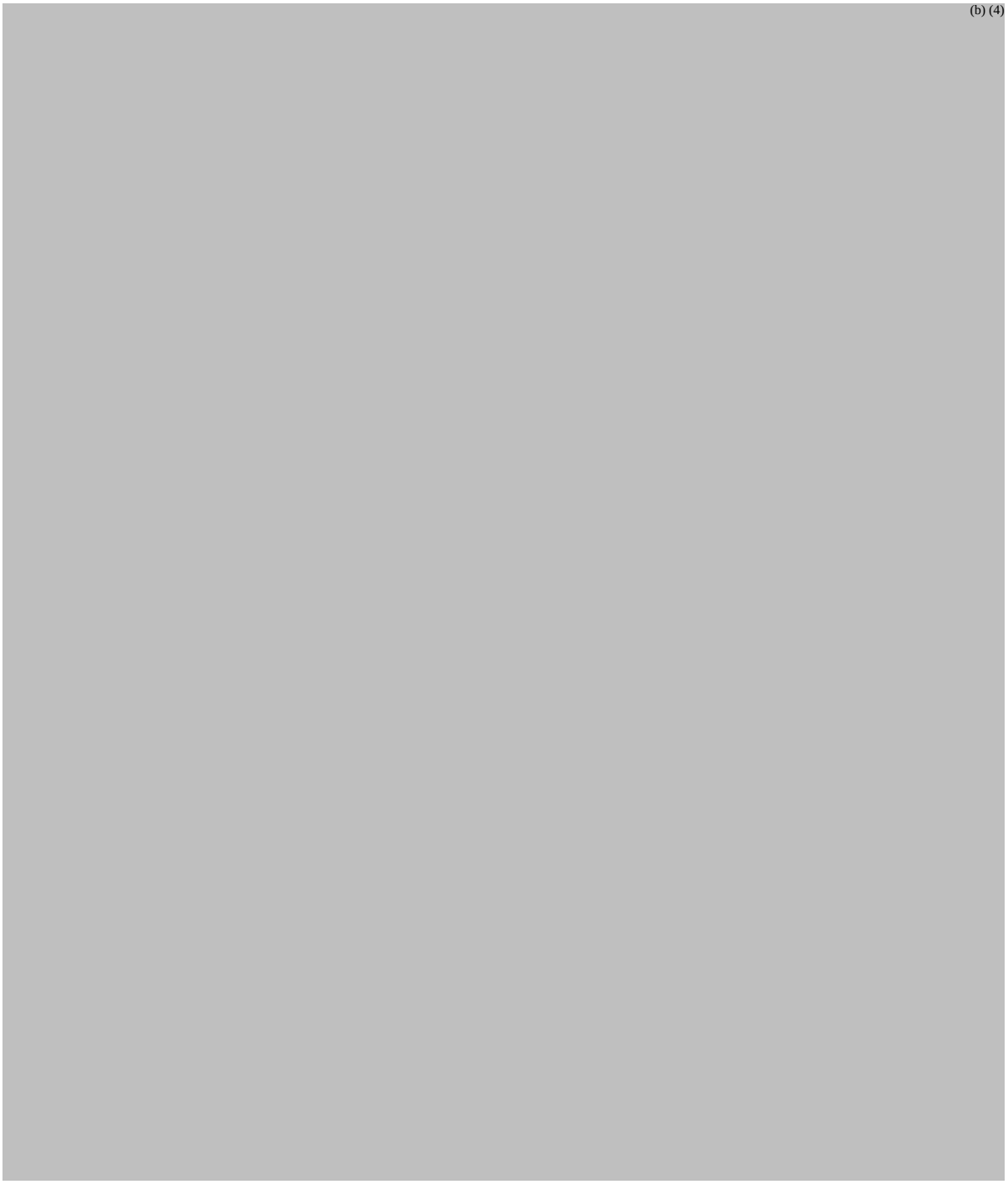

4 DISCUSSION & CONCLUSION

Although FDA has ‘accepted’ Cephalon’s pharmacy-centric model, there is no evidence to suggest that Archimedes’ prescriber-centric model would be any less effective. The current revised proposed REMS appears to be adequate, with minor modifications. However, we strongly recommend that the sponsors for the oral and nasal fentanyl products currently under review and future NDA holders work together to develop and participate in a single shared system.

Due to outstanding CMC deficiencies, DAAP plans to issue a CR letter. Therefore, DRISK defers further review and specific comments on the proposed Medication Guide, Instructions for Use, and the amended proposed REMS until the sponsor resubmits a satisfactory response to the CR action letter.

Please send us a new consult request when a complete response has been submitted. This review serves to close-out the consult request for (b) (4) NDA 22-569. Please let us know if you have any questions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

MEGAN M MONCUR
06/29/2010

CLAUDIA B KARWOSKI
06/29/2010
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 13, 2010
To:	Bob Rappaport. M.D., Director Division of Anesthesia and Analgesia Products (DAAP)
Thru:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK)
From:	Gita A. Toyserkani, Pharm.D., Acting Team Leader Jeanne Perla, Ph.D., Risk Management Analyst Megan Moncur, M.S., Risk Management Analyst
Subject:	Review of Risk Evaluation and Mitigation Strategy (REMS) for Oral Transmucosal Fentanyl Citrate (OTFC) and Nasal Citrate Fentanyl Spray (NCFS) products
Drug Name(s):	Actiq (NDA 20-747), Fentora (NDA 21-947), Abstral (NDA 22-510), (b) (4) (NDA 22-569)
OSE RCM #:	2009-2066

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1 INTRODUCTION

This review is to document the main concerns identified in the proposed Risk Evaluation and Mitigation Strategy (REMS) for the oral transmucosal fentanyl citrate (OTFC) and fentanyl citrate nasal spray (FCNS) products and to provide the Division of Risk Management's (DRISK) recommendations on the REMS requirements for these products.

The Agency is currently reviewing the REMS proposals for the following OTFC and FCNS products:

- Actiq (NDA 20-747/S-029); deemed REMS
- Fentora (NDA 21-947/S-009; received CR letter on December 30, 2009
- Abstral (NDA 22-510); PDUFA date June 5, 2010
- (b) (4) (NDA 22-569); PDUFA date June 30, 2010

During the review of the proposed REMS submission for these products, three main concerns with the REMS proposals were identified: (1) availability of these drugs in retail pharmacies; (2) documentation of safe-use condition to avoid drug being dispensed to opioid non-tolerant patients; and (3) compliance with patient counseling in retail pharmacy setting.

The safety issue team[1] is discussing these concerns internally as well as with Cephalon, the sponsor of Actiq and Fentora. Additionally, these issues were presented to the Opioid Small Steering Committee for input on March 12, 2010.

2 BACKGROUND

Oral transmucosal fentanyl citrate (OTFC) and fentanyl citrate nasal spray (FCNS) are potent opioid analgesics. They include the approved fentanyl buccal soluble film, Onsolis; the approved oral transmucosal fentanyl products, Actiq and Fentora; and the new drug applications for Abstral and (b) (4) an orally disintegrating fentanyl tablet and a fentanyl nasal spray, respectively. The approved or proposed indication for all of these products is for the management of breakthrough cancer pain in patients with cancer who are already receiving and who are tolerant to regular opioid therapy for their underlying persistent cancer pain.

The main safety concern with these products is use in opioid non-tolerant patients because of life-threatening respiratory depression in patients not taking chronic opioids. For this reason, these products are contraindicated in the management of postoperative pain, including headache, migraine, dental pain, or use in the emergency room. In order to take these products, patients must be opioid tolerant defined as: those who are

[1] The safety team issue is comprised of reviewers in the Division of Anesthesia and Analgesia Products, Office of Surveillance and Epidemiology, Office of Compliance, and the Division of Drug Marketing, Advertisement and Communications.

regularly taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oxymorphone/day , or an equianalgesic dose of another opioid for one week or longer. Additionally, based on the clear risk of abuse, overdose, and addiction associated with marketed potent opioid analgesics, all of these products pose a serious and significant public health concern.

To date, Onsolis (fentanyl buccal soluble film) is the only OTFC product that is approved with a REMS. Onsolis was approved July 16, 2009 and is available only through a restricted distribution program called the FOCUS Program. Under the FOCUS program, only prescribers, pharmacies, and patients registered with the program are able to prescribe, dispense and receive Onsolis. The program provides educational materials and patient counseling through a call center. Prescriptions can only be filled from participating pharmacies that courier the product directly to the patients' home. Currently, there is one specialty pharmacy that is participating in the program.

Actiq was listed in the Federal Register (Docket Number FDA-2008-N-0174) as a drug deemed to have in effect an approved REMS because it was approved under section 314.520 of title 21 of the Code of Federal Regulations.[2] Cephalon submitted a proposed REMS on September 17, 2008 for Actiq which was based on the approved Risk Minimization Action Plan (RiskMAP). (b) (4)

Fentora was approved September 25, 2006 and at the time Cephalon implemented a RiskMAP similar to Actiq. (b) (4) The Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and Drug Safety and Risk Management (DSaRM) recommended on May 6, 2008 that regardless of the indication, additional risk mitigation measures were needed to ensure the safe use of Fentora. Cephalon received a REMS Notification letter December 5, 2008 and a letter on July 16, 2009, outlining the required elements of a REMS for Actiq and Fentora.

Cephalon submitted a revised proposed REMS for Actiq and Fentora on April 2, 2009 and amended on September 11, 2009. Cephalon also provided an in-person presentation of the proposed REMS program for Actiq and Fentora on November 12, 2009. (b) (4)

Abstral and (b) (4) are new drug applications submitted on August 5, 2009 and August 31, 2009, respectively. REMS Notification Letters for these products have not been officially sent to the sponsors; however, during the pre-NDA meeting, the sponsors were informed of the need for a REMS and in the case of Abstral an outline of the REMS requirements was provided to the sponsor.

[2] § 314.520 Approval with restrictions to assure safe use

The REMS requirements for all four products as outlined in the Agency Letters are summarized in Appendix A.

3 METHODS AND MATERIALS

3.1 DATA AND INFORMATION SOURCES

- Onsolis REMS memo, dated August 4, 2008
- Actiq proposed REMS, dated September 17, 2008
- (b) (4)
- (b) (4)
- Actiq/Fentora proposed REMS, dated April 2, 2009 and amended September 11, 2009
- Onsolis REMS Approval Letter, dated July 16, 2009
- Actiq/Fentora Information Request Letter, dated July 16, 2009
- Abstral amended proposed REMS, dated February 1, 2010
- (b) (4) proposed REMS, dated August 31, 2009
- Cephalon's Responses to FDA Request on Actiq/Fentora proposed REMS, dated February 22, 2010

3.2 ANALYSIS TECHNIQUES

The proposed REMS submissions for Actiq, Fentora, Abstral, and (b) (4) were reviewed for conformation with Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) and compared to the approved Onsolis REMS.

4 RESULTS OF REVIEW

The proposed REMS for the above mentioned products are similar in that they require education and enrollment of prescribers and pharmacies, and enrollment and counseling of patients. However, there are differences in the drug's availability in different healthcare settings and in the proposals with regard to the requirements for documentation of safe-use conditions.

Table 1 below summarizes the main components for the already approved Onsolis REMS program and the three proposed REMS programs for Fentora/Actiq, Abstral, and (b) (4)

Table 1. Comparison of Proposed REMS Submissions for OTFC and FCNS

	Onsolis (Focus Program)	Actiq/Fentora (Secure Program)	Abstral (Assure Program)	(b) (4)
Physician	– Training,	(b) (4)		

Table 1. Comparison of Proposed REMS Submissions for OTFC and FCNS				
	Onsolis (Focus Program)	**Actiq/Fentora (Secure Program)**	**Abstral (Assure Program)**	(b) (4)
Enrollment (FDCA 505-1(f)(3)(A)	knowledge assessment and certification			(b) (4)
Pharmacy Enrollment (FDCA 505-1(f)(3)(B)	– Training and certification	–		
Dispensed in Certain Settings (FDCA 505-1(f)(3)(C)	– Specialty Pharmacy – Not available in retail pharmacies or hospitals	– –		
Dispensed with documentation of safe-use conditions (FDCA 505-1(f)(3)(D)	– Each patient is counseled and enrolled by the physician – Program call center counsels patient using scripted interaction – Patients are re-counseled at least every 2 years – Prescriber and pharmacy are notified of patient activation	– – – –		
Monitoring (FDCA 505-1(f)(3)(E)	– N/A	–		

Table 1. Comparison of Proposed REMS Submissions for OTFC and FCNS				
	Onsolis (Focus Program)	**Actiq/Fentora (Secure Program)**	**Abstral (Assure Program)**	(b) (4)
Patient Registry (FDCA 505-1(f)(3)(F)[3]	– N/A	(b) (4)		

(b) (4)

[3] Patient Enrollment is required under (FDCA 505-1(f)(3)(D), but patient follow-up and AE data collection is not required.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20747	SUPPL-29	CEPHALON INC	ACTIQ (ORAL TRANSMUCOSAL FENTANYL CITRAT
NDA-21947	SUPPL-9	CEPHALON INC	FENTORA (FENTANYL CITRATE)
SAFETY-290	ORIG-1	NO FIRM	FENTORA (fentanyl citrate) TABLET (buccal admin.)
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)
NDA-22510	ORIG-1	PROSTRAKAN INC	Abstral (fentanyl citrate) orally distintegrating tablets

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/s/

GITA A AKHAVAN TOYSERKANI
05/13/2010

CLAUDIA B KARWOSKI
05/13/2010
concur

REMS Interim Review Comments

Drug Name:	BLA/NDA:	Date:
(b) (4) (fentanyl nasal spray) Sponsor: Archimedes	NDA 22-569	March 30, 2010 **Comment Set # 2**
DRISK Scientific Lead: Megan Moncur, Risk Management Analyst		**Reviewers:** Gita Toyserkani, PharmD, MBA DRISK, Acting RMA TL Agnes Plante, BSN, RN Office of Compliance, CSO Marcia Britt, PhD DRISK, Health Education Reviewer Brian Gordon, MS DRISK, Social Science Reviewer
RCM #: 2009-1860		

Materials Reviewed:

- REMS submission received February 17, 2010 (eCTD Sequence# 0009), including:
  - Proposed REMS and REMS Supporting Document
  - Archimedes' responses to FDA's preliminary REMS comments, appended to their cover letter, to FDA's Preliminary Comments
- Proposed Prescribing Information and Medication Guide dated August 13, 2009 (Submitted August 28, 2009, eCTD Sequence #0000).

Introduction:

The following questions and requests for information are related to our review of the proposed (b) (4) REMS materials listed above.

Preliminary Comments for the Sponsor):
Following are questions and comments for discussion during the proposed teleconference. These are preliminary comments; as we continue our review, we will provide additional comments. Any responses or information that you can submit in advance of the teleconference will greatly enhance the efficiency of the meeting.

1. The following questions apply to the (b) (4)

(b) (4)

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

MEGAN M MONCUR
03/31/2010

GITA A AKHAVAN TOYSERKANI
03/31/2010

REMS Interim Review Comments

Drug Name: [redacted] (fentanyl nasal spray) Sponsor: Archimedes	**BLA/NDA:** NDA 22-569	**Date:** January 27, 2010 **Comment Set # 1**
DRISK Scientific Lead: Megan Moncur, Risk Management Analyst		**Reviewers:** Gita Toyserkani, PharmD, MBA DRISK, Acting RMA TL Agnes Plante, BSN, RN Office of Compliance, CSO
RCM #: 2009-1860		

Materials Reviewed:

- Proposed REMS and REMS Supporting Document received August 31, 2009.
- Proposed Prescribing Information and Medication Guide dated August 13, 2009.

Introduction:

A new drug application (NDA 22-569) for [redacted] was received on August 31, 2009. The following questions and requests for information are related to our review of the REMS materials listed above.

Preliminary Comments for the Sponsor:
These are preliminary comments; as we continue our review, we will provide additional comments. Please respond to this request within the next two weeks.

[redacted]

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	FENTANYL NASAL SPRAY

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/s/

MEGAN M MONCUR
01/27/2010