# CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 022569Orig1s000

# **OTHER REVIEW(S)**

#### **PMR/PMC** Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for <u>each</u> PMR/PMC in the Action Package.

PMR/PMC Description: A safety and pharmacokinetic study of Lazanda (fentanyl) nasal spray for the management of breakthrough pain, including cancer pain and pain due to chronic medical conditions, in opioid-tolerant children 7 through 16 years of age.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	12/31/2012
	Study/Trial Completion:	06/30/2015
	Final Report Submission:	12/31/2015
	Other:	MM/DD/YYYY

- 1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.
  - Unmet need
     Life-threatening condition
     Long-term data needed
     Only feasible to conduct post-approval
     Prior clinical experience indicates safety
     Small subpopulation affected
     Theoretical concern
     Other

Studies are ready for approval in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

3.	If the study/clinical trial is a <b>PMR</b> ,	check the applicable regulation.
	If not a PMR, skip to 4.	

#### - Which regulation?

Accelerated Approval (subpart H/E)

Animal Efficacy Rule

Pediatric Research Equity Act

FDAAA required safety study/clinical trial

### - If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

Assess a known serious risk related to the use of the drug?

Assess signals of serious risk related to the use of the drug?

☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

#### - If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

**Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A deferred safety and pharmacokinetic study in pediatric patients ages 7 through 16 years.

**Required** 

Observational pharmacoepidemiologic study

Registry studies

Primary safety study or clinical trial

Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

- Immunogenicity as a marker of safety
- Other (provide explanation)

#### Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

- 5. Is the PMR/PMC clear, feasible, and appropriate?
  - Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

#### **PMR/PMC Development Coordinator:**

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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MATTHEW W SULLIVAN 06/29/2011

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SHARON H HERTZ 06/29/2011

## Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Medication Error Prevention and Risk Management

Date:	June 21, 2011
Application Type/Number:	NDA 022569
To:	Bob Rappaport, MD, Director Division of Analgesia, Anesthesia and Addiction Products
Through:	Zachary Oleszczuk, Pharm.D., Team Leader Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Lazanda Labeling Comprehension and Human Factors Study Review
Drug Name and Strength:	Lazanda (Fentanyl) Nasal Spray 100 mcg per spray 400 mcg per spray
Applicant:	Archimedes Development Ltd.
OSE RCM #:	2011-2217

## **1 INTRODUCTION**

This review evaluates the labeling comprehension and Human Factors study entitled "Assessing Patient Comprehension of the Lazanda Medication Guide Instructions for Use" received on May 31, 2011 for Lazanda (Fentanyl) Nasal Spray in response to a request from the Division of Analgesia, Anesthesia and Addiction Products (DAAAP).

## 1.1 **REGULATORY HISTORY**

This NDA is a 505(b)(2) application. The Reference Listed Drug (RLD) is Actiq (Fentanyl Citrate) Oral Transmucosal Lozenge, NDA 020747. On June 30, 2010 a Complete Response (CR) action was taken on this application. The CR letter identified deficiencies related to safety concerns with the bottle closure and disposal of residual fentanyl. On September 30, 2010, the Applicant submitted a Class 2 Resubmission in response to the CR letter. The Agency later notified the Applicant of safety concerns related to patients being able to follow the Instructions for Use for Lazanda and use the product correctly according to those instructions. Subsequently, the Applicant submitted a proposed study protocol for a labeling comprehension study which was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) in OSE Review 2010-2138 and 2011-1146, dated April 15, 2011. The Applicant submitted a revised labeling comprehension study which is the subject of this review.

## **1.2 PRODUCT INFORMATION**

Lazanda is an opioid analgesic indicated only for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and are tolerant to regular opioid therapy for their underlying persistent cancer pain. The dose of Lazanda should be titrated to find the individual patient's effective and tolerable dose. Individually titrate from 100 mcg to 200 mcg to 400 mcg and up to a maximum of 800 mcg. A dose is a single spray into one nostril or a single spray into each nostril (two sprays) per episode. No more than four doses per 24 hours are recommended. Patients must wait at least 2 hours before treating another episode of breakthrough pain with Lazanda. There is no clinical data to support the use of a combination of dose strengths to treat an episode.

Lazanda has a boxed warning regarding the potential for abuse and the importance of proper patient selection. Lazanda is a Schedule II controlled substance. It will be available in two strengths. Each 100 mcL spray contains either 100 mcg or 400 mcg of fentanyl. Each bottle of Lazanda will deliver eight full sprays and will be supplied in a child-resistant container. Bottles in their child-resistant containers are supplied in cartons containing 1 or 4 bottles. Each carton will also contain a carbon-lined pouch(es) for disposal of priming sprays, unwanted doses and residual fentanyl solution.

Lazanda will have an associated Risk Evaluation and Mitigation Strategy (REMS).

## 2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the labeling comprehension and Human Factors study entitled "Assessing Patient Comprehension of the Lazanda Medication Guide Instructions for Use" submitted on May 31, 2011. Additionally, DMEPA reviewed the previous review (OSE Review 2010-2138 and 2011-1146, dated April 15, 2011) to ensure that all of DMEPA's recommendations have been incorporated into the protocol.

## 2.1 LABELING COMPREHENSION STUDY

DMEPA reviewed the labeling comprehension study entitled "Assessing Patient Comprehension of the Lazanda Medication Guide Instructions for Use" submitted by the Applicant on May 31, 2011. When reviewing the labeling comprehension study submitted by Archimedes Development Ltd., we focused on identifying areas of weakness in the study design that may have affected the utility of the study results. See Appendix A for an overview of the study.

## **3 RESULTS**

The following section describes the findings of the Lazanda labeling comprehension study.

## 3.1 LABELING COMPREHENSION STUDY

## 3.1.1 Implementation of DMEPA's Previous Recommendations

Our review of the labeling comprehension study noted most of the recommendations we provided in our previous review of the proposed study protocol were implemented. Our recommendation to provide the rationale for excluding patients with brain cancer or current use of intrathecal or epidural opioids was not provided. Additionally, our recommendations for the Lazanda Use Observation Form to have participants demonstrate rather than verbalize certain steps when possible was also not implemented.

We also identified the following additional deficiencies when evaluating the Labeling Comprehension and Human Factors Study:

- Participants were allowed to have a caregiver present
- The critical user tasks were evaluated in regards to their clinical impact should a failure occur
- An "acceptable" performance classification was counted as being a correct response if it did not involve a critical user task that was deemed not to be a safety issue if a failure occurred.

## 3.1.2 Participant Demographics

Forty four Participants were recruited from three clinical sites in Ohio, North Carolina and California. A total of 44 interviews were conducted between April 19, 2011 and May 19, 2011. A total of 20 women and 24 men were enrolled. The participants were predominantly Caucasian (n=38), but also include Black (n=3), Hispanic (n=2), and Asian (n=1). The minority groups were all included in the last group. Most participants were disabled or retired (n=38). The majority of the participants (n=25) had a high school education or less.

Ten participants also had a caregivers present during the study visit that were allowed to function and assist the participants as they normally would if they were at the participants' home. Each of the three rounds included caregivers (Round1 included 3 participants that had care givers present, Round 1a included 3 participants that have care givers present, and Round 2b had 4 participants that had care givers present.

## 3.1.3 Round 1 Results (n=16)

Initially, the first group that was tested included five participants. The findings from the first five interviews were reviewed by the Archimedes Development Ltd., and determined that there were no obvious issues within the Instructions for Use that needed immediate attention. An additional 11 participants were then interviewed and included in Round 1.

The findings from the combined 16 interviews (Round 1) were reviewed. All 16 participants correctly opened the Lazanda package and prepared Lazanda for use by correctly priming the dose. However, 1 participant did not administer the product correctly because they held the tip of the nasal spray 0.5 inch from their nose. The Applicant considered this an acceptable outcome. Additionally, 2 participants did not dispose of the excess Lazanda correctly. Both patients did not spray 4 times into the pouch after the counter reached "8". Based on review of these findings, changes were made to the Instructions for Use in all sections except *Using Lazanda*.

## 3.1.4 Round 2a (n=11)

Eleven more participants were interviewed using the revised Instructions for Use (Round 2a). All 11 participant correctly opened the Lazanda packaged and administered Lazanda correctly. However, 3 participants did not prime the product correctly. One participant left the protective cap on the nasal spray while priming instead of priming in the pouch, and the two other participants primed Lazanda into the air instead of the pouch. The Applicant categorized the incorrect priming with the cap on as an incorrect response, however, the Applicant categorized the two other participants that primed Lazanda into the air as acceptable responses.

Additionally, 2 participants did not dispose of the excess Lazanda correctly. Both patients did not spray 4 times into the pouch after the counter reached "8". The findings from these 11 interviews were reviewed and determined that a slight change was needed for the Disposing of Lazanda section of the Instructions for Use. The Applicant did not revise the section of the Instructions for Use regarding priming of the device.

## **3.1.5** Round 2b (n=17)

Seventeen participants were interviewed (Round 2b) using the final Instructions for Use. All 17 participant correctly opened the Lazanda packaged and administered Lazanda correctly. However, one participant did not prime the product correctly with no additionally details provided.

Additionally, 2 participants did not dispose of the excess Lazanda correctly. Both patients did not spray 4 times into the pouch after the counter reached "8".

#### 3.1.6 Combined Results

In the overall population (Rounds 1, 2a and 2b; n=44) completing the tasks correctly or acceptable was determined by the Applicant to be:

- 100% of the participants for Opening the Lazanda pack
- 95% of the participants for Preparing Lazanda for Use
- 100% of the participants for Using Lazanda
- 86% of the participants for Disposing of Lazanda

In the overall population (Rounds 1, 2a and 2b; n=44) completing the tasks correctly or acceptable was determined by DMEPA to be:

- 100% of the participants for Opening the Lazanda pack
- 93% of the participants for Preparing Lazanda for Use
- 98% of the participants for Using Lazanda
- 86% of the participants for Disposing of Lazanda

### 4 DISCUSSION

Our review of the labeling comprehension and human factors study noted most of the recommendations we provided in our review of the proposed study protocol were implemented. Although, our recommendations to provide the rationale for excluding patients with brain cancer or current use of intrathecal or epidural opioids and to have participants demonstrate rather than verbalize certain steps when possible was not implemented, we do not believe the failure to implement these recommendations negatively impacted the study.

However, we also identified three additional deficiencies in the study. One is that participants were allowed to have a caregiver assist them during the study and the results of their combined effort were included in the study results. Additionally, we were not able to identify which participants had care givers with them. Thus, it is difficult to determine what effect the involvement of the caregiver had on the results of the study.

Another deficiency is how the critical user tasks were evaluated in regards to their clinical impact should a failure occur. For example, the task of "demonstrating the correct steps for spraying Lazanda into nostril" was not considered a safety issue if the participant failed to perform this task correctly. However, failure to perform this task correctly could result in an incorrect dose being administered and should be considered a safety issue.

The third deficiency noted is the fact that an "acceptable" performance classification was counted as being a correct response if it did not involve a critical user task that was deemed not to be a safety issue if a failure occurred. Review of the subjective data indicates that, in some cases, participants who struggled to perform a step were classified as having performed the step in an "acceptable" manner and thus were determined to have performed the step correctly. Designating these "acceptable" performances as "correct" makes the study results appear more favorable. This accounts for the difference in correct responses identified by DMEPA and the Applicant. Additionally, we note that in many instances the participants required interviewer prompts to perform steps correctly which is not a reflection of a real-life scenario.

Although, these deficiencies make the data more difficult to interpret, the overall design of the study was well done and the study captured a large amount of subjective data which was very helpful in identifying those areas where some participants did not quite comprehend the instructions for use. For example, there were instances where participants did not fully depress the bottle grips when administering the placebo and, thus, only administered a partial dose. This concern about the potential to administer partial doses was raised with the Division during the application review process for this NDA; however, this was not considered by the Division to be a major concern.

We also note that, initially, some of the participants were confused about what the disposal pouch was (some thought it was a "wipe") and/or what it was supposed to be used for. Some participants stated the instructions for use are lengthy or had small print. Some participants were also concerned that when emptying the remaining Lazanda after "8" sprays were delivered that after spraying four times into the pouch that medicine could still be observed in the bottle. This caused some confusion about whether or not they needed to continue to spray until the bottle was completely empty. Additionally, all participants stated they would feel comfortable using Lazanda at home after going through the instructions and interview with staff.

Concerning disposal of the pouch, some patients expressed they would be reluctant to (b) (4) Additionally, this is the area that produced the most

incorrect responses.

Although, there were some instances of confusion, this study represented the worst case scenario. This product is going to be marketed in conjunction with a REMS which requires prescribers or a

designee go through the Medication Guide (which includes the IFU) with the patient prior to prescribing Lazanda. If the REMS, is followed, the instructions for use are adequate to ensure that patients are able to use Lazanda safely.

## 5 CONCLUSIONS AND RECOMMENDATIONS

The Instructions for Use section of the Lazanda Medication Guide will satisfactorily achieve its objective of ensuring that participants will understand how to effectively use and dispose of Lazanda if the REMS is successfully implemented and followed for this product. The REMS requires that healthcare professionals instruct patients on Lazanda's use when writing a prescription for Lazanda.

Additionally, DMEPA and DRISK made some recommendations concerning the final IFU used in the study including recommending that the Applicant provide a figure to more clearly show the plastic strip on the pouch and added an instruction to place the cap back on the Child Resistant Container (CRC) (<sup>b) (4)</sup> These recommendations will be captured in the Division of Risk Management's review of the Medication Guide (which includes the IFU). These minor revisions do not require retesting of the Instructions for Use.

Furthermore, because the disposal method of the pouch has been revised <sup>(b) (4)</sup> to placing the pouch in the CRC since the IFU has been tested, DMEPA would typically recommend that the revised instruction for use undergo at least one more round of testing similar to the ones conducted in this protocol with at least15 participants and using the same objectives and measurements. However, none of the participants in the study had trouble placing the nasal spray container into the CRC <sup>(b) (4)</sup> Additionally, there is sufficient room to fit the pouch and nasal spray into the CRC. Thus, DMEPA finds that the change in disposal instructions for the pouch would be unlikely to result in any confusion since participants have already demonstrated they can places the nasal spray container in the CRC without error.

## 6 **REFERENCE**

Holmes, L, OSE Review 2010-2138 and 2011-1146 ; Labeling Comprehension Study Protocol Review. April 15, 2011.

## APPENDIX A

#### LABELING COMPREHENSION STUDY

#### **Study Objective**

The objective of the study was to assess patient comprehension of the Lazanda medication guide Instructions for Use (IFU) in adult men and women cancer patients with breakthrough pain who are opioid tolerant.

#### Study Design

Study participants were recruited by clinical sites in the U.S. to participate in the study. Each study visit took place in a private, quiet space at the recruiting clinical site. Two staff members conducted each study visit in person. One staff member acted as the interviewer and one staff member observed and took notes. Prior to the start of each study visit, the interviewer explained the study and obtained written consent. Next, the participant completed a sociodemographic questionnaire and then read the Lazanda medication guide Instructions for Use. The participant then demonstrated preparing the placebo Lazanda device for use, using Lazanda, emptying unused medicine from the bottle into the disposal pouch, and disposing of the empty bottle and pouch based on his/her understanding of the Instructions for Use.

The study was performed as an iterative process by which feedback from an initial group of participants (Round 1) led to a modification of the Instructions for Use. A second group of participants then tested the modified Instructions for Use in two stages (Rounds 2a and 2b), with minor modifications made to the Instructions for Use after Round 2a.

#### **Participant Selection**

#### Inclusion Criteria

- Diagnosis of a malignant solid tumor or a hematological malignancy
- Chronic opioid use, defined as taking at least 60 mg oral morphine or equivalent for at least 1 week for cancer-related pain as regular, 24-hour medication for underlying persistent cancer pain
- Experiencing breakthrough pain at least one time per week
- 18 years of age or older
- Able to read and understand English
- Willing and able to provide informed consent to participate in the study

#### Exclusion Criteria

- Cancer of the brain
- Current use of intrathecal or epidural opioids
- Prior participation in a Lazanda clinical trial
- Presence of cognitive or other (visual, hearing) impairment that would interfere with participating in a one-on-one interview (based on the screener's opinion)

#### **Description of Interview**

#### Sociodemographic Form

Participants completed a Sociodemographic Format the start of the study visit. This form collected background information including race, employment, education, etc.

#### Interview Guide

The interview guide included questions designed to assess the participants' understanding of the Lazanda medication guide Instructions for Use.

#### Lazanda Medication Guide Instructions for Use

The Lazanda medication guide Instructions for Use was developed to assist patients with safe and effective use, or disposal of Lazanda at home. The initial IFU were slightly modified based on feedback from the first 16 study participants. The second IFU was reviewed by 11 additional participants, after which a final modification was made. The final IFU was reviewed by the remaining 17 participants.

#### Clinical Form

This form collected information about the participant's diagnosis, medication history, and treatment.

#### Lazanda Use Observation Form

This form was utilized by the observer to record the participant's actions during the study visit, including his/her adherence to the patient instructions.

#### **Risk Assessment**

In assessing patient risk, the following tasks were identified as critical user tasks to allow the patient to safely prepare and dispose of Lazanda

- Correctly identify the contents of the pack, including the disposal pouch
- Correctly prime bottle for use
- Prime bottle by spraying into the disposal pouch
- Demonstrate the correct steps for spraying Lazanda into nostril
- Spray remaining contents of Lazanda bottle into the disposal pouch

• (b) (4)

• Put empty bottle and plastic container into trash can

### **Evaluation**

The participants were evaluated on the following overall tasks: opening the Lazanda pack, preparing Lazanda for use, using Lazanda, and disposing of Lazanda. The participants were classified as having performed the tasks in each section overall as follows:

- Correct
- Acceptable
  - Performed the critical elements correctly, including with redirection, but incorrectly on a minor element with no associated safety issue (e.g., did not replace protective cap after use, but did place the bottle in CRC);
  - Acceptable was counted as "correct" when summarizing the data, as safety issues were the critical determinants of success or failure.
- Incorrect
  - Did not perform a critical element of the task correctly which could be associated with a safety issue (e.g. priming Lazanda in air rather than into the pouch).

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ZACHARY A OLESZCZUK 06/21/2011

CAROL A HOLQUIST 06/21/2011



## M E M O R A N D U M Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research

Date: June 17, 2011	
To:	Bob Rappaport, M.D., Director
	Division of Anesthesia, Analgesia, and Addiction Products
Through:	Michael Klein, Ph.D., Director
	Controlled Substance Staff
From:	JianPing (John) Gong, M.D., Ph.D. Medical Officer
	James R. Hunter, RPh, MPH, Senior Program Manager
	Controlled Substance Staff
Subject:	Lazanda FNS (Fentanyl Nasal Spray) NDA 22-569
	Indication: Breakthrough Cancer Pain
	Dosages: 100 mcg/spray (1 mg/ml,
	400 mcg/spray (4 mg/ml,
	Sponsor: SciLucent/Archimedes
Materials reviewed:	Drug disposal pouch <sup>(b) (4)</sup> study submitted March 24, 2011
	Label comprehension study submitted May 31, 2011.

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## I. Summary

### A. Background

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Controlled Substance Staff (CSS) regarding the safety risks and abuse potential of Lazanda FNS (Fentanyl Nasal Spray) Solution. This NDA received a Complete Response letter on June 30, 2010. The Sponsor resubmitted the NDA on September 30, 2010, which included proposals for modification to the drug-delivering device and revised methods for unused drug disposal.

CSS provided review consults to DAAAP for this NDA dated April 29, 2010, February 22, 2011, and March 22, 2011. Each of these reviews focused primarily on assuring safe and effective measures that reduce the risks associated with unintentional exposure and accidental overdose due to disposal of unused fentanyl in the product.

CSS found that method to be inadequate to assure safety, so in a resubmission dated September 30, 2010, the Sponsor proposed to spray the unused drug into an activated carbon cloth pouch and dispose in the household trash. In our review dated March 22, 2011, CSS assessed supplemental information submitted by the Sponsor addressing the amount of fentanyl extractable under various limited experimental conditions. These studies showed that 30-40% of the residual fentanyl in the pouch can be extracted using ethanol and acetone, and therefore, poses a risk of diversion and abuse. CSS continued to recommend that the Sponsor consider developing a method to inactivate or destroy residual drug, or set up a mail-back program to collect the used pouch and used device.

Subsequent to our above recommendations, in a teleconference between the Sponsor and DAAAP, the Sponsor was asked to consider whether the pouch could be

<sup>(b)(4)</sup> placing it directly into the trash. The Sponsor agreed to conduct studies to determine the <sup>(b)(4)</sup> of these pouches. The Sponsor submitted supplemental data from a <sup>(b)(4)</sup> study on March 24, 2011. On May 31, 2011, the Sponsor submitted additional information from a label comprehension study. These recently submitted materials are the subject of this CSS review.

#### **B.** Conclusions

- 1. The submitted data from the facile experiments is insufficient to determine the (b)(4)
- 2. A significant number of patients in the label comprehension study spontaneously reported their reluctance and resistance to complying with instructions <sup>(b)(4)</sup>. These concerns increase the likelihood that patients will not adhere to such disposal recommendations, and without alternative disposal recommendations, patients may engage in unsafe disposal practices.

(b) (4)

3. Additionally, due to the potential for significant patient non-adherence to a disposal method that is unacceptable to some patients for various reasons, the proposed disposal instructions directing patients to <sup>(b) (4)</sup>/<sub>(4)</sub> should be reconsidered as an acceptable method of disposal.

#### C. Recommendations

- 1. CSS continues to recommend that the Sponsor consider developing a method to inactivate or destroy residual drug, or set up a mail-back program to collect the used pouch and used device to dispose residual drug.
- 2. To mitigate risks associated with accidental unintentional exposure to the drug contained in the pouch, CSS alternatively recommends that patients be instructed to place the sealed pouch containing residual drug into the supplied child resistant container and place it in the household trash.

## II. Discussion

(b) (4)

CSS Review: Lazanda FNS NDA 22-569

(b) (4)



The Sponsor conducted this study to evaluate the Instructions for Use section of Lazanda Medication Guide in adult men and women with cancer who experience breakthrough pain (BTPc) and who are opioid tolerant. The results show that about 20% of the participants spontaneously expressed their concerns about <sup>(b) (4)</sup>

system (Table 2). Those subjects have various education backgrounds from college level to elementary school level.

Round	# of Participants	# Concerned abou <sup>(b) (4)</sup>	% Concerned about <sup>(b) (4)</sup>	Education level of Concerned about
1	16	3	19%	202- College 209- High School 211- High School
2a	11	3	27%	111-high school 112-high school 113-college
2b	17	4	24%	213-college 115-elementary 116-elementary 304-College
Total	44	10	23%	

 Table 2. Summary of participants expressing concerns of
 (b) (4) in Lazanda labeling comprehension study

Some of the written comments by the interviewers noted spontaneous concerns by the study participants about <sup>(b)(4)</sup>. Some participants were concerned that

(b) (4)

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CSS Review: Lazanda FNS NDA 22-569

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Jianping P GONG 06/17/2011

JAMES R HUNTER 06/17/2011

MICHAEL KLEIN 06/17/2011

## Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Medication Error Prevention and Risk Management

Date:	June 9, 2011
Application Type/Number:	NDA 022569
То:	Bob Rappaport, MD, Director Division of Analgesia, Anesthesia and Addiction Products
Through:	Todd Bridges, RPh, Acting Deputy Director Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Lazanda Label and Labeling Memorandum
Drug Name(s) and Strength:	Lazanda (Fentanyl) Nasal Spray 100 mcg per spray 400 mcg per spray
Applicant/Sponsor:	Archimedes Development Ltd.
OSE RCM #:	2010-2138

This memorandum evaluates the pouch labeling received on April 4, 2011 and the revised container labels and carton labeling received on May 31, 2011 for Lazanda nasal spray in response to a request from the Division of Analgesia, Anesthesia and Addiction Products (see Appendices A through D). The Division of Medication Error Prevention and Analysis finds the revised pouch labeling acceptable. We have the following recommendations for the container labels and carton labeling.

A. General Comments for all container labels and carton labeling

- 1. The established name lacks prominence. Increase the font weight of the established name and ensure it has a prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors including typography, layout, contrast and other printing features per 21CFR 201.10(g)(2).
- 2. The statement of strength is not prominent. Increase its prominence by increasing the font weight.
- B. Container Labels (100 mcg per spray and 400 mcg per spray)
  - 1. The strengths are not well differentiated. Expand the color bar so that it includes the statement of strength.
  - 2. The "Rx" symbol is too prominent. Unbold the font.
  - 3. The distributor information is too prominent. Decrease the size of the statement "Distributed by Archimedes Pharma".
- C. Carton Labeling (100 mcg per spray and 400 mcg per spray), 1-count and 4-count

The medication guide statement "Dispense the enclosed Medication Guide to Each patient" is not prominent. Increase the prominence of the medication guide statement by increasing its font weight.

## 4 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS b4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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LORETTA HOLMES 06/09/2011

CAROL A HOLQUIST 06/14/2011

## 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:	April 15, 2011
То:	Bob Rappaport, MD, Director Division of Anesthesia and Analgesia Products
Through:	Irene Z. Chan, PharmD, BCPS, Team Leader Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Labeling Comprehension Study Protocol Review
Drug Name:	Lazanda (Fentanyl) Nasal Spray 100 mcg per spray 400 mcg per spray
Application Type/Number:	NDA 022569
Applicant:	Archimedes Development Ltd.
OSE RCM #:	2010-2138 and 2011-1146

## **1 INTRODUCTION**

This review evaluates the proposed study protocol entitled "Assessing the Patient Comprehension of the How to Use and Dispose of Lazanda Sections of the Medication Guide" submitted on April 1, 2011 for Lazanda (Fentanyl) Nasal Spray in response to a request from the Division of Analgesia and Anesthesia Products (DAAP).

## 1.1 **REGULATORY HISTORY**

This NDA is a 505(b)(2) application. The Reference Listed Drug (RLD) is Actiq (Fentanyl Citrate) Oral Transmucosal Lozenge, NDA 020747. On June 30, 2010 a Complete Response (CR) action was taken on this application. The CR letter identified deficiencies related to safety concerns with the bottle closure and disposal of residual fentanyl. The Applicant submitted a Class 2 Resubmission in response to the CR letter on September 30, 2010. The Agency later notified the Applicant of safety concerns related to patients being able to follow the Instructions for Use for Lazanda and use the product correctly according to those instructions. Thus, the Applicant has submitted this proposed study protocol for a labeling comprehension study.

## **1.2 PRODUCT INFORMATION**

Lazanda is an opioid analgesic indicated only for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and are tolerant to regular opioid therapy for their underlying persistent cancer pain. The dose of Lazanda should be titrated to find the individual patient's effective and tolerable dose. Individually titrate from 100 mcg to 200 mcg to 400 mcg and up to a maximum of 800 mcg. A dose is a single spray into one nostril or a single spray into each nostril (two sprays) per episode; no more than four doses per 24 hours. Patients must wait at least 2 hours before treating another episode of breakthrough pain with Lazanda. There is no clinical data to support the use of a combination of dose strengths to treat an episode.

Lazanda has a boxed warning regarding the potential for abuse and the importance of proper patient selection. Lazanda is a Schedule II controlled substance. It will be available in two strengths. Each 100 mcL spray contains either 100 mcg or 400 mcg of fentanyl. Each bottle of Lazanda will deliver eight full sprays and will be supplied in a child-resistant container. Bottles in their child-resistant containers are supplied in cartons containing 1 or 4 bottles. Each carton will also contain a carbon-lined pouch(es) for disposal of priming sprays, unwanted doses and residual fentanyl solution.

Lazanda will have an associated Risk Evaluation and Mitigation Strategy (REMS).

## 2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis reviewed the proposed labeling comprehension study protocol entitled "Assessing Patient Comprehension of the How to Use and Dispose of Lazanda Sections of the Medication Guide."

When reviewing the materials submitted by Archimedes Development Ltd., we focused on identifying areas of weakness in the study design that may affect the utility of the study results.

## **3 RESULTS AND DISCUSSION**

The following section describes the findings and assessment of the proposed labeling comprehension study protocol.

### 3.1 LABELING COMPREHENSION STUDY PROTOCOL DESCRIPTION

#### **Study Objectives**

The objective of this qualitative research study is to assess patient comprehension of the How to Use and Dispose of Lazanda sections of the Medication Guide in adult men and women with cancer who experience breakthrough pain.

#### Study Design

Up to 30 adult men and women who experience breakthrough pain and who are opioid tolerant will be recruited from 2 or 3 clinical sites in the United States to participate in the study. Two staff members will conduct all study visits in person. One will act as the interviewer and the other will observe and take notes. Prior to the start of each study visit, a staff member will explain the study and obtain written informed consent. The participant will read the How to Use and Dispose of Lazanda sections of the Medication Guide and then demonstrate how to use the placebo Lazanda device with the document in front of him/her. The observer will record notes about the participant's actions including adherence to the patient instructions for use. The interviewer will probe for further feedback on the instructions, focusing on tasks that the participant did incorrectly or skipped. Following the device use and interview, participants will complete a sociodemographic questionnaire and will be paid for their participation. The study interviews will be audiotaped for subsequent transcription and analysis. All interviews will be conducted in English and will take approximately 1 to 1½ hours to compete.

#### **Participant Selection**

Inclusion Criteria

- Diagnosis of a malignant solid tumor or hematological malignancy
- Chronic opioid use, defined as taking at least 60 mg oral morphine or equivalent for at least one week for cancer-related pain as regular, 24-hour medication for underlying persistent cancer pain
- Experiencing breakthrough pain at least one time per week
- 18 years of age or older
- Able to read and understand English
- Willing and able to provide informed consent to participate in the study

#### Exclusion Criteria

- Cancer of the brain
- Current use of intrathecal or epidural opioids
- Prior participation in Lazanda clinical trial
- Presence of cognitive or other (visual, hearing) impairment that would interfere with participating in a one-on-one interview (based on the screener's opinion)

#### Participant Recruitment

To ensure the study participants have clinically verified breakthrough pain, participants for this study will be recruited from clinical sites. Up to 30 adult men and women will be recruited from the clinics' patient databases and/or individual medical records. Clinical site staff will review their patient database and/or individual medical records to identify patients who meet the clinical entry criteria per the Inclusion/Exclusion Criteria Form.

Once a potential participant is identified from the chart review, a member of; the clinical site staff will introduce the study over the phone or as the patient presents for his/her regularly scheduled clinical appointment. About five to seven participants will be interviewed initially. The team will then meet internally to review the findings to determine if there is any feedback from patients that needs immediate attention and/or revision that needs to be made to the interview guide. The remaining visits will continue until saturation of concepts is complete, up to a maximum of 30 participants.

#### Study Visit Procedures

Each study visit will take place in a private, quiet space at the recruiting clinical site. Prior to each interview, the interviewer will explain the study to the participant and obtain informed written consent. During the first part of the visit the participant will read the How to Use and Dispose of Lazanda sections of the Medication Guide. The participant will then demonstrate his/her ability to follow the instructions in How to Use and Dispose of Lazanda. The study interviews will be conducted in English and audiotaped for subsequent transcription and analysis. Study staff will document key patient variables such as medical history, diagnosis, current medications and comorbid conditions for each participant. The staff member will provide the completed forms to the interviewer at the conclusion of the visits at that site.

#### **Description of Interview**

#### Interview Guide

The interview guide includes topics, questions, and probes designed to assess the participants' understanding of the How to Use and Dispose of Lazanda sections of the Medication Guide. The interview guide begins with an overall introduction about the interview and then moved into a demonstration of the participant's understanding of the materials.

#### Lazanda Use Observation Form

This form will be utilized by the observer to record the participant's actions during the study visit, including adherence to the patient instructions.

#### Sociodemographic Form

The participants will complete this form at the conclusion of the study visit. The form collects background information including the participant's age, gender, race, etc.

#### Clinical Form

Study site personnel will complete this form for each eligible participant scheduled for a study interview. This form collects information about the participant's diagnosis, medical history and treatment.

#### 3.2 STUDY PROTOCOL DEFICIENCIES

Our evaluation of the proposed study protocol identified the following deficiencies:

#### Study Design

- According to the study design, up to 30 adult men and women will be recruited for the study. The Applicant has not noted the minimum number of participants they will require or if dropouts will be replaced.
- There is no indication that the Instructions for Use have been evaluated to determine the literacy level at which they were written.

- The study protocol does not state what will be done with the data once it is collected or how it will be used to revise the Instructions for Use.
- It is not stated what the critical user tasks are or what the clinical impact would be if a critical user task was missed or carried out incorrectly.
- The exclusion criteria include cancer of the brain and concurrent use of intrathecal or epidural opioids but it is unclear why they are excluded.

Participant Selection

- Approximately 5 to 7 participants will be interviewed and a determination made as to whether the interview guide requires revision. However, it is not clear how the data will be evaluated if the interview guide is revised and a different guide is used for the remaining 25 to 27 participants.
- The Sociodemographic Form is completed at the end of the interview which may limit the ability to obtain a diverse population sample up front.

Study Visit Procedures:

• The interviews will be conducted at a clinical site which is not representative of a real use environment.

Description of Interview:

- The Lazanda Use Observation does not ask participants what can be done to improve the Instructions for Use or what improvements can be made to the product to make it easier to use.
- In the Lazanda Use Observation Form patients are given the option to "demonstrate or verbalize" the step. Verbalization, rather than demonstration, may not detect potential problems with carrying out that particular step and may hinder the ability to gather useful data from the study.
- The Clinical Form does not ask how often the potential participant has breakthrough pain.

#### 4 CONCLUSIONS AND RECOMMENDATIONS

The study protocol is deficient and requires revision prior to implementation. We provide comments on the proposed protocol in Section 4.1 *Comments to the Division*.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Danyal Chaudhry, at 301-796-3813.

#### 4.1 COMMENTS TO THE DIVISION

A. General Comment

DMEPA's comments concerning the Instructions for Use (IFU) were captured in the Division of Risk Management's (DRISK) review of the Medication Guide (MG) communicated to the Division via email on April 12, 2011. We request the Applicant revise the MG/IFU as recommended and use the revised IFU in the study.

- B. General Comments for Study Design
  - 1. We acknowledge the study assesses user tasks; however, you did not submit a risk assessment that defined all of the critical user tasks needed for a patient to use

Lazanda safely, nor do you define the clinical impact that failure of these user tasks could incur. Ensure a complete risk assessment is included in the study protocol.

- 2. There is no indication that the Instructions for Use have been screened to determine the literacy level at which they were written. Determine the literacy level at which the IFU is written. The recommended literacy level is sixth to eighth grade.
- 3. According to the study design, up to 30 adult men and women will be recruited for the study so it is unclear what the intended goal is concerning the number of participants in the study. State the minimum number of participants that will be included in the study to ensure there are enough participants.
- 4. The study protocol does not state what will be done with the data once it is collected or how it will be used to revise the Instructions for Use. We recommend that revisions be made to the IFU based on the results obtained from the study in order to determine the best presentation of the information to optimize the safe use of Lazanda.
- 5. Provide the rationale for excluding patients with brain cancer or current use of intrathecal or epidural opioids.
- C. Selection of Participants
  - 1. *Participant Recruitment*: Approximately 5 to 7 participants will be interviewed and a determination made as to whether the interview guide requires revision. If the interview guide is revised for use with the 23 to 25 participants that follow, the data obtained from those 5 to 7 participants should be evaluated separately from the remaining 25 to 27 participants in the study. Additionally, any changes made to the interview guide should be discussed and the rationale provided.
  - 2. The Sociodemographic Form is completed at the end of the interview which may limit the ability to obtain a diverse population sample up front. Determine the sociodemographics up front during the participant selection process in order to ensure there is a diverse population representative of patients who will likely use Lazanda.
- D. Data Collection
  - 1. The Lazanda Use Observation Form does not ask participants what can be done to improve the Instructions for Use or what improvements can be made to the product to make it easier to use. Include this question in the Lazanda Use Observation Form.
  - 2. In the Lazanda Use Observation Form we note that in some of the steps the patient is given the option to "demonstrate or verbalize" the step. Verbalization, rather than demonstration, may not detect potential problems with carrying out that particular step and may hinder the ability to gather useful data from the study. In all instances where the step can be physically demonstrated, have the participant demonstrate the step.
  - 3. The Clinical Form does not ask how often the potential participant has breakthrough pain. Consider adding this question to the form to help screen potential participants.

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LORETTA HOLMES 04/15/2011

IRENE Z CHAN 04/15/2011

CAROL A HOLQUIST 04/15/2011



## MEMORANDUM

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

Date:	March 22, 2011		
To:	Bob Rappaport, M.D., Director		
	Division of Anesthesia and Analgesia Products		
Through:	Michael Klein, Ph.D., Director		
U	Silvia Calderon, Ph.D., Team Leader		
	Controlled Substa	Controlled Substance Staff	
From: JianPing (John) Gong, M.D., Ph.D. Medical Officer		ong, M.D., Ph.D. Medical Officer	
	Controlled Substa	nce Staff	
Subject:	Amendment to CSS's review on Lazanda dated February 22, 201		
-	NDA #:	22-569	
	Indication:	Breakthrough Cancer Pain	
	Strengths:	100 mcg/spray(1 mg/ml, (b) (4))	
	-	400 mcg/spray(4 mg/ml, (b) (4))	
	Sponsor:	SciLucent/Archimedes	
	<b>Document Date:</b>	January 7, 2011	

### Background

The Division of Anesthesia and Analgesia Products (DAAP) consulted the Controlled Substance Staff (CSS) regarding the safety risks and abuse potential of Lazanda FNS (Fentanyl Nasal Spray) Solution. This NDA received a Complete Response letter on June 30, 2010. The Sponsor resubmitted the application on September 30, 2010, with modification of the device and drug disposal method.

CSS submitted the second-cycle review into DARRTS on February 22, 2011. In this review CSS had the following recommendations to the Sponsor:

- 1. Your assay for testing the absorptive capacity needs to be described in more detail. You need to demonstrate that the assay for absorptive capacity is reproducible.
- 2. You need to test the limits of absorption of the pouch.
- 3. You need to systematically test the ability and feasibility of extracting fentanyl from the pouch using a wide range of solvents and test conditions.
- 4. You need to develop a method to inactivate or destroy residual drug, or set up a mail-back program to collect the used pouch and used device.



However, we then became aware that on February 21, 2011, the Sponsor submitted supplemental information addressing the absorptive capacity of the pouch as well as the amount of fentanyl extracted from pouches under various experimental conditions.

### Conclusion

- 1. From the data provided by the Sponsor, the pouch appears to retain the entire amount of the intact formulation when sprayed into the pouch.
- 2. CSS agrees with the conclusions of the Chemistry, Manufacturing and Controls (CMC) review (Pinto, Julia, NDA 22569, DARRTS, Chemistry Review, March 3, 2011) that the extraction studies used to determine the ease of extraction of the fentanyl from the pouch were facile experiments. Although the studies are not robust and may be limited in scope, the amount of fentanyl extracted is a concern. Extraction of 30% to 40 % of the residual fentanyl can be achieved under mild conditions using readily available solvents such as ethanol and acetone. Extraction of 30% of fentanyl from a used 4 mg/ml spray represents <sup>(b)(4)</sup> of fentanyl, and if all contents of a 4 mg/ml FNS bottle were sprayed into the pouch the amount of fentanyl extracted would be <sup>(b)(4)</sup>. Therefore, the amount of fentanyl that can be extracted from the pouch is a risk of diversion and abuse.

### Recommendation

- 1. Taking under consideration the data submitted by the Sponsor, CSS does not require additional absorption and extraction studies as previously recommended (Gong, JianPing, NDA 22569, DARRTS, CSS review, February 22, 2011).
- 2. CSS's prior recommendation to the Sponsor to develop a method to inactivate or destroy residual drug, or set up a mail-back program to collect the used pouch and used device remains.

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Jianping P GONG 03/22/2011

SILVIA N CALDERON 03/22/2011

MICHAEL KLEIN 03/22/2011



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:	March 4, 2011	
То:	Bob Rappaport, MD, Director Division of Anesthesia and Analgesia Products	
Through:	Irene Z. Chan, PharmD, BCPS, Acting Team Leader Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)	
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)	
Subject:	Label and Labeling Review	
Drug Name:	Lazanda (Fentanyl) Nasal Spray 100 mcg per spray 400 mcg per spray	
Application Type/Number:	NDA 022569	
Applicant:	Archimedes Development Limited	
OSE RCM #:	2010-2138	

## **1 INTRODUCTION**

This review evaluates Archimedes Development Limited's proposed labels, labeling, and packaging design for Lazanda (Fentanyl) Nasal Spray, 100 mcg per spray and 400 mcg per spray, submitted on September 30, 2010 as part of a Class 2 Resubmission. This NDA requires a Risk Evaluation and Mitigation Strategy (REMS).

## 2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton labeling, Medication Guide, Patient Instructions for Use (IFU), and packaging submitted as part of the September 30, 2010 submission (see Appendices A through D). Additionally, we reviewed the Substantially Complete Prescribing Information (SCPI), dated February 17, 2011.

- Container Labels: 100 mcg per spray and 400 mcg per spray
- Carton Labeling: 100 mcg per spray and 400 mcg per spray, 1-bottle and 4-bottle.
- Insert Labeling and Medication Guide/IFU: (no image)
- Packaging
  - o Bottle
  - o Child-resistant storage container
  - o Carbon pouch

## **3 RESULTS AND DISCUSSION**

DMEPA identified several safety concerns associated with the labels, labeling, and packaging of Lazanda. The following section describes our findings and analysis of the September 30, 2010 submission and the insert labeling.

## 3.1 PACKAGING DESIGN

Lazanda is packaged in a spray bottle with a spray counter that counts up from 1 to 8, indicating the number of sprays given, rather than down, indicating the number of sprays left in the bottle. Post-marketing surveillance indicates that greater patient comprehension occurs when a device counts the number of doses remaining. Therefore, this feature may provide a source of confusion for patients and caregivers since most drug product counters count down (e.g., from 8 to 0). DMEPA recommends that the Applicant change the direction of the spray counter so that it counts the number of sprays remaining rather than the number of sprays administered.

DMEPA also evaluated the risk of accidental exposure to Lazanda by household contacts as well as the risk for drug diversion with the packaging design. To address these risks, the Applicant has provided a child-resistant storage container to hold the Lazanda bottle when it is not in use. Additionally, the Applicant is proposing a carbon pouch that will be used for the priming process and the disposal of residual or unused drug from the bottle. Patients or caregivers will be required to direct sprays into this carbon pouch.

DMEPA is concerned that patients may not use the storage container or the pouch. The Applicant has not provided any data to demonstrate that patients will use these safeguards, nor has the Applicant provided any data indicating patients can correctly use these safeguards. To

address these concerns, we recommend the Applicant complete a usability study evaluating patients' willingness and ability to properly use these safeguards.

### 3.2 INSERT LABELING, MEDICATION GUIDE, AND PATIENT INSTRUCTIONS FOR USE

DMEPA's evaluation of the insert labeling identified illogical flow of information in the dosage and administration section. Additionally, we are concerned that the language utilized in the Full Prescribing Information is directed toward the patient rather than the prescriber. We also note inconsistency between the full prescribing information and the Patient Instructions for Use (IFU). We provide recommendations in Section 4 below for the insert labeling.

Moreover, DMEPA and the Division of Risk Management (DRISK) worked collaboratively on revisions to the proposed Medication Guide (MG) and Patient Instructions for Use (IFU). See the DRISK review for comments concerning the MG/IFU.

As currently presented, the Instructions For Use (IFU) for Lazanda are lengthy and complex. Proper use of this medication involves coordinating multiple instructions with auditory and visual cues, which may be difficult for some patients. In order to ensure that patients understand the instructions and can correctly follow them, a labeling comprehension study should be performed to evaluate the IFU. We recommend this labeling comprehension study be incorporated as part of a broader usability study designed to evaluate the novel packaging design of Lazanda in order to determine if Lazanda can be administered safely and effectively by patients and caretakers. This study should aim to identify any vulnerabilities that may lead to medications errors with the use of this product.

### 3.3 CONTAINER LABEL AND CARTON LABELING

DMEPA's review of the container label and carton labeling identified the following deficiencies:

- Inadequate established name presentation
- Confusing strength presentation
- Missing route of administration instruction
- Inadequate warnings and instructions

We provide recommendations for the container label and carton labeling in Section 4 below.

#### **4 RECOMMENDATIONS**

Our evaluation noted areas where information on the labels and labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling and product design in Section 5.1 *Comments to the Division*. Section 5.2 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 5.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Danyal Chaudhry, at 301-796-3813.

#### 4.1 COMMENTS TO THE DIVISION

- A. General Comments
  - 1. DMEPA and the Division of Risk Management (DRISK) worked collaboratively on revisions to the proposed Medication Guide and Patient Instructions for Use (see the DRISK review for comments concerning the MG/IFU).
  - 2. Due to the complexity of the product design and Patient Instructions for Use, DMEPA recommends a usability study that incorporates a labeling comprehension component be completed prior to approval of this application in order to determine the optimal product design and Instructions for Use to help minimize medication errors with the use of this product.
- B. Insert Labeling, Full Prescribing Information
  - 1. Section 2.1 *Dose Titration*--Some of the verbiage used appears to be written for patients rather than healthcare providers. Additionally, the instructions provided do not appear to flow in a logical manner and may be confusing. The information provided in this section should be directed towards healthcare providers and not patients and should be presented in a more logical manner. DMEPA will provide specific recommendations in Divisional labeling meetings.
  - 2. Section 2.3 Administration of TRADENAME—The instructions provided in this section are written for patients and are extensive. These instructions should not be in this section of the insert. This section should briefly describe how the product is administered.
  - 3. Section 16.2 *Storage and Handling TRADENAME* and Section 16.3 *Disposal of TRADENAME*—The instructions in these sections and the IFU should correspond.

## 4.2 COMMENTS TO THE APPLICANT

- A. General Comments for the Container Labels and Carton Labeling
  - 1. Ensure the established name (which includes the active ingredient and dosage form) is printed in letters that are at least ½ as large as the letters comprising the proprietary name and that the established name has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features [21 CFR 201.10(g)(2)].
  - 2. We note the use of "100" and "400" on the container labels and carton labeling, which appear to represent the strength; however, this is an incomplete strength presentation and may be confusing because there is no unit of measure or other indicator of what the numbers represent. Therefore, revise the "100" and "400" to read: "100 mcg per spray" and "400 mcg per spray". These statements may remain in their present locations.
  - 3. The "Rx" portion of the "Rx only" statement is too large and distracting due to its prominence. Decrease the size of the "Rx" portion of the statement.
- B. Container Labels
  - 1. As currently presented, the container labels appear crowded. Due to their limited size, ensure that the proprietary name, established name, and strength presentations are the most prominent information displayed. Consider removal of other unnecessary or less important information [see 21CFR 201.10(i)], but retain the statement "Return to child resistant container after use" and consider increasing its prominence since this statement is an important safeguard against accidental exposure.

#### C. Carton Labeling

- 1.
- 2. Per 21CFR 201.10(d)(1), any statement of the quantity of an ingredient should be expressed per unit (e.g., per spray). The current statement "equivalent to 100 mcg fentanyl base" on the principle display panel is incomplete. Additionally, there is already a statement on the side panel that reads "Each 100 microlitre spray contains fentanyl citrate equivalent to 100 mcg fentanyl base." Therefore, remove the statement on the principle display panel. Also change "microlitre" to read "microliter."
- The statement "
   <sup>(b) (4)</sup> is confusing and incomplete. Revise this statement to read, "Each bottle delivers 8 full sprays. Each spray delivers 100 microliters of solution."
- 4. The top panel of the 4-bottle carton has a statement that reads "See enclosed prescribing information" whereas the 1-bottle carton has a different statement that reads "See enclosed Medication Guide". These statements are inconsistent. Ensure these statements are the same on both carton presentations.
- 5. Add the Medication Guide statement "Dispense the enclosed Medication Guide to each patient" to the principle display panel.
- 6. Ensure a minimum of four Medication Guides are enclosed in each of the 4-bottle cartons to ensure that if a single bottle is dispensed from the 4-bottle carton, there will be enough Medication Guides to dispense with each bottle.
- The usual dosage statement reads "Usual dosage: see Medication Guide". The medication guide does not provide the dosage information needed by prescribers. Prescribers should be referred to the insert for dosage information. Therefore, revise the statement to read: Usual dosage: see enclosed prescribing information" or similar verbiage per [21 CFR 201.55].
- 8. Revise the statement <sup>(b) (4)</sup> to "Patients must be tolerant to around-the-clock opioid therapy" since the statement <sup>(b) (4)</sup> <sup>(b) (4)</sup> may be confusing to healthcare providers.
- 9. The warning statements "Keep out of reach of children," "Patients must be tolerant to regular opioid therapy (see comment C-8, above)," "Do not substitute TRADENAME for other fentanyl products," "Tradename can be harmful or fatal if given to someone for whom it was not prescribed," and "Store the bottle in the child-resistant container..." are on one of the side panels. These statements are important to the correct use of the product and require more prominence and visibility. Relocate these warning statements to the principal display panel and enclose them in a box. Additionally, consider using a graphic (such as a stop sign or triangle) near the word "Warning" in order to draw attention to the boxed statements.

consider moving the "Rx Only" statement to the side panel.

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LORETTA HOLMES 03/04/2011

IRENE Z CHAN 03/04/2011

CAROL A HOLQUIST 03/04/2011

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

### PATIENT LABELING REVIEW

Date:	March 2, 2011	
То:	Bob A. Rappaport, MD, Director	
	Division of Anesthesia and Analgesia Products (DAAP)	
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN	
	Acting Team Leader, Patient Labeling Reviewer	
	Division of Risk Management (DRISK)	
From:	Sharon R. Mills, BSN, RN, CCRP	
	Senior Patient Labeling Reviewer	
	Division of Risk Management	
Subject:	DRISK Review of Patient Labeling (Medication Guide/ Instructions for Use)	
Drug Name (established name):	LAZANDA (fentanyl) CII	
Dosage Form and Route:	nasal spray	
Application Type/Number:	NDA 22-569	
Applicant:	SciLucent/Archimedes	
OSE RCM #:	2009-1860	

#### 1 INTRODUCTION

This review is written in response to a request by the Division of Anesthesia and Analgesia (DAAP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and Patient Instructions for Use (IFU).

The Applicant submitted a Class 2 resubmission in response to the Agency's Complete Response Action letter dated June 30, 2010. LAZANDA (fentanyl) nasal spray is a member of the class of transmucosal immediate release fentanyl (TIRF) products. At a meeting held on October 28, 2010, DAAP informed sponsors of the TIRF products of standardized Risk Evaluation and Mitigation Strategy (REMS) materials that could be used in the development of a single shared system to implement REMS for all TIRF products. DAAP then sent a Pre-Approval REMS Notification Letter to the Applicant on November 12, 2010, notifying them that a REMS is needed to ensure the benefits outweith the risks of overdose, abuse, misues, addiction, and serious complications due to medication errors for the product. The Applicant was advised that the necessary REMS elements for LAZANDA (fentanyl) nasal spray should be implemented across the class of TIRF products.

LAZANDA (fentanyl) nasal spray is a 505 (b) (2) product and the Referenced Listed Drug is Actiq, NDA 20-747.

The proposed REMS is being reviewed by DRISK and will be provided to DAAP under separate cover.

#### 2 MATERIAL REVIEWED

- Draft LAZANDA (fentanyl) nasal spray Medication Guide (MG)/Instructions for Use received on September 30, 2010, revised by the review division throughout the review cycle and sent to DRISK on February 17, 2011.
- Draft LAZANDA (fentanyl) nasal spray prescribing information (PI) received September 30, 2010, revised by the Review Division throughout the current review cycle and received by DRISK on February 17, 2011.

#### 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG/IFU the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss.* The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG/IFU document using the Verdana font, size 11.

In our review of the MG/IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG/IFU is consistent with the prescribing information (PI)
- where possible, ensured that the MG/IFU is consistent with the ABSTRAL MG approved on January 7, 2011.
- removed unnecessary or redundant information
- ensured that the MG/IFU meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG/IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG/IFU is consistent with the approved comparator labeling where applicable.
- The enclosed MG/IFU review comments are collaborative DRISK and DMEPA comments.

### 4 CONCLUSIONS

The MG/IFU is acceptable with our recommended changes.

#### 5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- We defer to DMEPA regarding the need for a usability study to be conducted with the Instructions for Use. Given the complexity of the device Instructions for Use and the proposed pouch for priming and disposal of excess medication from LADANZA bottles, DRISK is concerned whether patients will be able to appropriately use LADANZA under real world conditions.
- Our annotated versions of the MG/IFU are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG/IFU.

Please let us know if you have any questions.

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SHARON R MILLS 03/03/2011

LASHAWN M GRIFFITHS 03/03/2011

#### **MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Division of Drug Marketing, Advertising, and Communications

#### \*\*PRE-DECISIONAL AGENCY MEMO\*\*

Date: February 22, 2011

To: Matt Sullivan – Regulatory Project Manager Division of Anesthesia, and Analgesia Products (DAAP)

From: Mathilda Fienkeng – Regulatory Review Officer Twyla Thompson – Regulatory Review Officer Division of Drug Marketing, Advertising, and Communications (DDMAC)

#### Subject: DDMAC draft labeling comments NDA 022569 Fentanyl citrate nasal spray C-II

DDMAC has reviewed the proposed product labeling (PI), Medication Guide, Carton and Container label for fentanyl citrate nasal spray C-II, submitted for DDMAC review on January 21, 2011.

The following comments are provided using the updated proposed PI and Medication Guide sent via email on February 17, 2011, by Matt Sullivan. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

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MATHILDA K FIENKENG 02/22/2011



## MEMORANDUM

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

Date:	February 22, 2011		
To:	Bob Rappaport, M.D., Director Division of Anesthesia and Analgesia Products		
Through:	Michael Klein, Ph.D., Director Controlled Substance Staff		
From:	JianPing (John) Gong, M.D., Ph.D. Medical Officer Stephen Sun, M.D. Medical Officer Controlled Substance Staff		
Subject:	Consultation on Fentanyl Nasal Spray (FNS) Solutio		
	Indication:	22-309 Breakthrough Cancer Pain	
	Strengths:	100  mcg/spray(1  mg/ml, (b) (4)) $400  mcg/spray(4  mg/ml, (b) (4))$	
	Sponsor:	SciLucent/Archimedes	
	<b>Document Date:</b>	January 7, 2011	

### Executive Summary

The Division of Anesthesia and Analgesia Products (DAAP) consulted the Controlled Substance Staff (CSS) regarding the safety risks and abuse potential of Fentanyl Nasal Spray Solution (FNS).

FNS is a new intranasal formulation of the analgesic drug fentanyl that utilizes a pectincontaining nasal delivery system. This NDA received a Complete Response letter on June 30, 2010. The Sponsor resubmitted the application on September 30, 2010, with modification of the device and drug disposal method.

After reviewing the resubmission, we agree that the alternative proposal to spray the drug into an activated carbon cloth pouch is an improvement for disposal of unused fentanyl when compared to the sponsor's original proposal to

<sup>(b)(4)</sup> However, the Sponsor did not provide in the current submission sufficient data to show that the pouch can absorb the maximum amount <sup>(b)(4)</sup> of fentanyl from a full bottle of product. The full bottle contains <sup>(b)(4)</sup> of fentanyl; the residual amount in the device is <sup>(b)(4)</sup>. The residual fentanyl in the pouch may still be accessible for intentional or accidental misuse or abuse. The sponsorprovided data does not adequately address the question of fentanyl extractability from the pouch for purposes of intentional misuse and abuse. Therefore, improper disposal of residual drug still presents diversion risks. To prevent diversion, we recommend the Sponsor develop a method to inactivate or destroy residual drug, or set up a mail-back program to collect the used pouch and used device.

## **Conclusions:**

- 1. The proposed residual drug disposal in the resubmission still presents diversion risks.
- 2. The Sponsor has not provided adequate data to demonstrate the absorptive capability for the entire unused drug, and the difficulty of extracting active drug.
- 3. There is a substantial amount of residual fentanyl in the used pouch and the used bottle.
- 4. The residual fentanyl remains accessible for misuse and abuse and could be extracted or recovered by potential drug abusers and diverters

### **Recommendations (to be conveyed to the Sponsor):**

- 1. Your assay for testing the absorptive capacity needs to be described in more detail. You need to demonstrate that the assay for absorptive capacity is reproducible.
- 2. You need to test the limits of absorption of the pouch.
- 3. You need to systematically test the ability and feasibility of extracting fentanyl from the pouch using a wide range of solvents and test conditions.
- 4. You need to develop a method to inactivate or destroy residual drug, or set up a mail-back program to collect the used pouch and used device.



### **CSS Review**

### **1.** Characterization of the Pouch

#### A, Absorptive capacity of the pouch

The Sponsor conducted a preliminary experiment to investigate the suitability of utilizing activated carbon cloth as a means for capturing and retaining fentanyl. We have the following comments on the data:

According to the instructions that should be provided with the labeling, all unused quantities of the drug product should be dispensed or discarded into the pouch. Thus, the entire unopened unit may be spent into the pouch. The 6cm x 6cm pouch assay shows absorption capability only up to 4 mg of fentanyl. However, a fully unopened, high-concentration unit is 4 mg/mL x <sup>(b)(4)</sup> of fentanyl. An assay that has an upper limit of >2x to 3x ability for drug absorptability would provide a better test for understanding the limits of absorptive capacity of the carbon pouch. Thus, we do not know based on the assay if the pouch can get saturated. The Sponsor should repeat the test to achieve a saturation point of the pouch.

In addition, based on the assay one-pager, the methodology needs to be better described: sampling (what was the quantity?), pouch fully immersed in solution the whole time, can a diagram of methodology be provided? Sponsor needs to provide better documentation of methodology so that the study can be reproduced.

## B, Extraction of fentanyl from the pouch

Although fentanyl can be absorbed and retained in the activated carbon pouch, it is not inactivated chemically and, therefore, the fentanyl is potentially recoverable. The Sponsor conducted several experiments to show the difficulty of extracting fentanyl from the pouch. After reviewing all of the details of the experiments, CSS has two comments for those assays:

Firstly, these studies are methodologically flawed because the pouches were sealed with their adhesive flaps before being placed into the different media solutions for incubation, and the outer layer of the pouch is a water-impermeable barrier.

Secondly, the choice of test media and conditions are too limited. The Sponsor only tested it with water (room temperature), simulated saliva ( $37^{\circ}$ C), simulated gastric fluid ( $37^{\circ}$ C) and simulated intestinal fluid ( $37^{\circ}$ C).

These experiments do not test extractability for the pouches if not sealed prior to disposal, or if the pouches are intentionally manipulated (that is, cut into pieces) to extract active drug for diversion purposes. Therefore, the experiments are inconclusive in terms of testing the extractability of fentanyl from the pouch for intentional misuse and abuse.

## 2. Drug Disposal

### A, Amount of fentanyl in used device

This product contains a total of <sup>(b)(4)</sup> of FNS solution. After priming <sup>(b)(4)</sup>), 8 dosing <sup>(b)(4)</sup> and expelling <sup>(b)(4)</sup>), the volume of residual drug in the bottle is about <sup>(b)(4)</sup>, which includes about <sup>(b)(4)</sup> and <sup>(b)(4)</sup> fentanyl, for 100 mcg and 400 mcg strengths, respectively.

## B, Amount of fentanyl absorbed in pouch

For the purpose of disposing of priming sprays, unused dose sprays, and liquids remaining in the bottle at the end of use, the Sponsor proposed to use a pouch lined with activated carbon cloth to absorb and retain the drug. Each FNS spray bottle will have one pouch.

The priming volume is (b)(4) (Table 3.2.P.2.4-27 in page 39, Sequence 0025) and (b)(4) of liquid can be expelled from FNS spray bottle with additional spraying after end-of-use (Table 3.2.P.2.4-29 in page 40, Sequence 0025). Therefore, the volume of fentanyl absorbed in each pouch should be more than (b)(4) which includes more than (b)(4) fentanyl, for the 100 mcg/mL and 400 mcg/mL dosing strengths, respectively

respectively.

## C, Disposal of used pouch and used device

The Sponsor is planning to dispose the used pouch and the used device, both with residual fentanyl, in the trash. The used device will be disposed in a child-resistant container.

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Jianping P GONG 02/22/2011

MICHAEL KLEIN 02/22/2011

#### **MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Division of Drug Marketing, Advertising, and Communications

#### \*\*PRE-DECISIONAL AGENCY MEMO\*\*

Date: June 22, 2010

- To: Matt Sullivan Regulatory Project Manager Division of Anesthesia, and Analgesia Products (DAAP)
- From: Mathilda Fienkeng Regulatory Review Officer Twyla Thompson – Regulatory Review Officer Division of Drug Marketing, Advertising, and Communications (DDMAC)

#### Subject: DDMAC draft labeling comments NDA 022569 PecFent (fentanyl) nasal spray C-II

DDMAC has reviewed the proposed product labeling (PI), Medication Guide, Carton and Container label for PecFent (fentanyl) nasal spray C-II (PecFent), submitted for DDMAC review on October 7, 2009.

The following comments are provided using the updated proposed PI and Medication Guide sent via email on June 9, 2010 by Matt Sullivan. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

Nas\_PI\_3.1\_13 Aug 09

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

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MATHILDA K FIENKENG 06/22/2010



## MEMORANDUM

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

April 29, 2010		
Bob Rappaport, M.D., Director Division of Anesthesia and Analgesia Products		
Michael Klein, Ph.D., Director Lori A. Love, M.D., Ph.D., Lead Medical Officer Controlled Substance Staff		
JianPing (John) Gong, M.D., Ph.D. Controlled Substance Staff		
Consultation on Fen NDA #: Indication: Strengths: Sponsor: Document Date: PDUFA Goal Date:	tanyl Nasal Spray (FNS) Solution 22-569 Breakthrough Cancer Pain 100 mcg/spray(1 mg/ml, <sup>(b) (4)</sup> ) 400 mcg/spray(4 mg/ml, <sup>(b) (4)</sup> ) SciLucent/Archimedes August 30, 2009 June 30, 2010	
	April 29, 2010 Bob Rappaport, M.I. Division of Anesthes Michael Klein, Ph.D. Lori A. Love, M.D., Controlled Substance JianPing (John) Gor Controlled Substance Consultation on Fen NDA #: Indication: Strengths: Sponsor: Document Date: PDUFA Goal Date:	

Materials Reviewed:	CSS reviewed the abuse relevant sections in NDA 22-569
	located in the EDR ( <u>\CDSESUB1\EVSPROD\NDA022569</u> ),
	CSS also reviewed the following relevant current memos from
	review division:
1) CMC	review by Dr. Shelly Markofsky on April 23, 2010.

2) Clinical safety review by Dr. Nick Olmos-Lau on April 9, 2010.

## I. Executive Summary

The Division of Anesthesia and Analgesia Products (DAAP) consulted the Controlled Substance Staff (CSS) regarding the safety risks and abuse potential of Fentanyl Nasal Spray Solution (FNS). FNS is a new intranasal formulation of the analgesic drug fentanyl that utilizes a pectin-containing nasal delivery system. After completing our review, we conclude that this product has several serious abuse-related safety concerns. The large amount of fentanyl in this product along with the possibility to compromise the device by deliberate or inadvertent tampering is an increased risk to the public health compared to other currently marketed fentanyl products. Improper disposal of the drug product and residual drug in the device presents additional safety and diversion risks. We conclude the following:

- There is a large amount of fentanyl <sup>(b) (4)</sup> respectively, for each concentration) in this product. A substantial amount (approximately one-third, or <sup>(b) (4)</sup>, respectively, for each concentration) of residual fentanyl remains in the bottles after complete use.
- The current device can easily be compromised to remove the available amount of fentanyl, that is, the complete dosage before use or any residual remaining after use.
- The current device is subject to malfunction or patient compliance problems, as demonstrated in phase 3 clinical studies.
- The current recommended disposal methods are inadequate to assure safety: these include (b)(4) and disposal of the device with residual drug in a proposed childproof container. The device priming method presents similar concerns.
- The *in vitro* study of FNS when mixed with human plasma is methodologically flawed, because of the sponsor's choice of anticoagulant used to prepare the plasma. Therefore, potential safety problems that may result with this product, if injected, are unknown.

## **Recommendations**

To improve the risk to benefit profile of this product, we recommend the following:

- Improve the bottle design [including the cap sealing], improve device reliability and minimize user errors.
- Propose an alternative method to dispose of the excess fentanyl solution when priming and for device lockout.
- Minimize the total volume of drug and decrease or destroy residual active pharmaceutical ingredient (API) at disposal.
- We normally recommend a lockout after each dosing for this kind of product. However, we recognize the special needs for adequate pain control associated with break through cancer pain.
- The Division should consider whether a label warning is necessary and appropriate if FNS is used by injection. We recommend the following statement be considered in labeling for the drug safety section: "If FNS is administered by injection, the potential risks are unknown."



• To assure safety, this product will require a REMS similar to other fentanyl breakthrough pain products.

### II. Review

### A. Background

Fentanyl Nasal Spray (FNS) is an intranasal formulation of the analgesic drug fentanyl that utilizes the PecSys<sup>TM</sup> nasal delivery technology. <sup>(b) (4)</sup> pectin, <sup>(b) (4)</sup> agent that allows fentanyl citrate to be delivered locally in the nose by standard spray pump. In the nose, the calcium in nasal mucosal secretions interacts with the pectin to form a gel. The fentanyl diffuses from the gel and is absorbed across the nasal mucosa.

Fentanyl is controlled as a Schedule II substance under the Controlled Substances Act (CSA).

### **B. Product Information**

FNS is indicated for management of BTCP (breakthrough cancer pain) in patients who are already receiving and who are tolerant to regular opioid therapy

The Sponsor developed two strengths of FNS for marketing: 1.0 mg/mL and 4.0 mg/mL fentanyl base, equivalent to 1.57 mg/mL and 6.28 mg/mL fentanyl citrate, respectively.

## C. Chemistry

#### **1. Large volume of fentanyl**

The FNS device contains of fentanyl solution in either 1 mg/ml or 4 mg/ml strengths. The total fentanyl citrate is 1.57 mg and 6.28 mg respectively.

Fentanyl is a synthetic primary  $\mu$ -opioid agonist. It is approximately 100 times more potent than morphine in analgesic activity. The large amount of fentanyl in this product is a significant public health risk.

#### 2. Device tamperability and malfunction

FNS is in a 5.3 mL capacity glass bottle sealed with a locking screw closure, metereddose nasal spray pump. The pump contains an integrated visual and audible spray-counter and mechanical end-of-use lock.

Industrial strength glue secures the device tops. This method is not sufficient to deter a person from overcoming the seal and gaining access to a substantial residual amount of fentanyl. The ease of tampering was demonstrated by a subject during the clinical trial. The CMC reviewer (Dr. Markofsky) noted that the top part of the pump (the nasal spray

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actuator) could be readily pulled off from the counter ring assembly. Furthermore, three members of the CMC staff were with their bare hands (without the use of any tools) able to unscrew the pump assemblies from three separate glass bottles filled with the placebo solution.

In phase 3 trials, the Sponsor reported 325 cases (1.9% of 17,182 bottles) of potential device malfunction. The Sponsor stated that "some of the reasons for device malfunction were that the bottle appeared empty before the counter reached 8, the counter was already advanced when first received or advanced for an unknown reason, doses were lost during priming, the device did not prime appropriately, medication was dried out in the bottle, and bottle caps came off or leaked."

The Sponsor's statements increase our concerns about the mechanical quality of the FNS device, which contains a C-II substance. We see ease for tempering as potential risks for inadvertent exposure as well as for abuse and diversion. The sponsor must improve the bottle design, the cap sealing, and the device reliability to reduce risks associated with access the residual drug.

## 3. Disposal of primed drug and unused drug in partially used bottle

The FNS prescribing information contains the following instructions for priming and disposal of Fentanyl Nasal Spray:

(b) (4)

In priming [two pump actuations], a total volume of <sup>(b) (4)</sup> fentanyl is sprayed out. At disposal the unused drug in partially used bottle can consist of <sup>(b) (4)</sup> fentanyl. <sup>(b) (4)</sup>. The sponsor needs to improve the safety of its device by using an alternative method to dispose of the excess fentanyl solution when priming, or to obtain device lockout.

## 4. Disposal of residual drug in fully used bottle

This commercial product contains a total of <sup>(b)(4)</sup> of FNS solution. When the device locks (after priming <sup>(b)(4)</sup> and 8 sprays <sup>(b)(4)</sup> there is still <sup>(b)(4)</sup> FNS theoretically <sup>(b)(4)</sup> from the Sponsor's experimental data) in the full use locked bottle. The amount of fentanyl base left in the locked bottle is <sup>(b)(4)</sup>, for 100 mcg and 400 mcg strengths, respectively.

The large amount of recoverable residual fentanyl in FNS bottles represents a significant public health hazard. It will increase the amount of opioid that could be abused or diverted. The sponsor needs to improve the safety of its device by minimizing the total



volume of drug and decrease or destroy residual active pharmaceutical ingredient (API) at disposal.

### 5. Safety of Intravenous Administration of FNS

FNS forms a gel when exposed to calcium ions in the nasal cavity. Fentanyl is a schedule II opioid substance that can be misused or abused by intravenous injection or other parenteral routes. During the development process (EOP2), the Sponsor agreed to conduct a study to determine the likelihood of gelling if FNS contacted with human blood plasma.

The Sponsor conducted *in vitro* studies using plasma prepared from citrated human blood. From the results obtained, the Sponsor concluded that FNS does not form a gel when mixed with plasma.

We do not agree with the Sponsor's conclusion. The *in vitro* study of FNS mixing with human blood plasma is methodologically flawed because of the sponsor's choice of citrate as an anticoagulant, which binds calcium. Therefore the potential safety problems that may result when this product is injected are unknown.

#### **D.** Clinical Experience

There are totally 8 clinical trials conducted by the Sponsor. Our review focused on drug accountability and abuse liability narratives.

#### **1. Drug Accountability**

In the Sponsor's summary, there were 3 reports of drug loss consisting of 2 reports of theft (1 and 18 bottles) and 1 report of accidental loss (2 bottles).

- 2 boxes containing 18 bottles were stolen from a patients' car
- 1 bottle in its CRC (child-resistant outer container) was removed from a shipment container that was damaged in transit.
- There was 1 incident of a kit (10 bottles) being lost by a patient (left on a bus); but 8 of the 10 bottles were subsequently recovered intact.

From the Sponsor's analysis of the Phase 2/3 clinical data, 17,182 8-spray bottles of FNS were the distributed and dispensed, of which 17,003 (99.0%) were returned, with 179 (1%) being diverted. For controlled substances, we are interested in both the total units of the drug and the dose. Thus using only returned bottle counts for drug accountability does not provide an adequate and accurate picture of drug accountability for a controlled substance. Furthermore, the Sponsor's current methods of disposal,

confounds the drug accountability issues of a controlled substance.

#### 2. Abuse Liability Narratives

# **FD** MEMORANDUM

The staff participating in the FNS trials was trained to detect signs of abuse of the drug product. From the safety review by Dr. Olmos-Lau, the following subjects were identified to have potentially aberrant behaviors during Phase 3 studies.

**Subject 393701** was a 65 year-old Hispanic subject in Study CP043 who was titrated to 400 mcg. After completing the double-blind phase of treatment he was rolled over to study CP045 and continued treatment. During this phase it was noted that his medication use was higher than the number of episodes reported in his diary. In one instance he reported treating 5 episodes in one day. On day #81 he was found to have intentionally abused/misused medication and he was withdrawn from the study, returning a considerable amount of unused study-medication. There was no previous history of drug abuse at enrollment.

**Subject 390703** was a 50 year-old Caucasian subject in Study CP043 who titrated up to 800 mcg of FNS. After successful completion of the double-blind phase was rolled into Study CP045. During the open-label treatment phase the subject persistently continued to treat 4 BTCP episodes daily, without recording them in the e-diary. The subject was withdrawn from the study on day #98 for non-compliance. There was no previous history of drug abuse.

**Subject 410704** was a 39 year-old Caucasian subject that started the titration process. This subject returned 3 days later complaining that the e-diary would not upload and was unable to record any pain episodes. The subject returned empty bottles of study drug and was withdrawn from the study from lack of efficacy. There was no previous history of medication abuse.

**Subject 393703** was a 59 year-old Caucasian subject in Study CP043 who titrated up to 800 mcg. The subject successfully completed the double-blind phase, and was rolled over to Study CP045. During the double-blind phase his medication use was noted to be higher than the number of episodes reported on the e-diary (+43%). In other words, there was a mismatch between the number of doses used and the number of episodes of BTCP recorded in the e-Diary. There was an average occurrence of 2.9 episodes daily, and not exceeding 4 episodes daily. On study day #36 he was reported to have abused medication. This apparently started previously and was detected during a telephone call where he admitted consuming all 80 doses available. The subject returned to site 7 days later (study day #41) and was withdrawn from the study for nausea and diarrhea. The subject returned all containers empty. He admitted to having experienced a previous episode of OxyContin withdrawal syndrome 8 months prior to enrollment.

These clinical studies were carried out in opioid-tolerant cancer population with breakthrough pain. In general, the cancer subpopulation is not considered to be the most vulnerable population for drug abuse, addiction and diversion. Even when the occurrence of the abuse related behaviors in the cancer population is low, the risks for abuse and addiction of this product in poly drug abuser population will still exist.

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

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Jianping P GONG 04/29/2010

LORI A LOVE 04/29/2010

LORI A LOVE on behalf of MICHAEL KLEIN 04/29/2010

#### CLINICAL INSPECTION SUMMARY

DATE: March 09, 2010 TO: Mathew Sullivan, Regulatory Project Manager Daniela Vanco, M.D., Medical Officer Division of Anesthesia, Analgesic, and Rheumatology Products Roy Blay, Ph.D. FROM: Good Clinical Practice Branch II **Division of Scientific Investigations** THROUGH: Tejashri Purohit-Sheth, M.D. **Branch Chief** Good Clinical Practice Branch II **Division of Scientific Investigations** SUBJECT: Evaluation of Clinical Inspections. NDA: 22-569 **APPLICANT:** Archimedes Development Ltd c/o Scilucent LLC PecFent DRUG: NME: No THERAPEUTIC CLASSIFICATION: Standard Review INDICATION: Treatment of breakthrough pain in opioid-tolerant cancer patients receiving around the clock opioids for their chronic pain. CONSULTATION November 9, 2009 **REQUEST DATE:** DIVISION ACTION GOAL DATE: June 18, 2010 PDUFA DATE: June 30, 2010

## I. BACKGROUND:

This application was submitted in support of the use of PecFent in the treatment of breakthrough cancer pain for those individuals on regular opioid therapy. The conduct of the pivotal study (Protocol CP043/06/FCNS entitled "A Multicenter, Placebo-Controlled, Double-Blind, Two-Phase Crossover Study of Nasalfent (Fentanyl Citrate Nasal Spray) in the Treatment of Breakthrough Cancer Pain (BTCP) in Subjects Taking Regular Opioid Therapy") was inspected.

PecFent is indicated for breakthrough pain in opioid-tolerant cancer patients receiving around the clock opioids for their chronic pain.

The primary objective of this study was to demonstrate the efficacy of Nasalfent (also known as PecFent) in the treatment of BTCP in opioid tolerant subjects who are receiving regular opioid therapy.

For this study, the primary efficacy endpoint was the Summed Pain Intensity Difference 30 minutes after dosing (SPID30min) defined as the cumulative sum of the recorded difference between pain intensity and baseline. Pain intensity was measured on an 11-point categorical scale where 0 = no pain and 10 = worst possible pain.

The following clinical sites were selected for inspection because of their high enrollments. In addition, Dr. Galan's site reported the largest number of protocol violations.

Name of CI, Location	Protocol #/	Inspection Dates	Final Classification
	# of Subjects/		
Mark R Wallace, M.D.	CP043/06/FCNS/	17 Dec 09-11 Jan 10	VAI
UCSD Clinical Trials Center	10/		
9310 Campus Pt. Drive			
Mod A, Rm 117			
UCSD Clinical Trials Center			
La Jolla, CA 92037			
United States			
Phone#: 602-252-6855			
Fax#: 602-252-2223			
E-Mail: markw@samaritan.edu			
Vincent Galan, M.D.	CP043/06/FCNS/	11-21 Jan 2010	VAI
SRMC Pain Clinic	15/		
11 Upper Riverdale Rd. SW			
Riverdale, GA 30274			
United States			
Phone#: 770-991-2289			
Fax#: 954-323-4094			
E-Mail: vgalan@msn.com			

## **II. RESULTS (by Site):**

Key to Classifications

- NAI = No deviation from regulations.
- VAI = Deviation(s) from regulations.
- OAI = Significant deviations from regulations. Data unreliable.
- Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.
- Mark R Wallace, M.D. UCSD Clinical Trials Center 9310 Campus Pt. Drive Mod A, Rm 117 UCSD Clinical Trials Center La Jolla, CA 92037
  - **a.** What was inspected: At this site, ten subjects were screened for the study, nine were enrolled, and eight completed the study. An audit of the records of all nine enrolled subjects was conducted. All informed consent documents were reviewed. IRB documentation was reviewed as was the reporting of intercurrent illnesses, concomitant medications, and adverse events. Records regarding adherence to inclusion/exclusion criteria, laboratory data, visit scheduling, and test article compliance and accountability were also reviewed.
  - **b.** General observations/commentary: A Form FDA 483 was issued at the conclusion of the inspection. Inspection revealed that Amendment 1 of the protocol was not submitted to the IRB for approval; however, this amendment was the protocol version used throughout the study. Also revealed were dosing discrepancies between electronic diary records and the Investigational Product Accountability Records (IPAR) for Subjects 07, 08, 09, and 010 that occurred during the titration period.

Dr. Wallace responded adequately to the inspectional findings in a letter dated February 1, 2010, in which he stated that it was an oversight that Amendment 1 of the protocol was not submitted to the IRB. Dr. Wallace noted that Amendment 1 changed the company responsible for reporting serious adverse events and that there were no changes affecting patient safety or protocol procedures. Dr, Wallace also accounted for the discrepancies in dosing for Subjects 07, 09, and 010. Subject 08 had a discrepancy in dosing having claimed to have taken seven 400 mcg doses which conflicted with both the IPAR and canister counter which indicated six doses taken. Dr. Wallace was unable to reconcile this discrepancy and furthermore noted that there was no record of such discrepancy in the subject's file. Dr. Wallace committed to adhering to IRB requirements in the future and has hired a regulatory specialist to ensure that future IRB documentation is handled in an appropriate, timely fashion. Dr. Wallace also acknowledged the need for additional oversight of Investigational Product accountability and committed to working closely with the institutional Investigational Drug Services to ensure consistent accountability across all related documentation.

- **c.** Assessment of data integrity: The review division may wish to consider excluding data from Subject 08 since it is unclear whether the subject received six or seven doses of the investigational product. Otherwise, the other noted regulatory violations are unlikely to affect data integrity in a substantive manner. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.
- Vicente Galan, M.D. 1365 Rock Quarry Road, Ste 304 Pain Care, LLC Stockbridge, GA 30281
  - **a.** What was inspected: At this site, fifteen subjects were enrolled with one subject being a screen failure. An audit of the records of all fifteen subjects was conducted. All study subjects were noted as having signed the appropriate informed consent document(s). IRB and monitoring correspondence was reviewed as were subject study records which consisted of, but were not limited to visit reports, medical records clinical laboratory results, concomitant medication listings, and data clarification forms. Adverse event reporting, drug accountability, and adherence to inclusion/exclusion criteria were also reviewed.
  - **b.** General observations/commentary: A Form FDA 483 was issued noting that all concomitant medications were not documented for Subjects 102, 109, and 113. Inspection revealed that study conduct was rendered somewhat problematic because of the subjects' use of Palm Pilots for data collection. Some subjects noted difficulty in downloading data or getting assistance in using the Palms from the firm that provided them for use. Inspection also noted that the containers of the test article were not numbered; instead, the packaging was numbered and if subjects were to mix up canisters out of the packaging, there would be no way to place the canisters back in the package in the correct order. Note that there were no issues identified that impacted drug dispensation to subjects, and subjects received the randomized therapy appropriately.
  - **c.** Assessment of data integrity: The review division may wish to consider excluding data from Subjects 102, 109 and 113 given the status of their concomitant therapies. Otherwise, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

### **III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

The clinical investigator sites of Drs. Wallace and Galan were inspected in support of this NDA. The review division may wish to consider excluding data from Subject 08 at Dr. Wallace's site because of inconsistencies in documenting intake of the investigational product. The review division may also wish to consider excluding data from Subjects 102, 109, and 113 at Dr. Galan's site because of omissions in documenting the use of concomitant medications. Although regulatory violations were noted at both sites, these findings are unlikely to impact overall data integrity, and otherwise, the study appears to have been conducted adequately, and the data generated by the clinical sites of Drs. Wallace and Galan appear acceptable in support of the respective indication.

### {See appended electronic signature page}

Roy Blay, Ph.D. Good Clinical Practice Branch II Division of Scientific Investigations

#### CONCURRENCE:

#### {See appended electronic signature page}

Tejashri Purohit-Sheth, M.D. Branch Chief Good Clinical Practice Branch II Division of Scientific Investigations

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

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ROY A BLAY 03/10/2010

TEJASHRI S PUROHIT-SHETH 03/10/2010