

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209128Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: November 1, 2018

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 209128

Product Name and Strength: Dsuvia (Sufentanil citrate) sublingual tablet
30 mcg

Applicant/Sponsor Name: AcelRx

FDA Received Date: November 1, 2018

OSE RCM #: 2018-966-2 and 2018-990-2

DMEPA Safety Evaluator: James Schlick, MBA, RPh

1 PURPOSE OF MEMORANDUM

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised Directions for Use for Dsuvia to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised Directions for Use (DFU) emailed on November 1, 2018 (to be submitted to the gateway by November 2, 2018) include the revised statement that pertains to the educational video (see Appendix A). We find the revision acceptable from a medication error perspective. We have no further recommendations at this time. We also reviewed the other labels and labeling received on November 1, 2018. We also find these acceptable and have no further comment this time.

^a Schlick J. Label and Labeling Review Memorandum for Dsuvia (NDA 209128). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Oct 17. RCM No.: 2018-966-1 and 2018-990-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED VIA EMAIL ON NOVEMBER 1, 2018

(b) (4)



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/s/

JAMES H SCHLICK
11/01/2018



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

Date: October 30, 2018

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Dominic Chiapperino, PhD, Acting Director
Silvia Calderon, Ph.D.
Senior Pharmacology Reviewer
Controlled Substance Staff (CSS)

From: James R. Hunter, BS Pharm., MPH, Senior Regulatory Reviewer

Subject: **Sufentanil Sublingual Tablet; NDA 209128**
Trade name: Dsuvia
Indication: Management of moderate-to-severe acute pain severe enough to require an opioid agonist, in adult patients in a medically supervised setting.
Dosages: Sufentanil citrate 30 mcg in a single-use, disposable single-dose applicator.
Sponsor: AcclRx Pharmaceuticals

Materials reviewed: Materials submitted under original NDA 209128 dated September 12, 2016 and resubmitted NDA 2019128 received May 3, 2018.

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I. SUMMARY

A. BACKGROUND

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted CSS to review NDA 209128 for Dsuvia (sufentanil sublingual tablet 30mcg) from a controlled substance/abuse potential perspective. The current consult refers to the second-cycle review of the original NDA 209128 submitted December 12, 2016. FDA review of the original NDA submission resulted in a CR letter. However, CSS did not note any of the concerns with the original submission that were the basis for the CR letter. The Sponsor re-submitted the 505(b)(2) drug application for Dsuvia on May 3, 2018. CSS was consulted for this second cycle application. In this resubmission, the Sponsor submitted data addressing concerns in the CR such as: the Human Factors validation study did not support safe and effective use due to potential for dropped tablets; the need for additional stability data; and the need for modifications to the proposed REMS intended to keep Dsuvia out of the home setting.

Sufentanil is a potent opioid and a Schedule II controlled substance. The sufentanil sublingual tablet 30 mcg (“SST 30 mcg”) is a drug-device combination product comprised of a (b) (4) single-dose applicator (SDA) containing the drug product (sufentanil sublingual tablet 30 mcg). The drug device combination allows the administration of a single microtablet for the management of moderate-to-severe acute pain severe enough to require an opioid agonist, for which alternative treatments are inadequate, in adult patients in a medically supervised setting. Dsuvia SST is not intended for outpatient use or by children. Each tablet contains 45 mcg of sufentanil citrate, equivalent to 30 mcg of sufentanil base, packaged in a single-use, disposable single-dose applicator. The single-dose applicator helps the patient place the microtablet under the tongue in the sublingual space. The proposed dosing regime is a single SST 30 mcg on an as needed basis and per patient request, with a minimum of 1 hour between doses. Dosing is not to exceed 12 tablets in 24 hours.

B. CONCLUSIONS

1. CSS has not identified additional issues of concern from the CSS perspective in a review of resubmitted NDA 209128.
2. Dsuvia SST contains one sublingual tablet which contains 45 mcg of sufentanil citrate equivalent to 30 mcg sufentanil base, a potent, Schedule II, μ -opioid agonist with a high abuse potential.
3. Dsuvia SST has features designed to limit unauthorized access, such as single-use packaging and restrictions on product use, such as caregiver-only administration for adult-only use in certified medical settings, with no allowance for outpatient dispensing or use.

4. The major risks associated with Dsuvia SST are: opioid overdose, if the caregiver dispenses more tablets over a shorter time interval than recommended; and unauthorized access to the product for purposes of misuse and abuse. The single-use applicator minimizes the chance that caregivers will inadvertently administer multiple tablets simultaneously, while also making additional tablets unavailable for future misuse and abuse if not consumed by the patient at time of dispensing.
5. Unauthorized access to sufentanil tablets in the Dsuvia SST could occur in the medical setting with improper storage or record keeping, or tampering of the single-use device to remove the tablet, however there is no reason to believe that the risk of occurrence would be greater or different from other Schedule II opiates also being dispensed at the facility.

C. RECOMMENDATIONS (SUGGESTED TO BE CONVEYED TO THE SPONSOR)

1. CSS has the following recommendations regarding Dsuvia SST labeling. Additions to the label are indicated in underlined text and deletion in strikethrough text:
 - a) In Section 5.4, WARNINGS AND PRECAUTIONS, Addiction, Abuse and Misuse; indicate in the first sentence that sufentanil has high abuse potential. The first sentence must read, “Dsuvia contains sufentanil, a Schedule II controlled substance with high abuse potential. (Note: This suggested labeling change was discussed with DAAAP at a recent labeling meeting, and DAAAP agreed to consider the suggested change in the next cycle of class labeling changes for all Schedule II opioid products.)”

II. DISCUSSION

Product Information:

The approved drug product sufentanil citrate solution (Sufenta®), classified as a CII narcotic since 1985, is the listed drug for this 505(b)(2) application. Sufenta is approved for intravenous (IV) anesthetic use in doses up to 30 mcg/kg for an operative procedure and is usually delivered as a single IV bolus or as an infusion by the anesthesiologist as an adjunct analgesic in the maintenance of anesthesia in patients who are intubated and ventilated. AcelRx did not request a change in scheduling.

Clinical Pharmacology:

According to the Sponsor, the proposed tablet formulation of Desuvia is an immediate-release drug product with high transmucosal bioavailability and low oral bioavailability (less than 10%). Sufentanil citrate is soluble in water, sparingly soluble in alcohol, sparingly soluble in acetone and chloroform, and freely soluble in methyl

alcohol. Solubility of sufentanil citrate in water is 46 mg/mL. Sufentanil's high potency, high affinity for the μ receptor, high lipophilic properties, rapid central nervous system penetration, and lack of active metabolites, along with the proposed tablet formulation's small tablet size (3mm), and high transmucosal bioavailability contribute to its high abuse liability. The sponsor has not performed formal laboratory studies on extraction of sufentanil from the product, and relies on results from process development, product characterization, and basic chemistry manufacturing data. The Sponsor states that the drug product is easily crushed and could be insufflated, and that the product can be dissolved in a readily available solvent and injected, resulting in higher bioavailability than administration by the intended sublingual route. Therefore, the proposed sublingual sufentanil tablet formulation in Desuvia has no features specifically designed to deter abuse through the intranasal or injectable route of administration. The low oral bioavailability (10%) of sufentanil citrate substance may limit its abuse liability by this route of administration; however, its high transmucosal bioavailability makes this route of abuse less clinically relevant.

The Sponsor, AcelRx, asserts that sufentanil has abuse potential but expects that the potential for abuse with Dsuvia SST would be reduced compared to currently marketed CII opioid-containing products due to: 1) intended use only in medically supervised settings restricts distribution, 2) the solid dosage form of the sufentanil tablets 3) C_{max} is 10x lower than C_{max} of dose equivalent to IV Sufenta®, 4) only single-dose available as packaged and administered, 5) clear packaging allows tablet to be seen and verified present before use, 6) low oral bioavailability when swallowed, 7) Adverse event profile observed in clinical trials was similar to that reported for other potent opioids in the post-operative setting.

Clinical Trials:

To investigate potentially abuse-related adverse event (AE) signals in clinical trials, the Sponsor identified AE terms possibly suggestive of drug abuse or overdose and monitored for these AEs in four pivotal safety and efficacy studies:

- SAP202, a multicenter, double-blind, placebo-controlled randomized study with oral hydrocodone rescue;
- SAP301, a multicenter, double-blind, placebo-controlled study; and
- SAP302 and SAP303, two multicenter, open label studies.
- Human Factors Study

The incidence of abuse-related AE's was very low in all groups of study patients, with no signals of abuse-related use of the study drug. One patient taking a 20mcg dose reported "Euphoric Mood."

REMS:

The Sponsor proposes a REMS for Dsuvia SST. The major risks to be mitigated are risks associated with use outside the hospital setting. The Sponsor states that the REMS for

Dsuvia SST will consist of a Communication Plan, Elements to Assure Safe Use (ETASU), an Implementation System, and a timetable for submission of various assessments.

The major ETASU is restricting distribution of the product to assure Dsuvia will be dispensed to patients only in supervised medical settings. REMS requirements designed to limit Dsuvia SST use to medical settings include: 1) a valid DEA license for receipt and dispensing of sufentanil, 2) experience with the administration of parenteral opioids, and 3) immediate access to supplemental oxygen and an appropriate opioid reversal agent. Other mitigation features include a REMS safety brochure to inform Health Care Practitioners (HCP) about the safe use of Dsuvia SST. Dsuvia SST is HCP-administered; patients will not handle the drug or the SDA.

CDER's Office of Surveillance and Epidemiology is the lead office in reviewing the adequacy of the REMS to mitigate identified risks of Dsuvia SST.

LABELING:

CSS proposes the following additions (indicated in underlined text) and deletions (indicated in strikethrough text) to draft labeling found under Module 1.14.1.3 (NDA 209128 submission dated 12/12/2016) for the following sections:

5.4 Addiction, Abuse and Misuse

In Section 5.4, this subsection should indicate in the first sentence that sufentanil has high abuse potential. This first sentence should be modified to read:

“Dsuvia contains sufentanil, a Schedule II controlled substance with high abuse potential.” This suggested change will be considered by DAAAP in a future cycle of implementing class labeling changes for Schedule II opioids.

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/s/

JAMES R HUNTER
10/30/2018

SILVIA N CALDERON
10/30/2018

DOMINIC CHIAPPERINO
10/30/2018

Internal Consults

*** Pre-decisional Agency Information ***

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Joan E. Blair, Health Communications Analyst,
Division of Risk Management (DRISK),
Office of Surveillance and Epidemiology (OSE)

From: Koung Lee, Regulatory Review Officer, OPDP

CC: Sam Skariah, Team Leader, OPDP
Ruth Maduro, Safety Regulatory Project Manager, OSE
Selena Ready, Team Leader, DRISK
Kate Heinrich Oswell, Senior Health Communication Analyst
LaShaun Washington-Batts, Risk Management Analyst, DRISK
Cynthia LaCivita, Director, DRISK
Doris Auth, Associate Director, DRISK
Carole Broadnax, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: October 26, 2018

Re: NDA 209128
DSUVIA™ (sufentanil sublingual tablet 30 mcg)
Comments on the draft DSUVIA Risk Evaluation and Mitigation Strategies
(REMS) Enrollment Form and DSUVIA REMS Website Screenshots
(Submission date: 10/19/2018)

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for DSUVIA:

- Healthcare Setting Enrollment Form
- DSUVIA REMS Website Screenshots

The version of the draft REMS materials used in this review were sent from DRISK LaShaun Washington-Batts via email on 10/22/2018. The REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for DSUVIA.

General Comment

Please remind AcelRx Pharmaceutical, Inc. that REMS materials are not appropriate for use in a promotional manner.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- Healthcare Setting Enrollment Form
- DSUVIA REMS Website Screenshots

Specific Comments

OPDP considers the following statement promotional in tone because it omits specific REMS related limitation of use information:

- DSUVIA REMS Website Screenshots:
 - **Indications/Use**

The proposed Indication on the DSUVIA website states:

- DSUVIA is indicated for use in adults in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments, for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

OPDP recommends that it be revised to include the following limitations of use that are REMS related.

- Not for home use or for use in children. Discontinue treatment with DSUVIA before patients leave the certified medically supervised setting.
- Only to be administered by a healthcare provider.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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/s/

KOUNG U LEE
10/26/2018

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: October 17, 2018
Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number: NDA 209128
Product Name and Strength: Dsuvia (Sufentanil citrate) sublingual tablet
30 mcg
Applicant Name: AcelRx
FDA Received Date: May 3, 2018
OSE RCM #: 2018-990-1 and 2018-966-1
DMEPA Safety Evaluator: James Schlick, MBA, RPh
DMEPA Team Leader: Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

AcelRx proposes the inclusion of references to an educational video that has not been evaluated by the Agency. For example, they propose to include the following statement in

(b) (4) Directions for Use:

(b) (4)

This video is considered nonessential information, and as such, the FDA has not evaluated the video. Statements linking to nonessential information may be allowable provided they do not compete with required labeling information and there is an appropriate disclaimer indicating the FDA has not evaluated the materials.

Therefore, we are providing recommendations to the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) and AcelRx to include the following revised language in the Prescribing Information and Directions for Use in Section 2 and 3 below.

2 RECOMMENDATIONS FOR THE DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS (DAAAP)

(b) (4)

3 RECOMMENDATIONS FOR ACELRX

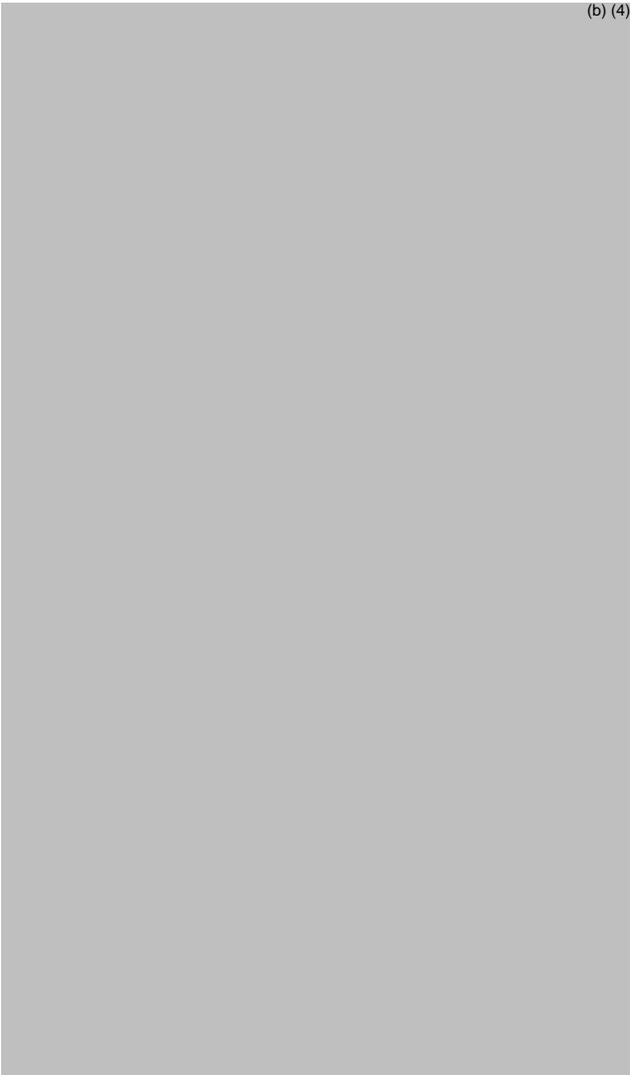
We recommend the following be implemented prior to the approval of this NDA:

- A. In the Directions for Use, revise the statement

(b) (4) to read:

“Additional information, including an instructional video, are available at www.dsuvia.com/video. The additional information has not been evaluated or approved by the FDA.”

APPENDIX A. IMAGES OF DIRECTIONS FOR USE FRONT PAGE RECEIVED ON MAY 3, 2018



(b) (4)

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/s/

JAMES H SCHLICK
10/17/2018

OTTO L TOWNSEND
10/17/2018

HUMAN FACTORS REPORT REVIEW, LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	August 24, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 209128
Product Type:	Combination Product
Drug Constituent Name and Strength	Dsuvia (Sufentanil citrate) sublingual tablet 30 mcg
Device Constituent:	Single-dose Applicator
Rx or OTC:	Rx
Applicant Name:	AcelRx Pharmaceuticals, Inc.
Submission Date:	May 3, 2018, June 7, 2018, and June 25, 2018
OSE RCM #:	2018-990 and 2018-966
Safety Evaluator:	James Schlick, MBA, RPh
Team Leader:	Otto L. Townsend, PharmD
Associate Director for Human Factors:	Quynh Nhu Nguyen, MS
Deputy Director:	Irene Z. Chan, PharmD, BCPS
Director (Acting)/Deputy Director (OMEPRM)	Lubna Merchant, M.S., PharmD.

1 EXECUTIVE SUMMARY

DMEPA reviewed AcelRx's human factors (HF) validation study to determine if the design of the product-user interface supports the safe and effective use of this product by the intended users, for its intended uses, and intended use environments. In the previous review cycle, AcelRx failed to provide data that supported this conclusion with a previously conducted HF validation study. During the previous review cycle, DMEPA identified failures in the study results that could result in dropped tablets, which could lead to accidental exposure of sufentanil. AcelRx did not implement any additional mitigation strategies to address these failures. Thus, we sent recommendations to AcelRx in the Complete Response (CR) letter dated October 11, 2017, advising them to implement risk mitigation changes to the user interface and provide additional HF validation data to demonstrate that the implemented changes to the user interface are effective.

AcelRx subsequently submitted another HF validation study protocol to evaluate the changes incorporated to the user interface based on our recommendations from the CR letter. We provided recommendations to the protocol, which they incorporated prior to testing.

We reviewed the results of the second human factors validation study received on May 3, 2018. Based on the data from this study, we have determined the product-user interface supports the safe and effective use of the product by the intended users, for its intended uses, and intended use environments. In addition, our expert and heuristic review of the proposed label and labeling did not identify any other concerns from a medication error perspective at this time.

2 REASON FOR REVIEW

AcelRx Pharmaceuticals has developed a new single-dose applicator (SDA) that delivers one 30 mcg sufentanil tablet sublingually for the treatment of acute moderate-to-severe pain. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) has requested that we review the human factors (HF) validation study results, device label, pouch label, carton labeling, Directions For Use (DFU), and Prescribing Information (PI) submitted by AcelRx to determine if they are acceptable from a medication error perspective.

3 PRODUCT DESCRIPTION

One Dsuvia (sufentanil) sublingual tablet, 30 mcg, will be housed in a single-dose applicator (SDA). A single tablet is 3 mm in size. One SDA will be packaged within a tamper evident laminate, foil pouch and supplied in 10 pouches per carton. Dsuvia will be administered to the patient's sublingual space, no more frequently than once per hour, by a health care practitioner (HCP) in a medically supervised setting.

4 REGULATORY HISTORY

We initially provided advice related to human factors testing to AcelRx Pharmaceuticals, Inc. during a Type B/Pre-NDA meeting on December 9, 2015 (Meeting Minutes finalized January 12, 2016).^a After evaluating

^a Schlick, J. Human Factors Meeting Package for Sufentanil Sublingual Tablet. IND 113059. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015, Dec 09. RCM No.: 2015-2496.

their proposed HF study protocol received on February 11, 2016,^b we recommended that they include an additional step in the DFU to confirm the placement of the tablet under the tongue.

We reviewed AcetRx's Human Factors Validation Study report received December 12, 2016 and March 21, 2017 and identified failures that could result in dropped tablets and accidental exposure to sufentanil.^c The Applicant did not implement any additional mitigation strategies to address these failures. Thus, we sent recommendations to the Applicant in the Complete Response letter dated October 11, 2017 to implement additional changes to the user interface and provide additional HF validation data to support the implemented changes to the user interface.

AcetRx incorporated our recommendations into their HF Validation Study Protocol and submitted their protocol materials on November 8, 2017, January 3, 2018, and January 25, 2018. We reviewed the proposed protocol and provided additional recommendations for AcetRx, which they incorporated into their validation protocol.^d See Appendix B.1 and B.3 for a summary of the revisions and recommendations. AcetRx submitted their HF Validation Study results report on May 3, 2018 as part of their re-submission in response to the October 11, 2017 Complete Response letter.

5 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Information Request	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

6 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Human Factors Validation Study Results

^b Schlick, J. Human Factors Protocol Review for Sufentanil Sublingual Tablet. IND 113059. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016, Apr 28. RCM No.: 2016-438.

^c Roosta, N. Human Factors Study Results Review for Sufentanil Sublingual Tablet. NDA 209128. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017, Aug 21. RCM No.: 2017-69.

^d Schlick, J. Human Factors Protocol Review for Sufentanil Sublingual Tablet. IND 113059 and NDA 209128. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018, Feb 20. RCM No.: 2017-2362.

- **Summary of Study Design**

The stated objective of this HF validation study was to demonstrate that the SDA can be used by representative users, without training, and under simulated use conditions without producing patterns of failures that could result in a negative clinical impact to patients or injury to the SDA users. All the recommendations we made for the DFU in the last review cycle were incorporated and the revised DFU was tested. The HF validation study was conducted with 45 untrained participants (15 PACU/Floor nurses, 15 ER nurses, and 15 Paramedics licensed in their profession) who were representative of the intended user groups. Each participant was asked to administer the medication three times (3 separately observed use scenarios), and all steps were tested (see Appendix C.1 for each step). Participants were asked six knowledge assessment questions related to important warnings and cautions or critical safety information within the DFU.

- **Results and Analysis**

No failures or close calls occurred during the simulated use task portion of the study. However, there was a study protocol deviation, which we discuss in Table 2 below. This protocol deviation occurred during the knowledge assessment portion of the study, which resulted in the Applicant’s re-categorization of a participant’s response to one knowledge assessment question. In addition to the protocol deviation discussion, we discuss the knowledge assessment results in Table 3 below.

Table 2 – Protocol Deviation			
Protocol Deviation- Knowledge Task Question 3	Correct Response:	Applicant’s Root Cause Analysis	DMEPA’s Analysis
“According to the Directions for Use, should you open the pouch BEFORE you are ready to administer the tablet?”	No	Some participants indicated that they did not understand that this was a “yes/no” question and were confused. The intent of the question was to determine if participants understood when it is acceptable to open the pouch, i.e., per the DFU, “Only when ready to administer the medication”. This was not clear or obvious to all the participants. Some participants initially thought that the question was if they should open the pouch <i>at all</i> before administering the tablet. The protocol deviation was identified after Participant 17 (P17) As such, the Applicant modified the moderator script to include more possible correct answers and re-analyzed the results. One score (P16) was modified from incorrect to correct.	We agree that confusion likely resulted from the wording of the knowledge assessment question. While the study protocol deviation has led to the Applicant’s recategorization of one participant’s response, we find that acceptable. The Applicant found the following responses acceptable for the question. o “When I am ready” o “Only/immediately before I am ready to administer/dose” o “Not until I am ready” o “Right before I am ready” o “Right before I administer

Table 3 - Human Factors Validation Study Results – Knowledge Task Error			
Knowledge Task	Number of Incorrect Responses	Applicant’s Root Cause Analysis	DMEPA’s Analysis and Recommendations
Question 3 - According to the Directions for Use, should you open the pouch BEFORE you are ready to administer the tablet?	1	<p>During root cause probing, she explained that English is her second language and she found the question confusing. She further commented “Should you open the pouch before you are ready? Yes, of course...I think it’s not ‘should you’ open the pouch, it’s ‘when’ should you...that would be more appropriate...if you say ‘should,’ well of course I should!”</p> <p>Root Cause – Study artifact</p> <p>Final Evaluation - This task passed usability validation because there was no pattern of error. The single error was caused by a study artifact.</p>	Confusion likely resulted from the wording of the knowledge assessment question. The subject’s comments suggest she understood, based on the information in the user interface, that that the pouch should be opened prior to administration.

Additionally, we sent an Information Request (IR) on June 1, 2018 to clarify information that was included on the task cards that were used in AcelRx’s HF validation study report and if there were any observance of dropped tablets. Our IR also requested they provide participants’ responses to the subjective feedback questions that the moderator asked the participants during the study (See Appendix F for a link to the Information Request). AcelRx responded on June 7, 2018 to our IR and provided their clarifications. With respect to task card information, they outlined the task to be completed, and they did not provide any leading information. Thus, we did not have any concerns with the information on the task cards. With respect to the observance of dropped tablets, AcelRx clarified there were no dropped tablets observed in any scenario. We’ve provided our analysis of the responses to the subjective questions below.

- **Analysis of Information Request Responses**

In the HF validation study results received on May 3, 2018, the Applicant did not include responses to the subjective feedback question that the moderator asked during the study: “Do you feel that at any time you made an error or mistake, or came close to making any errors or mistakes?” We determined that having the participants’ response to this question would help inform our review and, therefore, we issued an information request (IR) on June 1, 2018. In their June 7, 2018 response to our IR, the Applicant included a list of feedback obtained from participants (see Appendix F). As part of their response, the Applicant stated- “Even though no errors or mistakes were made in the performance of study tasks, some participants indicated they may have made an error or mistake or came close to making an error or mistake.” We were unclear whether additional discussions occurred to obtain additional subjective feedback from study participants in these instances and whether additional mitigations were implemented. As such, we sent a second IR to obtain additional clarification.

The June 25, 2018 response included a summary of the additional discussions and an analysis of the perceived error. As part of this response, the Applicant determined that no additional mitigations were necessary. We learned the perceived errors were related to steps in the IFU that would be helpful for preparation and administration, but were not imperative to successful use. For example, one participant indicated they did not

rest the SDA on the lips prior to pushing the dispenser plunger to deliver the tablet to the sublingual space. Although resting the SDA on the lips is helpful to steady the SDA and included in the IFU, it is not critical that a user must rest the SDA on the lips to successfully administer the product. We found the response acceptable and did not identify any additional mitigation strategies. See Appendix F.1 for links to the Applicant responses.

- **Label and Labeling Assessment**

We reviewed the container label, pouch labeling, carton labeling, and Prescribing Information, and we note that the Applicant addressed our previous label and labeling recommendations. They are acceptable from a medication error perspective and we have no further recommendations at this time.

7 CONCLUSION

Based on the data from this study, we have determined the product-user interface supports the safe and effective use of the product by the intended users, for its intended uses, and intended use environments. In addition, our expert and heuristic review of the proposed label and labeling did not identify any other concerns from a medication error perspective at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Dsuvia received on May 3, 2018 from AcclRx.

Table 4 Relevant Product Information for Dsuvia	
Initial Approval Date	N/A
Active Ingredient	Sufentanil citrate
Indication	Administration by a healthcare professional (HCP) as needed for management of acute moderate-to-severe pain; not to exceed 30 mcg sufentanil per hour.
Route of Administration	Sublingual
Dosage Form	Sublingual tablet
Strength	30 mcg
Dose and Frequency	As needed, not to exceed 30 mcg per hour
How Supplied	The primary container closure system is comprised of one 30 mcg sublingual tablet housed in a single-dose applicator (SDA) and packaged with an oxygen absorber packet; the SDA and oxygen absorber are packaged together in a laminate foil pouch.
Storage	(b) (4)
Container Closure	Each tablet is housed in and dispensed from a disposable SDA.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 PREVIOUS HUMAN FACTORS REVIEWS

B.1.1 Methods

On June 6, 2018, we searched DMEPA's previous reviews using the terms, Dsuvia.

B.1.2 Results

Our search identified three previous reviews^{e,f,g} and we confirmed that our previous recommendations were fully implemented or considered.

OSE RCM #	Review Date	Summary of Recommendations
2017-2362	February 20, 2018	<ul style="list-style-type: none">• Participants in the protocol are instructed by the moderator to read the DFU before attempting the tasks. Requesting participants to read the DFU prior to simulated tasks doesn't represent real-world use. We expect testing to be conducted with untrained participants.• The methodology of the moderator using leading questions to offer an educational video and demonstration of using sample SDAs to untrained participants in the testing environment is not representative of real-world use.• The proposal to conduct a focused human factors study is not adequate to evaluate the product user interface with representative users.• See B.3 below for a side by side comparison of the revisions made based on our recommendations from OSE# 2017-69
2017-69	August 21, 2017	<p>The Human Factors Validation Study identified failures that could result in dropped tablets and accidental exposure to sufentanil. The Applicant did not implement any additional mitigation strategies to address these failures, thus DMEPA recommended the Applicant implement additional risk mitigation strategies and provide additional HF validation data to support changes to the user interface.</p> <p>Our review of the proposed label and labeling identified several areas that can be changed to improve readability and minimize the risk for medication errors. We provided recommendations to the Applicant to address these concerns.</p>

^e Schlick, J. Human Factors Protocol Review for Sufentanil Sublingual Tablet. IND 113059 and NDA 209128. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018, Feb 20. RCM No.: 2017-2362.

^f Roosta, N. Human Factors Study Results Review for Sufentanil Sublingual Tablet. NDA 209128. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017, Aug 21. RCM No.: 2017-69.

^g Schlick, J. Human Factors Protocol Review for Sufentanil Sublingual Tablet. IND 113059. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016, Apr 28. RCM No.: 2016-438.

Table 5. Summary of Previous DMEPA Reviews for Dsuvia (Sufentanil citrate) Sublingual Tablet		
OSE RCM #	Review Date	Summary of Recommendations
2016-438	April 28, 2016	We reviewed the human factors protocol. We made one comment to convey to the Applicant to add an additional step in the DFU to confirm the placement of the tablet under the tongue.

B.2 PREVIOUS FDA/APPLICANT INTERACTIONS

Our search identified one FDA/Applicant interaction^h and we confirmed that our previous recommendations were fully implemented or considered.

Table 6. Summary of Previous FDA/Applicant Interactions for Dsuvia (Sufentanil citrate) Sublingual Tablet		
OSE RCM #	Review Date	Summary of Recommendations
2015-2469	December 09, 2015	We provided general human factors related recommendations to inform the Applicant's product development plan.

^h Schlick, J. Human Factors Meeting Package for Sufentanil Sublingual Tablet. IND 113059. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Dec 9. RCM No.: 2015-2469.

B.3 REVISIONS MADE TO HUMAN FACTORS VALIDATION STUDY PROTOCOL BASED ON RECOMMENDATIONS PROVIDED IN OSE# 2017-69 AND REVIEWED IN OSE# 2017-2362

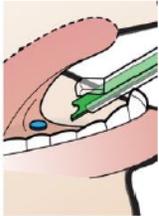
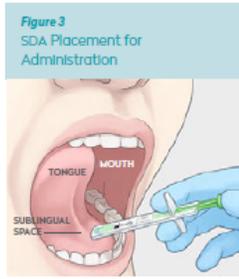
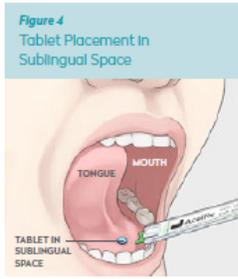
Table 7 – AcclRx Proposed Revisions submitted in November 8, 2017 Meeting Package	
FDA Recommendations in the Complete Response Letter	Proposed AcclRx Revisions
<p>Revise step 6 of the DFU: “Depress the green Pusher to deliver the tablet to the patient’s sublingual space and confirm tablet placement” into two separate steps</p> <p>6. Depress the green Pusher to deliver the tablet to the patient’s sublingual space and confirm tablet placement.</p> <p>7. Discard the used SDA.</p> 	<p>Separated the original Step 6 into two steps (Steps 6 and 7). The revised Step 6 states “GENTLY DEPRESS the green Pusher to deliver the tablet to the patient’s sublingual space (See Figure 3)”. The new Step 7 states “VISUALLY CONFIRM tablet placement in the sublingual space (see Figure 4)”</p> <p>3. TELL the patient to open their mouth and touch their tongue to the roof of their mouth if possible.</p> <p>4. REST the SDA lightly on the patient’s lower teeth or lips.</p> <p>5. PLACE the SDA tip under the tongue and aim at the floor of the patient’s mouth or sublingual space. See Figure 3.</p> <p>NOTE: Avoid direct mucosal contact with the SDA tip.</p> <p>6. GENTLY DEPRESS the green Pusher to deliver the tablet to the patient’s sublingual space. See Figure 3.</p> <p>7. VISUALLY CONFIRM tablet placement in the sublingual space. See Figure 4.</p> <p>NOTE: If tablet is NOT in the patient’s mouth, it is important to retrieve and dispose of the tablet according to Institutional CII waste procedures.</p> <p>8. DISCARD the used SDA.</p>
<p>Modify the figures that depict the patient’s mouth by labeling parts of the mouth, so they represent a more accurate representation of human anatomy. Labeling parts of the mouth within the graphics will help guide users in the proper administration technique.</p> <p>ue to the t’s teeth ie and uth. act with</p>  <p>rer the pace and</p> 	<p>The figures that depict the patient’s mouth have been modified as requested by the Agency to represent the anatomy of the mouth more accurately, as indicated in the Dsuvia DFU, PL-6403 Rev. E. In addition, the parts of the mouth have been labeled to help guide users in the proper administration technique.</p>  

Table 7 – AcelRx Proposed Revisions submitted in November 8, 2017 Meeting Package

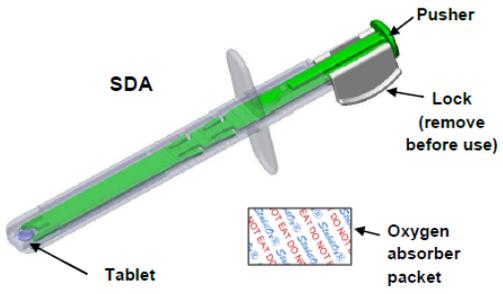
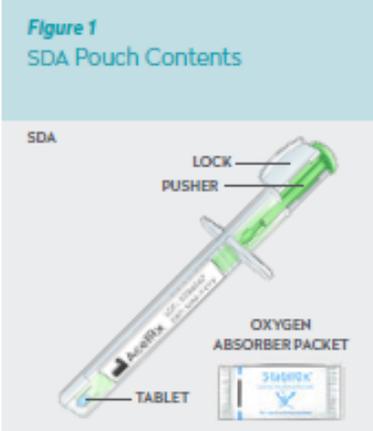
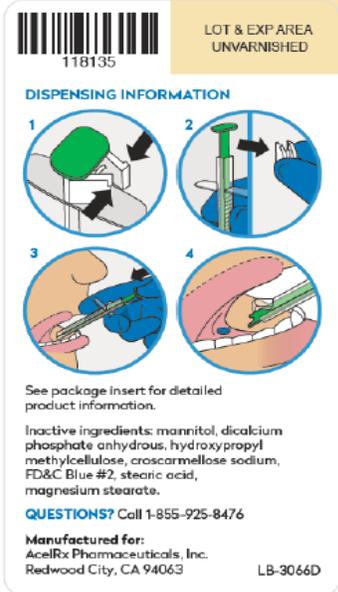
FDA Recommendations in the Complete Response Letter	Proposed AcelRx Revisions
<p>Label each figure (e.g., Figure 1, Figure 2) in the DFU and refer to the figures within the written instructions (e.g. “see Figure 1”).</p>  <p>The diagram shows a clear plastic SDA (Single Dose Administration) pouch. At the top, there is a green 'Pusher' and a grey 'Lock (remove before use)'. Inside the pouch, a blue 'Tablet' is visible at the bottom tip. An 'Oxygen absorber packet' is also shown next to the pouch. The entire assembly is labeled 'SDA'.</p>	<p>Each of the figures have been labeled with numbers and the reference is made to the numbers within the DFU to help guide users quickly to the relevant figures.</p>  <p>Figure 1 SDA Pouch Contents</p> <p>The figure shows the SDA pouch with its components labeled: SDA, LOCK, PUSHER, OXYGEN ABSORBER PACKET, and TABLET. The pouch is shown in a perspective view, with the tablet and oxygen absorber packet clearly visible inside.</p> <ol style="list-style-type: none"> 1. Only when ready to administer the medication, TEAR OPEN the notched pouch across the top. The pouch contains one clear plastic SDA with a single blue-colored tablet housed in the tip, and an oxygen absorber packet. See Figure 1.

Table 7 – AcelRx Proposed Revisions submitted in November 8, 2017 Meeting Package

FDA Recommendations in the Complete Response Letter	Proposed AcelRx Revisions
<p>Replace the simplified graphics on the back of the foil pouch with the complete DFU (written instruction with revised and labeled graphics) such that complete DFU cannot be easily separated from the foil packet prior to use or discarded along with the carton.</p> 	<p>The Dsuvia pouch labels have also been modified as requested by the Agency. The simplified graphics on the pouch back label have been replaced with the complete revised DFU, inclusive of all the changes listed above. The DFU is attached to <u>each</u> pouch as a foldout leaflet label. Ten pouches, each with a DFU attached, will be placed in a 10-Pack carton.</p> <p>See Appendix G for revised Directions for Use</p>
<p>Additional AcelRx Strategies to Further Mitigate the Risk of Dropped Tablets</p>	
<p>The Applicant added a note after Step 7 (visual confirmation of tablet placement), which directs the user on the steps to take if the tablet is not present in the mouth. <i>“Note: If tablet is NOT in the patient’s mouth, it is important to retrieve and dispose of the tablet according to institutional CII waste procedures.”</i></p>	
<p>Proposed AcelRx Modifications to the HF Validation Protocol</p> <p>The protocol has been simplified <u>to focus the validation tests on the changes implemented to the DFU</u> as described above, as other aspects of the previously conducted testing are still valid.</p> <p>The moderator will only score the following:</p> <ol style="list-style-type: none"> 1. Successful tablet dispensing into the patient’s sublingual space. 2. Visual confirmation of the tablet in the patient’s mouth. 3. In the event of a tablet being delivered outside the patient’s mouth, confirmation of the retrieval of the tablet and appropriate disposal of the tablet as CII waste. 4. Answering knowledge questions relating to the mitigations for dropped tablets. 	

APPENDIX C. HUMAN FACTORS STUDY

See Human Factors Validation Study results for detailed information on study design and reported results:

<\\cdsesub1\evsprod\nda209128\0026\m3\32-body-data\32p-drug-prod\sufentanilsublingualtablet-devicecomponents\32p7-cont-closure-sys\hf-summative-usability-validation.pdf>

C.1 SUBTASKS/STEPS TESTED IN HUMAN FACTORS VALIDATION STUDY

Subtask/Step
1. Tears open the notched pouch across the top of the medication
2. Removes Lock from the Pusher.
3. Places the SDA tip under the patient's tongue, into the sublingual space.
4. Depresses the Pusher to deliver the tablet to the patient's sublingual space.
5. Visually confirms tablet is in the sublingual space.
6. If applicable, in the event the tablet is NOT visible in the patient's mouth, effort was made to retrieve and dispose of tablet.
7. Did the HCP drop the SDA and tablet comes out and HCP does not notice?
8. Did the HCP drop the SDA and part comes off without the HCP noticing?
9. Did SDA parts come loose at any time during administration (Choking)?
10. Did the patient swallow any part of the SDA during administration?
11. For Task 2 and Task 3, did the HCP reuse the SDA from Task 1 or 2?

APPENDIX F. INFORMATION REQUEST ISSUED DURING THE REVIEW

F.1 Methods

We sent an Information Request (IR) on June 1, 2018. AcclRx responded on June 7, 2018 and the link to this submission is accessible in EDR via:

<\\cdsesub1\evsprod\nda209128\0028\m1\us\111-info-amend\response-human-factors-req-01jun2018.pdf>

We requested additional information in a second IR and AcclRx responded on June 25, 2018 to our request. The link to this submission is accessible in EDR via:

<\\cdsesub1\evsprod\nda209128\0030\m1\us\111-info-amend\response-hf-info-request-19jun2018.pdf>

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,ⁱ along with postmarket medication error data, we reviewed the following Dsuvia labels and labeling submitted by AcelRx.

- Container label received on May 3, 2018
- Carton labeling received on May 3, 2018
- Instructions for Use received on May 3, 2018
- Prescribing Information (Image not shown) received on May 3, 2018

G.2 Label and Labeling Images



6 Pages have been Withheld in Full as
Draft Labeling Immediately Following this
Page

ⁱ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAMES H SCHLICK
08/24/2018

OTTO L TOWNSEND
08/24/2018

QUYNHNHU T NGUYEN
08/24/2018

LUBNA A MERCHANT on behalf of IRENE Z CHAN
08/27/2018

LUBNA A MERCHANT
08/27/2018

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: April 10, 2018

To: Alison Meyer, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Lisa Basham, Associate Director for Labeling, (DAAAP)

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP labeling comments for Dsuvia (Sufentanil) Tablets

NDA/BLA: NDA 209128

This memo is in response to DAAAP's labeling consult request dated April 20, 2017. Reference is made to a Complete Response letter that was issued on October 11, 2017. Therefore, OPDP defers comment on the proposed labeling at this time, and requests that DAAAP submit a new consult request during the subsequent review cycle. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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

/s/

LATOYA S TOOMBS
04/10/2018

HUMAN FACTORS VALIDATION STUDY PROTOCOL REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: February 20, 2018

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 209128
IND 113059

Product Type: Combination Product

Drug Constituent Name and Strength Dsuvia (Sufentanil citrate) sublingual tablet
30 mcg

Device Constituent: Sublingual Dose Applicator

Rx or OTC: Rx

Applicant/Sponsor Name: AcelRx Pharmaceuticals, Inc.

Submission Date: November 8, 2017, January 3, 2018, and January 25, 2018

OSE RCM #: 2017-2362

DMEPA Safety Evaluator: James Schlick, MBA, RPh

DMEPA Team Leader: Otto L. Townsend, PharmD

DMEPA Associate Director for Human Factors: Quynh Nhu Nguyen, MS

1. REASON FOR REVIEW

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested a Human Factors consultative review of a human factors validation study protocol submitted as part of the November 8, 2017 meeting package for Dsuvia (sufentanil) sublingual tablet. DAAAP also requested that we answer human factors related questions found in the meeting package.

This device is a combination product with a proposed sublingual tablet dose applicator and is intended to treat moderate to severe acute pain.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH) and FDA/Sponsor Interactions	B
Human Factors Validation Study Protocol	C
Review of Product Sample	D N/A
Information Requests Issued During the Review	E
CDRH Human Factors Consult Review	F N/A

3 BACKGROUND

We reviewed AcclRx's previous human factors (HF) validation study (see Appendix B.1.2, OSE# 2017-69) and identified failures that could result in dropped tablets and accidental exposure to sufentanil. The Applicant did not implement any additional mitigation strategies to address these failures. Thus, we sent recommendations to the Applicant in the Complete Response letter dated October 11, 2017 to implement additional changes and provide additional HF validation data to support changes to the user interface. AcclRx has considered our recommendations and proposed revisions to their human factors protocol to address the deficiencies. Table 2 provides a side by side comparison of the FDA identified deficiencies and AcclRx's proposed revisions, along with other AcclRx proposed changes to the human factors validation study protocol.

Table 2 – AcelRx Proposed Revisions submitted in November 8, 2017 Meeting Package

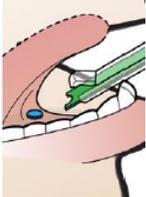
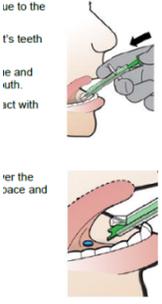
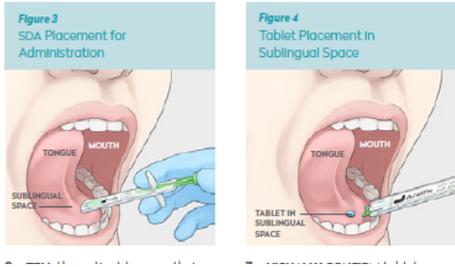
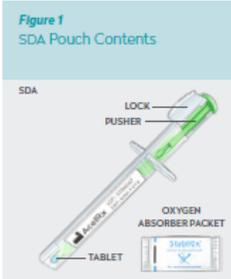
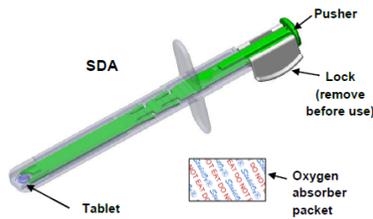
FDA Recommendations in the Complete Response Letter	Proposed AcelRx Revisions
<p>Revise step 6 of the DFU: “Depress the green Pusher to deliver the tablet to the patient’s sublingual space and confirm tablet placement” into two separate steps</p> <p>6. Depress the green Pusher to deliver the tablet to the patient’s sublingual space and confirm tablet placement.</p> <p>7. Discard the used SDA.</p> 	<p>Separated the original Step 6 into two steps (Steps 6 and 7). The revised Step 6 states “GENTLY DEPRESS the green Pusher to deliver the tablet to the patient’s sublingual space (See Figure 3)”. The new Step 7 states “VISUALLY CONFIRM tablet placement in the sublingual space (see Figure 4)”</p> <p>3. TELL the patient to open their mouth and touch their tongue to the roof of their mouth if possible.</p> <p>4. REST the SDA lightly on the patient’s lower teeth or lips.</p> <p>5. PLACE the SDA tip under the tongue and aim at the floor of the patient’s mouth or sublingual space. See Figure 3.</p> <p>NOTE: Avoid direct mucosal contact with the SDA tip.</p> <p>6. GENTLY DEPRESS the green Pusher to deliver the tablet to the patient’s sublingual space. See Figure 3.</p> <p>7. VISUALLY CONFIRM tablet placement in the sublingual space. See Figure 4.</p> <p>NOTE: If tablet is NOT in the patient’s mouth, it is important to retrieve and dispose of the tablet according to Institutional CII waste procedures.</p> <p>8. DISCARD the used SDA.</p>
<p>Modify the figures that depict the patient’s mouth by labeling parts of the mouth so they represent a more accurate representation of human anatomy. Labeling parts of the mouth within the graphics will help guide users in the proper administration technique.</p> 	<p>The figures that depict the patient’s mouth have been modified as requested by the Agency to more accurately represent the anatomy of the mouth, as indicated in the Dsuvia DFU, PL-6403 Rev. E. In addition, the parts of the mouth have been labeled to help guide users in the proper administration technique.</p> 
<p>Label each figure (e.g., Figure 1, Figure 2) in the DFU and refer to the figures within the written</p>	<p>Each of the figures have been labeled with numbers and the reference is made to the numbers within the DFU to help guide users quickly to the relevant figures.</p>

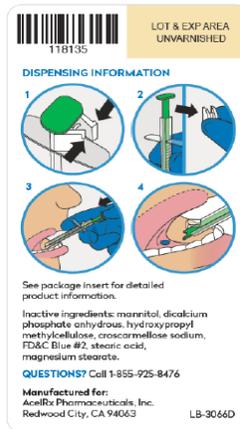
Table 2 – AcelRx Proposed Revisions submitted in November 8, 2017 Meeting Package

instructions (e.g. “see Figure 1”).



1. Only when ready to administer the medication, **TEAR OPEN** the notched pouch across the top. The pouch contains one clear plastic SDA with a single blue-colored tablet housed in the tip, and an oxygen absorber packet. **See Figure 1.**

Replace the simplified graphics on the back of the foil pouch with the complete DFU (written instruction with revised and labeled graphics) such that complete DFU cannot be easily separated from the foil packet prior to use or discarded along with the carton.



The Dsuvia pouch labels have also been modified as requested by the Agency. The simplified graphics on the pouch back label have been replaced with the complete revised DFU, inclusive of all the changes listed above. The DFU is attached to each pouch as a foldout leaflet label. Ten pouches, each with a DFU attached, will be placed in a 10-Pack carton.

See Appendix C for link to revised Directions for Use

Additional AcelRx Strategies to Further Mitigate the Risk of Dropped Tablets

The Sponsor added a note after Step 7 (visual confirmation of tablet placement), which directs the user on the steps to take if the tablet is not present in the mouth. *“Note: If tablet is NOT in the patient’s mouth, it is important to retrieve and dispose of the tablet according to institutional CII waste procedures.”*

The instruction to visually confirm tablet placement is also included in the REMS Safety Brochure.

Proposed AcelRx Modifications to the HF Validation Protocol

The protocol has been simplified to focus the validation tests on the changes implemented to the DFU as described above, as other aspects of the previously conducted testing are still valid.

Table 2 – AcelRx Proposed Revisions submitted in November 8, 2017 Meeting Package

The moderator will only score the following:

1. Successful tablet dispensing into the patient’s sublingual space.
2. Visual confirmation of the tablet in the patient’s mouth.
3. In the event of a tablet being delivered outside the patient’s mouth, confirmation of the retrieval of the tablet and appropriate disposal of the tablet as CII waste.
4. Answering knowledge questions relating to the mitigations for dropped tablets.

4. REVIEW SUMMARY AND DISCUSSION

AcelRx made formatting changes to the Directions for Use (DFU) along with their proposed revisions listed in Table 2. We find the formatting changes and AcelRx’s proposed revisions to the DFU acceptable.

The sponsor proposed that all study participants will be “untrained”. However, these participants will be directed by the moderator to read the DFU before performing the simulated task. We find this methodology does not represent real-world use as we consider this training.

AcelRx also proposes to offer an educational video for participants and demonstration single-dose applicators (SDAs) prior to participants conducting the first task. The moderator script from the HF validation study protocol is as follows:

Before you start your test tasks, you can also request to watch an educational video. In addition, some demonstration SDAs will be available for you to try before you start the test tasks. Would you like to see the educational video? Would you like to try some demonstration SDAs?

The educational video and demonstration SDAs were not included in the previous HF validation study protocol. AcelRx’s noted in their information request response dated January 22, 2018 (see Appendix E for the link to the information request response) that a statement on the DFU will include the following statement:

(b) (4)

In addition, the Sponsor proposed to conduct a focused human factors validation testing on the specific areas of revisions that affect critical steps within the DFU. However, we do not agree with the Sponsor's proposal since untrained users represent a user group that will interact with the entire product user interface. Therefore, the protocol should be revised to include the evaluation of all critical tasks. See our comments and responses in Section 5.1 below.

Our overall assessment of the Human Factors validation study protocol contained in the submission indicated that

The testing conditions are not representative of actual use and the protocol requires revisions to ensure that adequate data regarding the safe and effective use of this product is collected. We have identified the following deficiencies:

- i. Participants in the protocol are instructed by the moderator to read the DFU before attempting the tasks. Requesting participants to read the DFU prior to simulated tasks doesn't represent real-world use. We expect testing to be conducted with untrained participants. As such, the sponsor can determine if they need to also include the trained participants in this study.
- ii. The methodology of the moderator using leading questions to offer an educational video and demonstration of using sample SDAs to untrained participants in the testing environment is not representative of real-world use.
- iii. The proposal to conduct a focused human factors study is not adequate to evaluate the product user interface with representative users.

We provide recommendations in Section 5.1 under the response to question #2 to address this.

5. CONCLUSION & RECOMMENDATIONS

We find that the Human Factors validation study protocol

Not Acceptable. Please see section 5.1. We advise the Sponsor to implement our recommendations prior to commencing their human factors validation study. We also address the human factors related questions submitted in the November 8, 2017 meeting package in Section 5.1.

5.1 RECOMMENDATIONS FOR ACELRX

Responses to Questions in November 8, 2017 AcclRx meeting package.

Question 2.

Does the Division have any comments on the additional instructional mitigations added to the DFU, inclusive of the changes recommended by the Agency, to address the potential risks of dropped tablets? Does the Agency concur that the effectiveness of these changes can be validated per the study

design and criteria set forth in HF protocol PRT-ARX04-P018 (Appendix 3)? If not, what specific changes would the Agency recommend on the protocol?

DMEPA Response:

Based on the available information submitted to us at this point, we do not have any additional comments on the proposed mitigation strategies to address the potential risks of dropped tablets from a human factors perspective.

Please note, however, that we do not agree with three areas in the methodology specified within your human factors validation protocol:

1. Your requirement to have each participant read the Directions for Use (DFU) prior to conducting the simulated use tasks does not appear to reflect real-world use. Our experience indicates that it is unlikely that all health care practitioners will consistently read the Directions for Use (DFU) prior to interacting with this product for the first time. Thus, we are concerned that you do not have an untrained user group in your proposed study because each participant in the untrained group is directed to read the DFU, which constitutes consistent training. If consistent training is not expected to be provided routinely to every user prior to using the product, we recommend that you include an untrained user group in human factors validation testing.
2. Also, we do not agree with the moderator's use of leading questions to offer participants to watch the educational video and practice with available Single Dose Applicator (SDA) samples prior to conducting the simulated tasks. If a participant mentions the educational video, then the moderator may allow the participant to watch the video. The study set up for this portion of the study should be representative of how intended users would be viewing the video. With respect to the demonstration of SDAs, many HCPs will not have access to sample SDAs in a real-world environment prior to using the product for the first time. Thus, we recommend you revise your protocol to accordingly to address these concerns.
3. In addition, you proposed to conduct a focused human factors validation testing. However, we do not agree with your proposal given that the untrained users will represent a new user group that will need to interact with the entire product user interface. As such, we recommend that the human factors validation testing to cover all critical tasks associated with use of the product.

Question 6

We appreciate the Division's feedback in the CRL regarding the proposed Dsuvia labels and Dsuvia logo presentation. A mock-up of the revised carton label with new logo design is provided (Appendix 4). Do the proposed revisions to the labels and logo adequately address the Agency's concerns?

DMEPA Response:

Our preliminary review of the carton and pouch labeling appears to address our initial concerns. However, we recommend you increase the prominence of the dosage form and strength to make this important information more prominent. Our final decision on the acceptability of the labels and labeling will be a review issue.

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Dsuvia that AcclRx submitted on November 8, 2017.

Table 2. Relevant Product Information for Sufentanil citrate	
Initial Approval Date	N/A
Active Ingredient	Sufentanil citrate
Indication	Administration by a healthcare professional (HCP) as needed for management of acute moderate-to-severe pain; not to exceed 30 mcg sufentanil per hour.
Route of Administration	Sublingual
Dosage Form	Sublingual tablet
Strength	30 mcg
Dose and Frequency	As needed, not to exceed 30 mcg per hour
How Supplied	The primary container closure system is comprised of ARX-04 SST 30 mcg housed in a SDA and packaged with an oxygen absorber packet; the SDA and oxygen absorber are packaged together in a laminate foil pouch
Storage	(b) (4)
Container Closure	Each tablet is housed in and dispensed from a disposable single-dose applicator (SDA).

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On December 4, 2017, we searched the L:drive and AIMS using the terms, Dsuvia to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified two previous reviews^{a,b} and we confirmed that our previous recommendations were fully implemented or considered.

OSE RCM #	Review Date	Summary of Recommendations
2017-69	August 21, 2017	The Human Factors Validation Study identified failures that could result in dropped tablets and accidental exposure to sufentanil. The Applicant did not implement any additional mitigation strategies to address these failures, thus DMEPA recommended the Applicant implement additional changes per our recommendations and provide additional HF validation data to support changes to the user interface. Our review of the proposed label and labeling identified several areas that can be changed to improve readability and minimize the risk for medication errors. We provided recommendations to the Applicant to address these concerns.
2016-438	April 28, 2016	We reviewed the human factors protocol. We made one comment to convey to the Applicant in Section 4.1 to add an additional step in the DFU to confirm the placement of the tablet under the tongue.

B.2 PREVIOUS FDA/SPONSOR INTERACTIONS

Our search identified one FDA/Sponsor interaction^c and we confirmed that our previous recommendations were fully implemented or considered.

OSE RCM #	Review Date	Summary of Recommendations
2015-2469	December 10, 2015	We provided general human factors related recommendations to inform the Applicant's product development plan.

^a Roosta, N. Human Factors Study Results Review for Sufentanil Sublingual Tablet. NDA 209128. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017, Aug 21. RCM No.: 2017-69.

^b Schlick, J. Human Factors Protocol Review for Sufentanil Sublingual Tablet. IND 113059. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016, Apr 28. RCM No.: 2016-438.

^c Schlick, J. Human Factors Meeting Package for Sufentanil Sublingual Tablet. IND 113059. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Dec 10. RCM No.: 2015-2469.

APPEARS THIS WAY ON ORIGINAL

APPENDIX C. HUMAN FACTORS VALIDATION STUDY PROTOCOL

The HF study protocol is accessible in EDR via:

<\\cdsesub1\evsprod\nda209128\0023\m1\us\16-meetings\meeting-req-meeting-bg-materials-type-a.pdf>

APPENDIX D. REVIEW OF PRODUCT SAMPLE N/A

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

- The Sponsor did not include the revised pouch labeling in the November 8, 2017 meeting package. Thus, we sent an information request to obtain the revised pouch labeling based on comments sent to the Applicant in the October 11, 2017 Complete Response letter under the section heading '*Container Label and Carton Labeling Comments*'.

On January 3, 2018, the Applicant submitted the revised pouch labeling, and the link to this submission is accessible in EDR via:

<\\cdsesub1\evsprod\nda209128\0024\m1\us\114-labeling\114a-draft-label\pouch-label-directions-for-use.pdf>

- On January 25, 2018 the Applicant submitted the educational video that was described in the November 8, 2017 meeting package. The link to this submission is accessible in EDR via:

<\\cdsesub1\evsprod\nda209128\0025\m1\us\115-promot-material\1152-materials\fdapmt30\dsuvia-011718-nomusic.mp4>

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

/s/

JAMES H SCHLICK
02/20/2018

OTTO L TOWNSEND
02/20/2018

QUYNHNHU T NGUYEN
02/22/2018



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

Date: September 19, 2017

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Dominic Chiapperino, PhD, Acting Director
Silvia Calderon, Ph.D.
Senior Pharmacology Reviewer
Controlled Substance Staff (CSS)

From: James R. Hunter, BS Pharm., MPH, Senior Regulatory Reviewer
Alan Trachtenberg, M.D., M.P.H., Medical Officer
CSS

Subject: **Sufentanil Sublingual Tablet; NDA 209128**
Trade name: Dsuvia
Indication: Management of moderate-to-severe acute pain severe enough to require an opioid agonist, in adult patients in a medically supervised setting.
Dosages: Sufentanil citrate 30 mcg in a single-use, disposable single-dose applicator.
Sponsor: AcclRx Pharmaceuticals

Materials reviewed: Materials submitted under NDA 209128 dated September 12, 2016.

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I. SUMMARY

A. BACKGROUND

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted CSS to review NDA 209128 for Dsuvia (sufentanil sublingual tablet 30mcg) from a controlled substance/abuse potential perspective. Sufentanil is a potent opioid and a Schedule II controlled substance. The sufentanil sublingual tablet 30 mcg (“SST 30 mcg”) is a drug-device combination product comprised of a (b) (4) single-dose applicator (SDA) containing the drug product (sufentanil sublingual tablet 30 mcg). The drug device combination allows the administration of a single microtablet for the management of moderate-to-severe acute pain severe enough to require an opioid agonist, in adult patients in a medically supervised setting. Dsuvia SST is not intended for outpatient use or by children. Each tablet contains 45 mcg of sufentanil citrate, equivalent to 30 mcg of sufentanil base, packaged in a single-use, disposable single-dose applicator. The single-dose applicator helps the patient place the microtablet under the tongue in the sublingual space. The minimum amount of time permitted between dispensed doses is 1 hour.

B. CONCLUSIONS

1. Dsuvia SST contains one sublingual tablet which contains 45 mcg of sufentanil citrate equivalent to 30 mcg sufentanil base, a potent, Schedule II, μ -opioid agonist with a high abuse potential.
2. Dsuvia SST has features designed to limit unauthorized access such as single-use packaging and restrictions on product use such as caregiver-only administration adult only use in medical settings.
3. The major risks associated with Dsuvia SST are: opioid overdose, if the caregiver dispenses more tablets over a shorter time interval than recommended; and unauthorized access to the product for purposes of misuse and abuse. The single-use applicator minimizes the chance that caregivers will inadvertently administer multiple tablets simultaneously, while also making additional tablets unavailable for future misuse and abuse if not consumed by the patient at time of dispensing.
4. Unauthorized access to sufentanil tablets in the Dsuvia SST could occur in the medical setting with improper storage or record keeping, or tampering of the single-use device to remove the tablet, but there is no reason to believe the risk of occurrence would be greater or different from other Schedule II opiates also being dispensed at the facility. (b) (4)

(b) (4)

C. RECOMMENDATIONS (TO BE CONVEYED TO THE SPONSOR)

1. CSS has the following recommendations regarding Dsuvia SST labeling. Additions to the label are indicated in underlined text and deletion in strikethrough text:
 - a) In Section 9.2, second sentence should identify sufentanil as a drug with a risk of fatal overdose. This section should read, "Opioids, such as sufentanil also have a risk of fatal overdose due to respiratory depression."
 - b) Desuvia has not been evaluated for its tamper resistant properties, thus Section 16.1, first sentence should read: "Each Dsuvia tablet 30 mcg is housed in a single-dose applicator (SDA) and packaged within a ~~tamper-evident~~ laminate foil pouch."
 - c) In Section 5.3, indicate in the first sentence that sufentanil has high abuse potential. The first sentence must read, "Dsuvia contains sufentanil, a Schedule II controlled substance with high abuse potential."

II. DISCUSSION

Product Information:

The approved drug product sufentanil citrate solution (Sufenta®), classified as a CII narcotic since 1985, is the listed drug for this 505(b)(2) application. Sufenta is approved for intravenous (IV) anesthetic use in doses up to 30 mcg/kg for an operative procedure and is usually delivered as a single IV bolus or as an infusion by the anesthesiologist as an adjunct analgesic in the maintenance of anesthesia in patients who are intubated and ventilated. AcelRx did not request a change in scheduling.

Clinical Pharmacology:

According to the Sponsor, the proposed tablet formulation of Desuvia is an immediate-release drug product with high transmucosal bioavailability and low oral bioavailability (less than 10%). Sufentanil citrate is soluble in water, sparingly soluble in alcohol, sparingly soluble in acetone and chloroform, and freely soluble in methyl alcohol. Solubility of sufentanil citrate in water is 46 mg/mL. Sufentanil's high potency, high affinity for the μ receptor, high lipophilic properties, rapid central nervous system penetration, and lack of active metabolites, along with the proposed tablet formulation's small tablet size (3mm), and high transmucosal bioavailability contribute to its high abuse liability. The sponsor has not performed formal laboratory studies on extraction of sufentanil from the product, and relies on results from process development, product characterization, and basic chemistry manufacturing data. The Sponsor states that the drug product is easily crushed and could be insufflated, and that the product can be dissolved in a readily available solvent and injected, resulting in higher bioavailability than administration by the intended sublingual route. Therefore, the proposed sublingual sufentanil tablet formulation in Desuvia has no features specifically designed to deter abuse through the intranasal or injectable route of administration. The low oral

bioavailability (10%) of sufentanil citrate substance may limit its abuse liability by this route of administration; however its high transmucosal bioavailability makes this route of abuse less clinically relevant.

The Sponsor, AcelRx, asserts that sufentanil has abuse potential but expects that the potential for abuse with Dsuvia SST would be reduced compared to currently marketed CII opioid-containing products due to: 1) intended use only in medically supervised settings restricts distribution, 2) the solid dosage form of the sufentanil tablets 3) C_{max} is 10x lower than C_{max} of dose equivalent to IV Sufenta®, 4) only single-dose available as packaged and administered, 5) clear packaging allows tablet to be seen and verified present before use, 6) low oral bioavailability when swallowed, 7) Adverse event profile observed in clinical trials was similar to that reported for other potent opioids in the post-operative setting.

Clinical Trials:

To investigate potentially abuse-related adverse event (AE) signals in clinical trials, the Sponsor identified AE terms possibly suggestive of drug abuse or overdose and monitored for these AEs in four pivotal safety and efficacy studies:

- SAP202, a multicenter, double-blind, placebo-controlled randomized study with oral hydrocodone rescue;
- SAP301, a multicenter, double-blind, placebo-controlled study; and
- SAP302 and SAP303, two multicenter, open label studies.

The incidence of abuse-related AE's was very low in all groups of study patients, with no signals of abuse-related use of the study drug. One patient taking a 20mcg dose reported "Euphoric Mood."

REMS:

The Sponsor proposes a REMS for Dsuvia SST. The major risks to be mitigated are risks associated with use outside the hospital setting. The Sponsor states that the REMS for Dsuvia SST will consist of a Communication Plan, Elements to Assure Safe Use (ETASU), an Implementation System, and a timetable for submission of various assessments.

The major ETASU is restricting distribution of the product to assure Dsuvia will be dispensed to patients only in supervised medical settings. REMS requirements designed to limit Dsuvia SST use to medical settings include: 1) a valid DEA license for receipt and dispensing of sufentanil, 2) experience with the administration of parenteral opioids, and 3) immediate access to supplemental oxygen and an appropriate opioid reversal agent. Other mitigation features include a REMS safety brochure to inform Health Care Practitioners (HCP) about the safe use of Dsuvia SST. Dsuvia SST is HCP-administered; patients will not handle the drug or the SDA.

CDER's Office of Surveillance and Epidemiology is the lead office in reviewing the adequacy of the REMS to mitigate identified risks of Dsuvia SST.

LABELING:

CSS proposes the following additions (indicated in underlined text) and deletions (indicated in strikethrough test) to draft labeling found under Module 1.14.1.3 (NDA 209128 submission dated 12/12/2016) for the following sections:

- 5.3 Addiction, Abuse and Misuse
- 9.2 Drug Abuse and Dependence,
- 16.1. How Supplied

In Section 9.2, the Sponsor should identify sufentanil as a drug with a risk of fatal overdose. We propose a new second sentence so the first paragraph of section 9.2 would now read:

“Dsuvia contains sufentanil, a substance with a high potential for abuse similar to other opioids including (fentanyl, morphine, oxycodone, hydromorphone). Opioids, such as sufentanil also have a risk of fatal overdose due to respiratory depression. Dsuvia can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions (5.3)*].”

Since Desuvia has not been evaluated for its tamper resistant properties reference to tamper evident in Section 16.1 should be deleted. Thus Section 16.1, first sentence would be revised to read:

“Each Dsuvia tablet 30 mcg is housed in a single-dose applicator (SDA) and packaged within a ~~tamper evident~~ laminate foil pouch.”

In Section 5.3, this subsection should indicate in the first sentence that sufentanil has high abuse potential. This first sentence must be modified to read:

“Dsuvia contains sufentanil, a Schedule II controlled substance with high abuse potential.”

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/s/

JAMES R HUNTER
09/19/2017

ALAN I TRACHTENBERG
09/19/2017

SILVIA N CALDERON
09/20/2017

DOMINIC CHIAPPERINO
09/20/2017

Date: September 18, 2017

To: Steven Kinsley, Regulatory Health Project Manager
OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI

Office of Combination Products at combination@fda.gov

Through: Nazia Rahman, Lead Compliance Officer, Division of Manufacturing and Quality, Office of Compliance, CDRH

From: Therese Barber, Consumer Safety Officer, OC, CDRH

Applicant: AceRx Pharmaceuticals
351 Galveston Drive
Redwood City, California 94063
FEI # 3006386491

Application # NDA-209128

Consult # ICC-1600892/ICCR2016-00369

Product Name: Sufentanil Sublingual Tablet (30 mcg) with a Single Dose Applicator

Post-Approval Inspection: Yes

Documentation Review: Approvable

Final Recommendation: **APPROVABLE**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA-209128. The firm's response to the QS deficiencies was received from Steven Kinsley on May 3, 2017.

PRODUCT DESCRIPTION

The device under review is named Zalviso (Sufentanil sublingual tablet system). Zalviso is comprised of Sufentanil (a synthetic high therapeutic index opioid), tablet (a proprietary, non-

invasive sublingual dosage form) and a hand-held, factory-programmed PCA system (patient-controlled analgesia system that enables patient-controlled delivery of tablets in the hospital setting). Zalviso is designed for the management of acute post-operative pain in adult patients within a hospital setting as an alternative to intravenous patient controlled analgesia. It is a patient-activated drug-device and is assembled by the healthcare professional at the point of patient use.

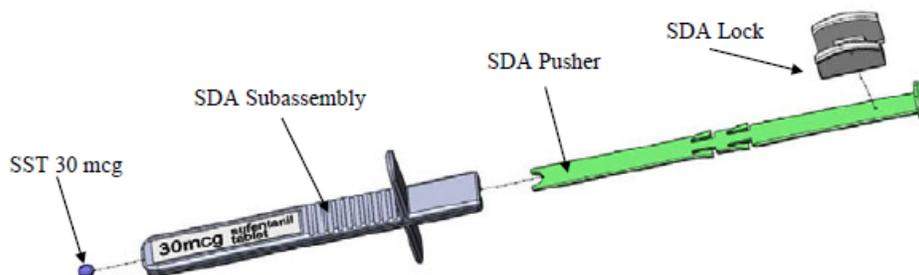
A single sufentanil sublingual tablet (SST), 30 mcg, is packaged in a single-use Single Dose Applicator (SDA) shown in Figure 3.2.P.7.2: 1. The tablet has been developed for the treatment of moderate-to-severe acute pain in a medically supervised setting. Each sufentanil tablet contains 30 mcg of sufentanil, a potent opioid and a controlled substance. Since each tablet is small, 3 mm diameter by 0.85 mm thick, the SDA was developed to aid in delivering the tablet to the patient's sublingual space. The SDA is held and actuated in a manner similar to a standard syringe. The SDA is manufactured by [REDACTED] (b) (4) and is comprised of three components (SDA Subassembly; SDA Pusher; and SDA Lock). The three components of the SDA are packaged and shipped to the contract packager. At the contract packager, the SDA Subassembly is filled with a single SST 30 mcg, the SDA Pusher and SDA Lock are assembled together and inserted into the SDA Subassembly, the filled SDA is placed into a pouch with an oxygen absorber and the pouch is heat sealed.

Figure 3.2.P.7.2: 1 Single Dose Applicator



Figure 3.2.P.7.2.2 is an exploded view of the different components of the SDA.

Figure 3.2.P.7.2: 2 SDA Exploded View with Components



REGULATORY HISTORY

The following facility was identified as being subject to applicable Quality System Requirements under 21 CFR Part 820:

1. AcelRx Pharmaceuticals
351 Galveston Drive, Redwood City, California 94063
FEI # 3006386491

Responsibility – This firm is the applicant and is responsible for maintaining the quality responsibility for the review of GMP production and test documentation, and for the disposition of the final drug product and finished devices. Therefore, this facility is subject to 21 CFR 820 QS requirements.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted on June 17, June 19, June 25, June 26, and June 30, 2014. The inspection covered medical device QS requirements and was classified VAI.

- The inspection covered Design Controls, Management Controls, Corrective & Preventive Actions, Purchasing Controls, and Acceptance Activities. A one-item FDA-483 (for Corrective and Preventative action) was issued. In addition, the inspection revealed the following incomplete activities:
 - 1) Design Transfer to Manufacturing. Awaiting formal transfer post-NDA approval.
 - 2) Labeling updates due to CDER requests, including product reference as “sufentanil sublingual tablet system”.
 - 3) Design Change: Software update due to CDRH requests; submitted electronically to CDER on 6/17/14, SN0028; 6/24/14 new request for clarification.
 - 4) Validation of Manufacturing processes. Awaiting final validation post-NDA approval.

Inspection Recommendation:

A post-approval inspection is required because:

- The firm is responsible for major activities related to maintaining the quality responsibility for the review of the GMP production/test documentation, and for the disposition of the final drug product and finished devices; and,
- The firm has not been inspected since June 30, 2014.

AMENDED REGULATORY HISTORY – 18 September 2017

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR Part 820:



[Redacted] (b) (4)

Inspectional History – An analysis of the firm’s inspection history [Redacted] (b) (4) showed that an inspection was conducted in [Redacted] (b) (4). The inspection was an Ad Hoc limited inspection covered focused on an investigation of final Field Alert Report (FAR) dated [Redacted] (b) (4).

The previous inspection was a drug GMP and pre-approval (PAI) inspection occurring [Redacted] (b) (4). It was classified VAI.

Inspection Recommendation:

A post-approval inspection is recommended because:

- [Redacted] (b) (4)

3. [Redacted] (b) (4)

Inspectional History – An analysis of the firm’s inspection history [Redacted] (b) (4) showed that an inspection was conducted on [Redacted] (b) (4). The inspection was a QSIT GMP inspection and covered the firm's Corrective and Preventive Actions and Production and Process Controls [Redacted] (b) (4) [Redacted] (b) (4) and was classified NAI.

[Redacted] (b) (4)

Inspection Recommendation:

An inspection is not required because:

- The firm recently received a QSIT inspection covering the firm's Corrective and Preventive Actions and Production and Process Controls.

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RECOMMENDATION

The approvability of application for Product – Application #BLA-103795-5556 should be delayed for the following reasons:

- (1) The firm did not provide documentation to address the requirements of 21 CFR 820.20 (Management Controls), 21 CFR 820.50 (Purchasing Controls), and 21 CFR 820.100 (Corrective and Preventive Action).
- (2) The firm did not provide documentation illustrating the production flow of the Single Dose Applicator.
- (3) A pre-approval inspection is recommended for the following facility:
 - a) AcelRx Pharmaceuticals, 351 Galveston Drive, Redwood City, California 94063; FEI # 3006386491.

AMENDED RECOMMENDATION – 18 September 2017

Based on the information provided in the firm's response from May 2017, the deficiencies, related to the Quality System Requirements in 21 CFR 820, were addressed.

- (1) A post-approval inspection is recommended for the following facility:
 - b) AcelRx Pharmaceuticals, 351 Galveston Drive, Redwood City, California 94063; FEI # 3006386491.

Note: *The inclusion of Application #BLA-103795-5556 was a mistake by the Office of Compliance, CDRH reviewer. The 'Amended Recommendation' has been updated to include the correct application number.*

ADDITIONAL INFORMATION – 18 September 2017

On September 11, 2017, email correspondence was received from CDER's representatives regarding 1) the inspectional status of AcelRx Pharmaceuticals and 2) the inclusions of (b) (4) in the review memo from the Office of Compliance. With regards to the inspectional status of AcelRx Pharmaceuticals, an excerpt from the email states "AcelRx has ultimate control over the finished product, and given both its favorable history as a device manufacturer for a currently marketed CDER-led product [based on last inspection, recalls (none), and FARs (none)], and an adequate description of the relevant 820/Part 4 summaries, CDER/OPF believes that a pre-approval inspection can be waived and a post-approval recommended." Based on this statement, the Office of Compliance, CDRH, concurs with this assessment to conduct a post-approval inspection of AcelRx Pharmaceuticals.

With regards to the inspection status of (b) (4) the Office of Compliance,

CDRH, notes that this site has not received a recent medical device inspection however CDRH defers to CDER for the final recommendations pertaining to this company and whether it should receive a post approval inspection.

AMENDED RECOMMENDATION - 18 September 2017

The application for Product – Application # NDA-209128 is approvable from the perspective of the applicable Quality System Requirements.

- (1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.
- (2) The Office of Compliance, CDRH, concurs with CDER's assessment to conduct a post-approval inspection of AcclRx Pharmaceuticals.
- (3) The Office of Compliance, CDRH, recommends a post-approval inspection but defers to CDER for final decision with regards to the inspectional status of (b) (4)

(b) (4)

Therese Barber

21 CFR Part 4 Compliance

NOTE: The responses to the deficiencies cited below were adequately addressed in the firm's response provided by Steven Kinsley on May 3, 2017.

The following documentation deficiencies related to the NDA-209128 were identified in reference to 21 CFR Part 4 and 21 CFR 820 for the finished combination product, Sufentanil Sublingual Tablet (30 mcg) with a Single Dose Applicator should be sent to the Applicant/Licensure of the Application.

(b) (4)



Please be noted that combination products manufactured under the CGMP drug operating system, the Applicant/Licensure must also fulfill the requirements under 21 CFR Part 4.4b to show compliance to 21 CFR Part 4 for the finished combination product. To assist in the preparation of the above summaries related to the 21 CFR 820.20, 21 CFR 820.30, 21 CFR 820.50 and 21 CFR 820.100, you are recommended the FDA Guidance 'Quality System

Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003) located at the link:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

Prepared: TBarber: February 2, 2017
Reviewed: VVuniqui: February 6, 2017
Revised: TBarber: February 7 and 8, 2017
Revised: TBarber: May 11, 2017 (Response to QS Deficiencies)
Revised: TBarber: September 18, 2017
Final: NRahman: September 18, 2017

CTS No.: ICC1600892
ICCR No.: ICCR2016-00369
Application Number: NDA-209128

To: ORA

Inspectional Guidance

Firm to be inspected:

1. AcelRx Pharmaceuticals, 351 Galveston Drive, Redwood City, California 94063; FEI # 3006386491

CDRH recommends that the Post-Approval inspection of the firm listed above covers, compliance with all the requirements of 21 CFR Part 4, including the applicable Quality System (21 CFR 820) requirements – Management Controls (21 CFR 820.20), Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), and Corrective and Preventative Action (21 CFR 820.100). CDRH also recommends that Quality System requirements for Production and Process Controls (21 CFR 820.70) and Acceptance Activities (21 CFR 820.80) are covered during this inspection.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation(s) is/are drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Therese Barber
Consumer Safety Officer
Physical Medicine, Orthopedic, Neurology and Dental Device Branch
Division of Manufacturing and Quality
Office of Compliance, WO66 RM 3441
Phone: 301-796-3021

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Nazia Rahman
Division of Manufacturing and Quality
Office of Compliance, WO66 RM 3458
Phone: 301-796-3849

Matthew Krueger (returns from his detail on March 4, 2017)
Chief
Physical Medicine, Orthopedic, Neurology and Dental Device Branch
Division of Manufacturing and Quality
Office of Compliance, WO66 RM 3448
Phone: 301-796-5585

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION.

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

/s/

STEVEN A KINSLEY
09/18/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: September 12, 2017 **Date consulted:** February 22, 2017

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Drug: Dsuvia (sufentanil sublingual tablet, 30 mcg)

NDA: 209128

Applicant: AcelRx Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling Recommendations

Indication: for the management of moderate-to-severe acute pain severe enough to require an opioid agonist, in adult patients in a medically supervised setting

Materials Reviewed:

- April 11, 2014. Leyla Sahin, MD and Amy Taylor, MD, MHS. Citizens Petition and Petition for Stay regarding Neonatal Opioid Withdrawal Syndrome (NOWS) labeling changes. DARRTS. Reference ID 3488324
- December 12, 2016, New Drug Application, NDA 209128

- February 22, 2017, Maternal Health, DPMH consult, DARRTS Reference ID 4059568
- March 20, 2017, Hydrocodone polistirex/Chlorpheniramine polistirex/pseudoephedrine polistirex (HPCPPP) combination product review, Jane Liedtka, MD, NDA (b) (4) DARRTS Reference ID 4072824
- April 10, 2017, submission to NDA 209128, response to 74 day letter clinical information request related to PLLR labeling
- October 26, 2016, Jane Liedtka, M.D., DPMH consult, Fentanyl Injectable, NDA 19101, 19115 and 16619, DARRTS Reference ID 4004602
- Draft Guidances for Industry: Analgesic Indications: Developing Drug and Biological Products (February 2014); and, Abuse Deterrent Opioids-Evaluation and Labeling (January 2013)

Consult Question: “This submission contains the PLLR label. Please review the PLLR”

INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate format and content of the pregnancy, lactation, and males and females of reproductive potential subsections of Dsuvia (sufentanil sublingual tablets) labeling.

REGULATORY HISTORY

On December 12, 2016, AcelRx Pharmaceuticals, Inc., submitted NDA 209128 for Dsuvia (sufentanil sublingual tablet, 30 mcg) for the management of moderate-to-severe acute pain severe enough to require an opioid agonist, in adult patients in a medically supervised setting. NDA 209128 is a 505(b)(2) application relying on the safety and efficacy of Sufentanil (sufentanil citrate) injection, NDA 19050. Additionally, the clinical study reports from the clinical development program for Zalviso (sufentanil sublingual tablet system, 15 mcg), (b) (4) (b) (4), which is not yet approved in the U.S., were also submitted for review. At the Pre-NDA meeting for NDA 209128, on December 9, 2015, the Agency agreed to use clinical information from (b) (4), which received a Complete Response on September 27, 2013.

- Sufenta (sufentanil citrate) injection, NDA 19050 was originally approved on May 4, 1984, and has the following approved indications:
 - As an analgesic adjunct in the maintenance of balanced general anesthesia in patients who are intubated and ventilated,
 - as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, in patients who are intubated and ventilated, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated, and
 - for epidural administration as an analgesic combined with low dose (usually 12.5 mg per administration) bupivacaine usually during labor and vaginal delivery

BACKGROUND

Drug Characteristics^{1,2}

- Sufentanil is an opioid agonist and is a combination drug/device with a patient-controlled analgesic system allowing up to three 15 mcg sufentanil tablets to be administered per hour; the system has a 20 minute lock-out and can be used for up to 3 days to manage moderate to severe pain
- The exact mechanism of action is unknown; however, the effects are thought to be through opioid-specific receptors, primarily the mu opioid receptor in the central nervous system (CNS)
- The sublingual dosage form has a bioavailability of 53% and is mainly hepatically metabolized through the CYP3A4 enzyme
- Terminal half-life of 14.2 hours
- Central volume of distribution of 120 L
- Molecular weight of 386.55 Daltons

Serious adverse events include: opioid withdrawal, respiratory depression, neonatal opioid withdrawal syndrome, addiction, abuse and misuse, increased intracranial pressure, bradycardia or hypotension, profound sedation and CNS depression.

Opioids and Pregnancy

Opioid use in the United States has been increasing rapidly over the decades. The abuse of opioids in pregnancy includes heroin and the misuse of prescription opioid medications.³ Recent studies have demonstrated that 14 to 22% of pregnancy women filled at least one opioid prescription during pregnancy with rates up to 42% in some areas of the United States. Neonatal abstinence syndrome is one of the most common adverse outcomes following opioid exposure during pregnancy and has become one of the fastest growing reasons for neonatal hospital admissions occurring in 4.3 to 5.9 per 1000 births.⁴ Other possible risks include neural tube defects, congenital heart defects, gastroschisis, growth problems, placental abruption, stillbirth and preterm birth.⁵ Currently the standard of care for pregnant women with opioid addiction is referral to an opioid-assisted therapy center for methadone or buprenorphine along with counseling.⁶

¹ Sufenta. sufentanil citrate injection. RLD labeling, 2/2014

² December 12, 2016, New Drug Application, NDA 209128

³ The American College of Obstetrics and Gynecologists. Women's Health Care Physicians. Committee Opinion. Opioid Abuse, Dependence and Addiction in Pregnancy, Number 524, May 2012, Reaffirmed 2016.

⁴ Falk J et al., 2017, Opioid use during pregnancy: a population-based cohort study, CMAJ Open, 5(2):E517-E523.

⁵ Centers for Disease Control and Prevention. Pregnancy and Opioid Pain Medication [Brochure]. US Department of Health and Human Services. https://www.cdc.gov/drugoverdose/pdf/pregnancy_opioid_pain_factsheet-a.pdf. Accessed 24 July 2017.

⁶ The American College of Obstetricians and Gynecologists. Patient education Fact Sheet. Important Information About Opioid Use Disorder And Pregnancy, PFS012, June 2016. <https://www.acog.org/Patients/FAQs/Important-Information-About-Opioid-Use-Disorder-and-Pregnancy>. Accessed 24 July 2017.

Opioid Analgesic Drug Products' Class Labeling⁷

On September 10, 2013, the FDA implemented safety labeling changes related to neonatal opioid withdrawal syndrome (NOWS) for extended-release/long-acting (ER/LA) opioid analgesics. The Office of Regulatory Policy received a citizen petition from the National Advocates for Pregnant Women on October 17, 2013. On April 11, 2014, DPMH completed a review in response to the citizen's petition and discussed recommended labeling for NOWS.⁸ Class labeling for opioid analgesic drug products originally applied to Schedule II controlled substances that are extended release or long acting (ER/LA). DAAAP has expanded class labeling for opioid analgesics to include immediate-release (IR) opioid formulations as well. As part of the opioid class labeling, boxed warnings are required for addiction, abuse and misuse, respiratory depression (that can lead to overdose and death) and NOWS (which may be life threatening in neonates whose mothers required prolonged opioid therapy while pregnant). In addition to the boxed warnings, there is class labeling in several sections and sub-sections.⁹ Class labeling that has been developed for the pregnancy and lactation subsections of opioid product labeling is described below.

REVIEW

PREGNANCY

Nonclinical Experience

In animal reproduction studies in rats and rabbits, maternal toxicity and embryoletality was demonstrated in doses 0.7 and 1.4 times the maximum human daily dose when administered during organogenesis. In a pre- and post-natal development study in rats, maternal toxicity and decreased pup weight and survival was demonstrated in doses at 0.2 and 0.7 times the maximum human daily dose in intravenous sufentanil. The reader is referred to the Pharmacology/Toxicology review by reviewer BeLinda Hayes, Ph.D, June 19, 2004 for (b) (4) (b) (4).

Review of Literature

Applicant's Review of Literature

The applicant conducted a search of published literature regarding the use of sufentanil in pregnant women using the US National Library of Medicine Toxnet Toxicology Data Network. All results of sufentanil use during pregnancy involve the injectable form Sufenta (sufentanil citrate) as it is approved as an epidural analgesic for use during labor and vaginal delivery. There are no publications that include the oral sublingual route of sufentanil. The results of this search are summarized below and in Appendix A.

Reviewer comment: DPMH notes that NDA 209128 for Dsuvia (sufentanil) sublingual has a proposed indication for the management of moderate-to-severe acute pain severe enough to require an opioid agonist, in adult patients in a medically supervised setting and not for use as

⁷ March 20, 2017, HPCPPP combination product review. Jane Liedtka, MD, NDA (b) (4), DARRTS.

⁸ Leyla Sahin, MD and Amy Taylor, MD, MHS. Citizens Petition and Petition for Stay regarding Neonatal Opioid Withdrawal Syndrome (NOWS) labeling changes. April 11, 2014. DARRTS. Reference ID 3488324

⁹ *Draft Guidances for Industry: Analgesic Indications: Developing Drug and Biological Products (February 2014); and, Abuse Deterrent Opioids-Evaluation and Labeling (January 2013).*

an epidural analgesic for use during labor and vaginal delivery as the reference listed drug (RLD) Sufenta is indicated.

Sufentanil has been shown to cross the placenta. Limited published literature demonstrate cardiac effects in neonates whose mothers received epidural or intrathecal sufentanil during labor and delivery; however, some studies have failed to demonstrate an increased risk of cardiac effects (see Tables and Appendix A).^{10,11,12,13,14,15} Additionally, sufentanil was often given in the various studies with concomitant medications.

DPMH's Review of Literature

DPMH conducted a review of published literature using Embase and PubMed and the following search terms, “sufentanil” and “pregnancy”, “sufentanil and “spontaneous abortion” and “sufentanil” and “feta malformations.” No additional articles were found relevant for reviewed by DPMH. There are no available data with the sublingual formulation of sufentanil.

In previous labeling reviews and a review of a citizens petition by DPMH,^{7,8} class labeling has been developed for the opioid class products to include language for mothers who require prolonged opioid therapy while pregnant which also discuss opioid dependence treatment and language about neonatal withdrawal syndrome. This language has been developed not to be used as clinical practice guidelines but to provide concise information to inform the safe and effective use of these drug products. Additionally, even though Dsuvia is not indicated for long-term use this language is still important to convey in labeling as this information applies to the entire class.

Neonatal Opioid Withdrawal Syndrome

Infants of patients who took opioids during pregnancy are at risk for NOWS, which may be life-threatening if the infant is not recognized early and does not get appropriate treatment. Infants of mothers who are using opioids throughout pregnancy should be carefully monitored for signs of withdrawal after birth. The reader is referred to the FDA Draft Guidance related to NOWS for ER/LA opioid analgesics¹⁶ and the DPMH review by Leyla Sahin, MD, and Amy Taylor, MD, MHS, that discusses the response to the Citizen Petition regarding NOWS labeling change for further details.⁸

¹⁰ Loftus J et al., 1995, Placental Transfer and Neonatal Effects of Epidural Sufentanil and Fentanyl Administered with Bupivacaine during Labor, American Society of Anesthesiologists, Inc., 83:300-308.

¹¹ Palot M et al., 1992, Placental Transfer and Neonatal Distribution of Fentanyl, Alfentanil and Sufentanil After Continuous Epidural Administration for Labor, Anesthesiology, 77(3A):A991.

¹² Van de Velde M et al., 2001, Fetal Heart Rate Abnormalities After Regional Analgesia for Labor Pain: The Effect of Intrathecal Opioids, Reg Anesth Pain Med, 26:257-262.

¹³ Cohen S et al., 1992, Intrathecal Sufentanil for Labor Analgesia – Sensory Changes, Side Effects, and Fetal Heart Rate Changes, Anesth Analg, 77:1155-60.

¹⁴ Nielsen P et al, 1996, Fetal Heart Rate Changes After Intrathecal Sufentanil or Epidural Bupivacaine for Labor Analgesia: Incidence and Clinical Significance, Anesth Analg, 83:742-6.

¹⁵ Becker J et al., 2011, Intrapartum epidural analgesia and ST analysis of the fetal electrocardiogram, ACTA Obstetrica et Gynecologica, 1364-1370.

¹⁶ Draft Guidances for Industry: Analgesic Indications: Developing Drug and Biological Products (February 2014); and, Abuse Deterrent Opioids-Evaluation and Labeling (January 2013).

Fetal Malformations

Overall, the cumulative data on opioid exposure during pregnancy and congenital malformations are very limited. In an FDA Drug Safety Communication issued on January 9, 2015, the FDA noted that they reviewed opioids, including oxycodone, hydrocodone, hydromorphone, morphine and codeine, and evaluated the risk of birth defects of the brain, spine or spinal cord in infants born to women who took these products during the first trimester of pregnancy. The FDA found that all of the studies reviewed have limitations in their designs; therefore, it is not possible to draw any conclusions regarding the risks of malformations following exposure to opioids during pregnancy.¹⁷ The reader is referred to DPMH reviews by Carol Kasten, MD, Miriam Dinatale, DO, and Leyla Sahin, MD, for further details.^{8,18,19}

Summary

All available published literature with sufentanil and pregnancy consist of exposure during labor or delivery as the RLD, Sufenta (sufentanil citrate) injection, is approved for epidural administration as an analgesic combined with low dose bupivacaine during labor and delivery. Sufentanil has been shown to cross the placenta and cardiac effects have been demonstrated in limited published literature; however, there is not enough information to indicate a drug associated risk as some publications demonstrate no increased risk.

Dsuvia labeling will be structured in the PLLR format using IR opioid labeling.

LACTATION

Nonclinical Experience

There is no available non-clinical data with regard to sufentanil and lactation.

Review of Literature

Applicant's Review of Literature

The applicant used LactMed to locate information related to sufentanil exposure and lactation. According to Cuypers, et al. (1995),²⁰ twenty-nine patients given epidural anesthesia (0.5% bupivacaine and 20 mcg sufentanil) for elective cesarean delivery were included in the study. Patients were randomized into three blinded post-operative treatment groups (see table 1 below). Breast milk samples (when available) were taken on days 1, 2 and 3 and all samples were assayed for sufentanil.

¹⁷ FDA Drug Safety Communication: FDA has reviewed possible risks of pain medicine use during pregnancy. January 9, 2015. <http://www.fda.gov/Drugs/DrugSafety/ucm429117.htm>

¹⁸ DPMH Review: Zohydro ER (hydrocodone bitartrate), NDA 202880/S-003. Carol Kasten, MD. January 28, 2015. DARRTS Reference ID 3693127.

¹⁹ DPMH Review: Targiniq ER (oxycodone hydrochloride/naloxone hydrochloride), NDA 205777. Miriam Dinatale, DO. June 20, 2014. DARRTS Reference ID 3526040.

²⁰ Cuypers L et al., 1995, Epidural sufentanil for postcesarean pain: breast milk levels and effects on the baby, Acta Anaesthesiologica Belgica, 46(2):P104-105.

Table 1. Sufentanil and Lactation*

Publication	Exposure post-cesarean	n	Sufentanil concentrations (pg) mean	Conclusion
Cuypers, et al. (1995) ²⁰	Patient controlled epidural analgesia (PCEA) 0.125 % bupivacaine and .75 mcg/ml sufentanil	day 1 = 3; day 2 = 5 day 3 = 4	96 ± 50 134 ± 33 155 ± 60	Sufentanil was detected in breast milk in all 3 groups 72 hours after the initial dose of 20 mcg during the cesarean surgery; sufentanil concentrations were higher in breast milk than in blood; highest levels were detected in the PCEA bupivacaine and sufentanil treatment group
	PCEA with 0.125 bupivacaine	day 1 = 2 day 2 = 4 day 3 = 2	0 88 49	
	Intramuscular piritramide 0.25 mg/kg	day 1 = 2 day 2 = 2 day 3 = 4	119 117 49	

*Reviewers table

DPMH's Review of Literature

DPMH performed a search of *Medications and Mother's Milk*²¹, the Drug and Lactation Database (LactMed)²², and Micromedex²³ and in PubMed using the search terms “sufentanil” and “breastfeeding” or “lactation.” The results of that search are described below. The Medications and Mothers' Milk, Micromedex and PubMed search did not furnish additional information.

According to LactMed,²² “when used epidurally or intravenously during labor or for a short time immediately postpartum, amounts of sufentanil ingested by the neonate would not be expected to cause any adverse effects in breastfed infants,” and “because of sufentanil's long half-life during continued intravenous infusion or repeated intravenous administration, sufentanil levels in milk would be expected to increase if used for an extended period postpartum.” Additionally, LactMed references an article by Madej T and L Strunin (1987),²⁴ which describes a study of nine pregnant women who received sufentanil 50 mcg epidurally immediately after delivery. In the study, colostrum was obtained one hour after sufentanil dosing, and sufentanil was undetectable in colostrum. However, in a study by Cuypers L, et al. (1995) discussed above, sufentanil was detected in breast milk 72 hours after the last dose in patients who received sufentanil in an epidural and also after delivery for post caesarean pain treatment (see Table 1 above). This study did not, however, allow for estimation of sufentanil infant dose from milk due to reporting errors.

²¹ Hale, Thomas, Ph.D., *Medications and Mother's Milk* 2017, Springer Publishing Company.

²² <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

²³ www.micromedexsolutions.com. Accessed 8/1/2017.

²⁴ Madej T and L Strunin, 1987, Comparison of epidural fentanyl with sufentanil, *Anaesthesia*, 42:1156-1161.

Summary

There is no available non-clinical data on the use of sufentanil during lactation. Limited published literature demonstrates that sufentanil is present in human milk immediately following delivery; however, there is no information on milk production or effects on the breastfed infant from sufentanil. Additionally, because there is only published data on the presence of sufentanil during the first 72 hours immediately following delivery it is difficult to say what stage of breastmilk was present as there are three types of breastmilk when a woman is breastfeeding (colostrum, transitional milk and mature milk). Each stage of breastmilk has different levels of water, fat content and pH levels. Because of this each stage has the potential to differ in the amount of drug delivered during lactation.²⁵ However, regardless of the presence of drug in milk or the short-term intended use of Dsuvia, it is important to inform the provider that infants exposed to sufentanil through breast milk should be monitored for excess sedation and respiratory depression. Therefore, Dsuvia labeling will be structured in the PLLR format using IR opioid labeling. DPMH recommends the following language in subsection 8.2 Lactation under Clinical Considerations:

Infants exposed to sufentanil through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breastfeeding is stopped.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

In fertility and early embryonic development studies in male and female rats doses 14 days prior to mating through gestation, increased mortality was noted at doses 0.005, 0.02 and 0.08 mg/kg sufentanil intravenous. Additionally, lower pregnancy rates were seen at 0.02 and 0.7 times the maximum human daily dose based on body surface area. Increased resorptions of fetuses and reduced litter size was noted in the high dose females at 0.7 times the maximum daily human dose suggesting fetotoxicity likely due to maternal toxicity. The reader is referred to the Pharmacology/Toxicology review by reviewer BeLinda Hayes, Ph.D, June 19, 2004 (b) (4)

(b) (4)

Review of Literature

The applicant did not provide a search of published literature regarding females and males of reproductive potential. The applicant notes that current opioid drug labeling describes that reduced fertility in males and females of reproductive potential can occur from chronic use of opioids; however, the intended use of sufentanil and the immediate release formulation to be used in an acute care setting only and administered by health care providers will limit this concern.

DPMH performed a search of published literature with regard to sufentanil and effects on fertility, and no information was located.

²⁵ Guidance for Industry, Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling, FDA Draft Guidance. February 2005.

Summary

The effects of opioids on fertility have been shown in animal reproductions study and in published literature in humans. In 2014, the Division of Bone, Reproductive and Urologic Products (DBRUP) reviewed the literature to evaluate the association between chronic opioid administration and hypogonadism. Based on that review, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) updated the immediate and extended release opioid labels to include information about the potential for chronic opioid use to influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency. It was determined that Section 8.3, Females and Males of Reproductive Potential, of opioid labeling will now include the following statement:²⁶

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

CONCLUSIONS

The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of Dsuvia labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” section of labeling was formatted in the PLLR format to include: “Risk Summary,” “Clinical Considerations,” and “Data” sections.
- **Lactation, Section 8.2**
 - The “Lactation” section of labeling was formatted in the PLLR format to include: the “Risk Summary,” and “Clinical Considerations,” sections.
- **Females and Males of Reproductive Potential, Section 8.3**
 - The “Females and Males of Reproductive Potential” section of labeling was formatted in the PLLR format to include: the “Infertility” section.
- **Patient Counseling Information, Section 17**
 - The “Patient Counseling Information” section of labeling was updated to correspond with changes made to sections 8.1, 8.2 and 8.3 of labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

The Highlights of Prescribing Information contains a boxed warning (see Full Prescribing Information below for language). DPMH does not recommend any changes to that boxed warning at this time.

²⁶ October 26, 2016, Jane Liedtka, M.D., DPMH consult, Fentanyl Injectable, NDA 19101, 19115 and 16619, DARRTS Reference ID 4004602

FULL PRESCRIBING INFORMATION

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. (b) (4) There are no available data with sufentanil in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. (b) (4)

(b) (4)

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset (b) (4) duration and severity of neonatal opioid withdrawal syndrome (b) (4) vary. Observe newborns for (b) (4) of neonatal opioid withdrawal syndrome and manage accordingly [see *Warnings and Precautions* (5.8)].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid induced respiratory depression in the neonate. Opioid analgesics can prolong labor through actions (b) (4) temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data



8.2 Lactation

Risk Summary



(b) (4) The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sufentanil and any potential adverse effects on the breastfed infant from sufentanil or from the underlying maternal condition.

Clinical Considerations

Infants exposed to sufentanil through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breastfeeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible (b) (4)

17 PATIENT COUNSELING INFORMATION

Pregnancy

(b) (4)

Lactation

Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs [see *Use in Specific Populations (8.2)*].

(b) (4)

Appendix A – Summary of Published Literature of Sufentanil Exposure during Pregnancy*

Table 1. Placental Transfer – Sufentanil Exposure during Pregnancy

Publication	Medication Exposure	Umbilical Vein/Maternal Vein ratio	Maternal and Cord Plasma Opioid Concentration (UV)	Maternal and Cord Plasma Opioid Concentration (UA)	Maternal and Cord Plasma Opioid Concentration (MV)	Authors Conclusion
Loftus (1995) ¹⁰	Bupivacaine alone (n=13)	Not reported	Note reported	Not reported	Not reported	Placental transfer appeared greater with sufentanil than fentanyl; however lower maternal venous sufentanil concentrations results in less fetal exposure to sufentanil; fentanyl was detected in most umbilical arterial and 1 sufentanil sample
	Bupivacaine with fentanyl 75mcg (n=14)	0.37 ± 0.08	0.18 ± 0.03	0.10 ± 0.07	0.52 ± 0.03	
	Bupivacaine with sufentanil 15 mcg (n=9)	0.81 ± 0.07	0.016 ± 0.002	0.006 ± 0.006	0.019 ± 0.005	

* Reviewers table

Table 2. Placental Transfer – Sufentanil Exposure during Pregnancy*

Publication	Medication Exposure	Umbilical Vein/Maternal Vein ratio	Authors Conclusion
Palot (1992) ¹¹	Bupivacaine (0.25% followed by 0.0625% at 10 mL/h)	Not reported	Sufentanil was not detectable in umbilical arterial blood; placental transfer (umbilical vein/maternal vein) was statistically significantly higher in the fentanyl group than in the sufentanil or alfentanil groups; opioids were measurable in every sample of gastric fluid in the fentanyl and alfentanil groups and in 9/21 samples in the sufentanil group.
	Sufentanil (15 mcg followed by 0.5 mcg/mL at 10 mL/h, n=25)	(0.33 ± 0.14)	
	Fentanyl (50 mcg followed by 2 mcg/mL at 10 mL/h, n=28)	(0.57 ± 0.24)	
	Alfentanil (600 mcg followed by 15 mcg/mL at 10 mL, n=25)	(0.34 ± 0.14)	

* Reviewers table

Table 3. Studies/Trials – Sufentanil Exposure during Pregnancy*

Publication	Country	Prospective or Retrospective Data – study type	Maternal Exposure (dose/duration)	Total Pregnancies	Miscarriages	Congenital Abnormality/Complication	Conclusion
Van de Velde (2001) ¹²	Not reported	Retrospective chart review of singleton, term, active labor patients who received an epidural were reviewed for the	10 mL bupivacaine 0.125% and sufentanil 0.75 mcg/mL; combined	1,293	N/A	Not reported	Intrathecal sufentanil in a dose of 7.5 mcg has the potential to result in more non-reassuring fetal heart rate tracings

Publication	Country	Prospective or Retrospective Data – study type	Maternal Exposure (dose/duration)	Total Pregnancies	Miscarriages	Congenital Abnormality/Complication	Conclusion
		occurrence of no reassuring fetal heart rate tracings, uterine hyperactivity, and neonatal and labor outcome	spinal and epidural (CSE) using intrathecal sufentanil (7.5 mcg); and CSE using intrathecal bupivacaine (2.5 mg) and sufentanil (1.5 mcg) during active labor				compared with both intrathecal analgesia using bupivacaine (2.5 mg)/sufentanil (1.5 mcg) mixture and epidural analgesia using bupivacaine, sufentanil and epinephrine; however this results did not increase cesarean deliveries or detrimental neonatal outcomes
Cohen (1992) ¹³	United States	The evaluation of intrathecal sufentanil for labor analgesia with respect to sensory changes, side effects and fetal heart rate changes	Sufentanil intrathecal during active labor	90	N/A	N/A	Decreased sensation to pinprick and cold occurred, perineal itching, fetal heart rate (FHR) changes occurred in 15% (11/73) but were not associated with adverse neonatal outcomes, hypotension
Nielsen (1996) ¹⁴	United States	Prospective comparison study to evaluate patients enrolled from April to September 1994 for labor at a University hospital to compare incidence of intrapartum fetal heart tracing (FHT) abnormalities and the obstetric outcome after intrathecal sufentanil versus epidural bupivacaine	Sufentanil 110 mcg in 2 mL normal saline single intrathecal dose via a combined spinal epidural technique; then received epidural analgesia at least 1 hour after	129	N/A	N/A	No differences observed in the incidence of clinically significant FHT abnormalities (late recurrent decelerations and/or bradycardia) between the two groups; equal rates of hypotension were notes between the two groups
Becker (2011) ¹⁵	Netherlands	Nested case-control study at single center in the Netherlands with 72 women who received epidural analgesia using bupivacaine combined with sufentanil and 72 control group women looking for the occurrence of ST events of the fetal ECG	Bupivacaine 125 mg/ml and sufentanil 0.5 mcg/ml	72	N/A	N/A	No difference between the two groups regarding the numbers of ST events, types of ST events; differences of T/QRS ratios before and after the moment of epidural infusion were comparable between cases and control; epidural analgesia had no effect on the number or types of ST events

* Reviewers table

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/s/

CARRIE M CERESA
09/12/2017

MIRIAM C DINATALE
09/12/2017

LYNNE P YAO
09/12/2017

Clinical Inspection Summary

Date	August 31, 2017
From	Navid Homyouni, M.D., Medical Officer Janice Pohlman, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Steven Galati, M.D., Medical Officer Josh Lloyd, M.D., Cross Discipline Team Leader Allison Meyer, Senior Regulatory Project Manager Division of Anesthesia, Analgesia, and Addiction Products
NDA #	209128
Applicant	AcelRx Pharmaceuticals, Inc.
Drug	Sufentanil
NME (Yes/No)	No
Therapeutic Classification	Opioid Analgesics
Proposed Indication(s)	Management of moderate-to-severe acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate, in adult patients in a medically supervised setting.
Consultation Request Date	February 1, 2017
Summary Goal Date	August 31, 2017
Action Goal Date	October 12, 2017
PDUFA Date	October 12, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study SAP301 was submitted to FDA in support of NDA 209128. Two clinical investigators, Dr. David Leiman, M.D. (Site 4) and Dr. Harold Minkowitz, M.D. (Site 3) were selected for audit by the Agency. Additionally, inspection of two clinical investigators, Dr. Shankar Lakshman, M.D. (Site 1) and Dr. Timothy Melson, M.D. (site 2) and the Contract Research Organization (CRO), (b) (4), was conducted by European Medicine Agency (EMA) from August 7-25, 2017.

The data for Study SAP301 submitted by the Sponsor to the Agency in support of NDA 209128 appear reliable based on available information from the inspection of two clinical sites. There were no significant inspectional observations for clinical investigator, Dr. David Leiman, M.D., and final inspection classification is No Action Indicated (NAI). Although

regulatory violations were observed during the inspection of Dr. Harold Minkowitz, M.D., these violations are unlikely to significantly impact the determination of efficacy and safety and the final classification for the inspection is Voluntary Action Indicated (VAI).

There were no major inspectional findings for Drs. Lakshman and Melson. There were no critical findings for [REDACTED] ^{(b) (4)} during the EMA inspection. While there were inspectional findings at the CRO, they are unlikely to substantially impact the determination of efficacy and safety of the clinical trial. If indicated, an Inspection Summary addendum will be following receipt and review of the EMA Integrated Inspection Report.

II. BACKGROUND

AcelRx Pharmaceutical, Inc. seeks approval of sufentanil, a synthetic opioid analgesic, for management of moderate-to-severe acute pain in a medically supervised setting. Sufentanil has no active metabolites, therefore dosing need not be adjusted in elderly patients with reduced renal clearance or patients with active renal disease. Study SAP301 forms the basis for the clinical evaluation of sufentanil for the determination of safety and efficacy.

This was a two-arm study, comparing the efficacy and safety of sufentanil sublingual tablet 30 mcg to the placebo sublingual tablet for the short-term management of acute moderate-to-severe pain in patients after abdominal surgery. The primary efficacy endpoint was time-weighted summed pain intensity difference (SPID) over the 12-hour study period (SPID12).

The study was conducted from March 10, 2015 to June 23, 2015. There were 161 subjects randomized to treatment (107 Investigational Arm, 54 Placebo Arm). There were 4 sites in United States where subjects were enrolled.

As reported by the Sponsor, SAP301 demonstrated that sufentanil sublingual tablet 30 mcg was effective and superior to placebo for the management of acute moderate-to-severe pain in patients who had undergone abdominal surgery. Sufentanil showed significantly superior pain control compared with placebo for the primary efficacy endpoint (time-weighted SPID12).

GCP inspection by the Agency was conducted at two clinical investigator (CI) sites. The CI sites for inspection were chosen because of significant primary efficacy results for Dr. Leiman and high enrollment with low failure rates for Dr. Minkowitz.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non- U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Classification
David Leiman, M.D. Site Number: 4 2001 Hermann Drive Houston, TX 77004	Protocol: SAP301 Number of Subjects Enrolled: 30	April 18-21, 2017	NAI
Harold Minkowitz, M.D. Site Number: 3 5108 Valerie Street Bellaire, TX 77401	Protocol: SAP301 Number of Subjects Enrolled: 72	May 17-19, 26, 30, 2017	VAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. David Leiman, M.D. (Site 4)

The clinical site screened 37 subjects and 30 were enrolled and randomized. At the time of this inspection, 27 subjects had completed the study and 3 subjects had withdrawn from the study. An audit of 20 subject's records was conducted.

The inspection evaluated subject informed consent forms, source records, eligibility criteria, blinding and randomization procedures, test article accountability logs, subject diaries, use of concomitant medications, adverse events, protocol violations and sponsor monitoring files to determine study conduct and oversight. Source documents and records of the audited subjects were compared to the data listings and found to be the same.

There were no significant inspectional observations and no Form FDA-483, Inspectional Observations, issued. The raw data used to calculate primary efficacy endpoint was verifiable. There was no evidence of under reporting of AEs. There were several minor out-of-window doses of the investigational product. Specifically, seven subjects received early doses on isolated occasions (one or two instances out of multiple administrations), prior to the protocol specified timepoint of 60 minutes. Most of the deviations were between 2 to 4 minutes, with the exception of Subject (b) (6) who was dosed 8 minutes early on one occasion. The sponsor did report most of these as minor protocol deviations.

The inspectional observations summarized above represent exceptions to the overall conduct of the study at this site and should not substantially impact study outcomes, or have placed subjects at undue risk. Study conduct at the site appeared to be in compliance with good clinical practice.

2. Harold Minkowitz, M.D. (Site 3)

The site screened 75 subjects and 72 were enrolled and randomized. One randomized subject was withdrawn prior to treatment after allergy to codeine (an exclusion criterion) was noted. Sixty four (64) of the remaining subjects (71) completed the protocol and 7 subjects were withdrawn due to lack of efficacy. An audit of 25 subject's records was conducted.

The inspection evaluated subject informed consent forms, source records, eligibility criteria, blinding and randomization procedures, case report forms, test article accountability logs, concomitant medications, adverse events, protocol violations and study monitoring visits to determine study conduct and oversight. Source documents and records of the audited subjects were compared to the data listings and found to be the same.

At the conclusion of the inspection, a two-item Form FDA 483 was issued to the clinical investigator for the following two observations:

- (1) An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. Specifically there were protocol deviations with respect to subjects being dosed in a manner not consistent with the clinical protocol:
 - a. Three of the 25 subject records reviewed (Subject #s [REDACTED] (b) (6)) showed a single episode of premature (out-of-window) dosing of IP (2, 15, and 1 minute(s), respectively).
 - b. Nine of the 25 subjects whose records were reviewed had administration of morphine for rescue medication despite not having received investigational product within the prior 60 minutes; the study protocol specified that these subjects should have received another dose of investigational product first and subsequent rescue with morphine if pain was not relieved. Importantly, the sponsor did report all of these as major protocol deviations and there were no new or unreported protocol deviations noted during the inspection.
 - c. There was an isolated instance of the wrong study drug being administered to Subject [REDACTED] (b) (6), who was mistakenly given Subject [REDACTED] (b) (6)'s study drug. The study team identified the error on the same day. A hospital variance was obtained, the IRB was notified and documentation was made in the regulatory binder and clinical research patient chart. The inspection found no other instances of wrong study drug administration.

- (2) Investigational drug disposition records were not adequate with respect to quantity and use by subjects. Specifically, there were four instances of drug accountability discrepancies showing investigational drug disposition logs that were not adequate with respect to quantity and use by subjects:
 - a. Three observations pertained to discrepancies in the number of used or unused pouches within three specific kits of investigational product between the clinical site and drug return depot. Each kit contained ten pouches that had an applicator

preloaded with a dose of study medication (sufentanil) or placebo. These discrepancies appeared to be relatively minor. The study coordinator also indicated that these discrepancies were noted as being from one of the two pharmacies utilized by this CI for the study. This pharmacist has been replaced at that site.

- b. The fourth observation was a minor discrepancy in “tablet returned count” (refers to tablets contained with applicators) from the clinical site (239) and receiving drug depot (241) for “Return of Controlled Substance.” Essentially the drug depot responsible for collecting unused supply received back more drug than the site stated (no diversion of drug).

The clinical investigator responded to the observations in a letter dated June 16, 2017, agreeing with most of the findings and outlining corrective action plan to prevent these types of errors in the future. Although he has dedicated clinical study personnel available to assist him, they were covering across two hospital sites. He attributes most of the observations to hospital personnel or nursing agency staff that were not fully trained or resourced to be involved in the study. He acknowledged his oversight responsibility and did take time for retraining while the study was ongoing. He plans to hire dedicated study personnel to perform study responsibilities and to not use the hospital that proved to be problematic in this study.

In addition to the two Form FDA 483 observations, the following observations were communicated to the clinical investigator during the inspection closeout: (1) Poor documentation practices including numerous write-overs, cross-outs, and changes to handwritten data on subjects' study drug logs and IP subject dispensing log that were not initialed, dated or explained; (2) Missing or late entries for some of the frequent vital sign assessments, primarily BP and HR for multiple subjects in the 25 subject records reviewed; (3) Several blood samples for analysis of sufentanil concentration collected at 1, 12 and 24 hours drawn out-of-window for a few patients; and (4) Pain intensity and pain relief assessments not done at certain time points with 11 instances noted in the 25 subject records reviewed.

Although regulatory violations were noted at the clinical site, they do not appear to significantly impact study outcomes, or have placed subjects at undue risk. The raw data used to calculate the primary efficacy endpoint was verifiable. There was no evidence of under reporting of AEs.

The inspection of the clinical investigators, Dr. Shankar Lakshman, M.D. (Site 1) and Dr. Timothy Melson (Site 2) and [REDACTED] (b) (4) (CRO) discussed below was conducted by EMA from August 7 to 25, 2017 and the results communicated to OSI.

3. Shankar Lakshman, M.D. (Site 1)

This inspection was performed by European Medicines Agency (EMA) as a routine data audit. The clinical site screened 85 subjects and 47 were enrolled and randomized. Informed consent documents for all subjects were audited. Study personnel qualifications and training, sponsor and IRB correspondence, eligibility criteria, blinding and randomization procedures, test article accountability logs, use of concomitant medications, adverse events, protocol violations and

sponsor monitoring files to determine study conduct and oversight were evaluated by EMA inspectors. Study source documents and records of the audited subjects were compared to the data listings and found to be the same.

There were no major inspectional observations at this site that would affect data quality or have placed subjects at undue risk. Overall, the site was well organized and the study conduct appeared to be in compliance with good clinical practice.

4. Timothy Melson, M.D. (Site 2)

This inspection was performed by European Medicines Agency (EMA) as a routine data audit. The clinical site screened 15 subjects and 13 were enrolled and randomized. Informed consent documents for all subjects were audited. Study personnel qualifications and training, sponsor and IRB correspondence, eligibility criteria, blinding and randomization procedures, test article accountability logs, use of concomitant medications, adverse events, protocol violations and sponsor monitoring files to determine study conduct and oversight were evaluated by EMA inspectors. Study source documents and records of the audited subjects were compared to the data listings and found to be the same.

There were no major inspectional observations at this site that would affect data quality or have placed subjects at undue risk. Overall, the site was well organized and the study conduct appeared to be in compliance with good clinical practice.

5. CRO [REDACTED] (b) (4)

This inspection was performed by European Medicines Agency (EMA) as a routine data audit. The sponsor transferred many of the sponsor responsibilities for the conduct of Study SAP301 to the CRO which included CRF development, TMF set-up, IRB submission, trial management, clinical and medical monitoring, data management, and quality assurance.

There were 43 adverse events (AE) deleted by the CRO during the study. Twenty three (23) of the deleted AEs were “transient hypoxia”. Eighteen (18) were in the sufentanil arm and 5 in the placebo arm. These events were deleted based on the Sponsor’s request because they did not meet AE criteria according to the revised protocol which defined hypoxia as O₂ saturation < 92%. All the subjects with deleted AEs had recorded O₂ saturation that was ≥ 92%.

The remaining twenty (20) deleted AEs mainly included nausea, extremities twitching and headache as well as other miscellaneous events. Of these, nineteen (19) did not meet AE criteria because they either occurred before administration of the first dose of the investigational product (10 deleted AEs) or were reported more than 12 hours after administration of the final dose of the investigational product (9 deleted AEs). The protocol specified that reporting of adverse events ends 12 hours after the last dose of the investigational product. One (1) deleted AE was reported as severe adverse event (SAE).

Although violations were noted at this site, the EMA inspection found no critical deficiencies that would significantly impact study outcomes, or have placed subjects at undue risk.

{See appended electronic signature page}

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/s/

NAVID N HOMAYOUNI
08/31/2017

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08/31/2017

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08/31/2017

HUMAN FACTORS VALIDATION STUDY, LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: August 21, 2017

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 209128

Product Name and Strength: Dsuvia (Sufentanil citrate) sublingual tablet
30 mcg

Product Type: Combination Product

Rx or OTC: Rx

Applicant/Sponsor Name: AcclRx Pharmaceuticals, Inc.

Submission Date: December 12, 2016 and March 21, 2017

OSE RCM #: 2017-69

DMEPA Primary Reviewer: Nasim Roosta, PharmD

DMEPA Team Leader: Otto L. Townsend, PharmD

Associate Director for Human Factors : Quynh Nhu Nguyen, MS

DMEPA Deputy Director Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

AcelRx Pharmaceuticals has developed a new single-dose applicator (SDA) that delivers one 30 mcg sufentanil tablet sublingually for the treatment of acute moderate-to-severe pain. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) has requested that we review the human factors (HF) validation study results, device label, pouch label, carton labeling, Directions For Use (DFU), and Prescribing Information (PI) submitted by AcelRx to determine if they are acceptable from a medication error perspective.

1.1 PRODUCT DESCRIPTION

One Dsuvia (sufentanil) sublingual tablet, 30 mcg, will be housed in a single-dose applicator (SDA). A single tablet is 3 mm in size. One SDA will be packaged within a tamper evident laminate, foil pouch and supplied in (b) (4) 10 pouches per carton (b) (4). Dsuvia will be administered to the patient's sublingual space, no more frequently than once per hour, by a health care practitioner (HCP) in a medically supervised setting.

1.2 REGULATORY HISTORY

We previously provided advice to AcelRx Pharmaceuticals, Inc. during a Type B/Pre-NDA meeting on December 9, 2015 and after evaluating their proposed HF study protocol submitted on February 10, 2016.^{ab} Our previous recommendations included the addition of a step in the DFU to confirm the placement of the tablet under the tongue.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D-N/A

^a Schlick, J. Human Factors Meeting Package for Sufentanil Sublingual Tablet. IND 113059. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015, Dec 10. RCM No.: 2015-2496.

^b Schlick, J. Human Factors Protocol Review for Sufentanil Sublingual Tablet. IND 113059. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016, Apr 28. RCM No.: 2016-438.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G
Excerpts from Prescribing Information	H

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3 HUMAN FACTORS VALIDATION STUDY RESULTS

The sections below provide a summary of the study design, errors observed with critical tasks (Table 2), and our analysis of the HF validation study results.

3.1 SUMMARY OF STUDY DESIGN

The objective of this HF validation study was to test participant’s ability to safely and accurately administer a sufentanil sublingual tablet using the Single Dose Applicator (SDA).

The HF validation study was conducted with 45 untrained participants (15 PACU/Floor nurses, 15 ER nurses, and 15 Paramedics licensed in their profession) who were representative of the intended user groups. Each participant was asked to administer the medication four times (4 separately observed use scenarios): in three of the four use scenarios, the product was administered to three different mock patients and in the last use scenario the participant was requested to administer the medication to a mock patient, but the participant was intentionally given torn packaging to evaluate how they might handle this use scenario in the real world. We note that although the participants were untrained on use of the device, they were provided the DFU and instructed to read the DFU before attempting the tasks. At the end of the session, participants were asked eight knowledge assessment questions related to important warnings and cautions or safety critical information within the DFU.

3.2 RESULTS AND ANALYSIS

Overall we disagree with some of the subtask categorizations (e.g. essential vs. critical tasks) assigned by the Applicant and have identified this in the analysis that follows. Failures observed in the HF validation study involved both essential and critical tasks. After evaluating the errors pertaining to essential tasks, we agree with the Applicant that no additional mitigation strategies are necessary, and we determined that the residual risk is acceptable.

Table 2 below summarizes and focuses on the results observed with critical tasks, including knowledge tasks, that were evaluated in the HF validation study along with the Applicant’s

provided root cause analysis for each failure/close call/use difficulty. The Applicant did not propose any further mitigation strategies to address any of the failures/close calls/use difficulties. The table also includes our assessment of the critical task failures.

APPEARS THIS WAY ON ORIGINAL

Table 2: Analysis of Use Errors

Subtask	Use Error	Root Cause Analysis	Additional Analysis and General Recommendations from DMEPA
<p>Subtask 3 (E): Places the SDA tip under the patient's tongue, into the sublingual space</p> <p><i>(DMEPA does not agree with the categorization of this subtask. This subtask should be C (critical).)</i></p>	<p>- 2 failures (PACU/floor nurse and ER nurse)</p> <p>One participant did not realize the drug was contained within the device. She thought she was going to be given the medication to load into the device. Independently, the participant realized the drug was already housed within the applicator. She self-corrected and administered the dose successfully.</p> <p>The other participant attempted to open the desiccant packet to load the tablet into the applicator, as he is accustomed to doing this with another product he administers at his job.</p>	<p>During post-test interviews of both participants:</p> <ul style="list-style-type: none"> - Negative transfer: one participant reported he currently uses a device that must be loaded with medication - Study artifact: one participant thought she was testing the applicator only 	<p>We note that both the front of the foil pouch label and the DFU includes the statement “1 single-dose Applicator containing 1 tablet”, to indicate to the user that this is a combination product containing one tablet. We determined that the DFU describing how to place the applicator in the patient’s sublingual space contains adequate direction. The submitted root cause information did not suggest that the user interface contributed to the failure. We do not have any recommendations, and find the residual risk acceptable.</p>
<p>Subtask 4 (E): Depresses the pusher to deliver the tablet to the patient's sublingual space</p>	<p>- 2 failures (PACU/floor nurse and ER nurse)</p> <p>Both participants experienced dropped tablets.</p>	<p>According to the Applicant, the first failure’s root cause was unknown as one participant did not know why the tablet ejected from the SDA onto the floor. In a response to a DMEPA issued IR, the Applicant later reported that the most likely</p>	<p>Based on the submitted information, it is difficult to determine what role, if any, the design of the user interface may have contributed to the failure. Dropped tablets present the risk of accidental exposure, over-dosing (more than 1 dose per hour), under-dosing, and possible diversion of the drug. However, our evaluation determined that it</p>

Subtask	Use Error	Root Cause Analysis	Additional Analysis and General Recommendations from DMEPA
<p>(DMEPA does not agree with the categorization of this subtask. This subtask should be C (critical).)</p>	<p>One participant administered the medication and the tablet ejected onto the floor of the exam room. The participant was able to locate the tablet on the floor.</p> <p>One participant was unable to successfully administer the tablet due to the patient's tongue was moving back and forth and knocked the tablet out of his mouth during administration.</p>	<p>root cause is that the SDA was inadvertently actuated after the lock was removed, but before the SDA tip was placed in the patient's sublingual space.</p> <p>The second failure was attributed to study artifact where one participant indicated that she would not administer this type of medication to a patient visibly moving around during administration.</p>	<p>is unlikely that additional changes to the user interface can reduce the risk further. We do not have any recommendations and find the residual risk acceptable.</p>
<p>Subtask 5 (E): Confirmation of tablet placement in the patient's sublingual space</p> <p>(DMEPA does not agree with the categorization of this subtask. This subtask should be C (critical).)</p>	<ul style="list-style-type: none"> - 8 failures <ul style="list-style-type: none"> 1 PACU/Floor Nurse 4 ER Nurses 3 paramedics - One participant did not notice instructions in the DFU. - One participant misinterpreted 'confirm tablet placement' by asking the patient instead of visual confirmation - One participant assumed 	<p>Applicant determined that the root cause was related to the following:</p> <ul style="list-style-type: none"> - DFU design: one participant did not notice instructions, but the Applicant did not elaborate on why the participant did not notice the instructions - Mental model: one participant misinterpreted 'confirm tablet placement' as asking the patient instead of visual confirmation and one participant assumed that checking the SDA before and after administration indicated 	<p>We note that the DFU does not specify if the HCP should visually or verbally confirm the placement of the tablet, which may contribute to confusion for the user. If the HCP does not visually confirm that the tablet has been deposited into the patient's sublingual space, then the tablet may be dropped. Dropped tablets pose a risk for accidental exposure, over-dosing (more than 1 dose per hour), under-dosing, and diversion. We determined that the DFU can be improved to further minimize the residual risk. We recommend a revision to step 6 of the DFU so that visual confirmation of the tablet placement is a distinct separate task as follows: "Step 6: Depress the green Pusher to deliver the tablet to the patient's sublingual space."</p>

Subtask	Use Error	Root Cause Analysis	Additional Analysis and General Recommendations from DMEPA
	<p>that checking the SDA before and after administration indicated confirmation</p> <ul style="list-style-type: none"> - Two participants indicated they knew they should visually confirm placement but forgot - One participant did not confirm tablet placement because the mock patient was not receiving actual medication and instead was receiving a placebo - Two participants misunderstood moderator's the question "Did you confirm placement" after moderator failed to directly observe user; answered incorrectly 	<p>confirmation</p> <ul style="list-style-type: none"> - Mental model and Human error: two participants knew they should visually confirm placement but forgot - Study artifact: one participant did not confirm tablet placement because the patient was not receiving actual medication and instead was receiving a placebo - Study artifact: two participants misunderstood the question and answered incorrectly but stated they did initially visually confirm 	<p><i>Step 7: Visually confirm tablet placement in the patient's sublingual space."</i></p>

4 LABELING AND PACKAGING ASSESSMENT

4.1 PACKAGING ASSESSMENT

Since the combination product contains a Schedule II controlled substance, it will require storage in a secure, limited access location, such as an Automated Dispensing Cabinet (ADC). Storage in an ADC may result in discarding both the carton and the PI (containing complete DFU). Subsequent HCP's will only have immediate access to the simplified graphics printed on the back of the individual foil packets; (b) (4)

(b) (4)

(b) (4) Therefore, we suggest revising the DFU to include labeling the pertinent parts of the mouth. Additionally, we recommend that the Applicant consider replacing the simplified graphics on the back of the foil pouch with the complete DFU (written instruction with revised graphics) such that it cannot be easily separated from the foil packet prior to use or discarded along with the carton.

4.2 LABELS AND LABELING ASSESSMENT

The drug's proprietary name, "Dsuvia", is divided into 2 different colors, (b) (4)

(b) (4)

(b) (4). Thus, we recommend the proprietary name "Dsuvia" is presented in all the same color without any intervening matter for improved readability and product identification.

The SDA (container) label only contains the product established name, strength, and dosage form. Per 21 CFR 201.10(i), the minimum information required on a container label must include the proprietary name, established name, lot or control number, and name of manufacturer, packer or distributor of the drug. See recommendation made in Section 5.2.B.

Section 2: "*Dosage and Administration*" of the PI could be reformatted to improve readability and clarify information on the patient selection, use environment, dose, and administration of the drug product. To organize and simplify this information and to separate the recommended dosage, 'Dosing' could be moved to a new subsection (i.e., "*2.2 Dosing*") and subsection 2.1 could be renamed "*Important Dosage and Administration Instructions*". See recommendation made in Section 5.1.A.1.

5 CONCLUSION & RECOMMENDATIONS

The Human Factors Validation Study identified failures that could result in dropped tablets and accidental exposure to sufentanil. The Applicant did not implement any additional mitigation strategies to address these failures, which we do not agree with. Additionally, our review of the proposed label and labeling identified several areas that can be changed to improve readability and minimize the risk for medication errors. We recommend the Applicant implement additional changes per our recommendations and provide additional HF validation data to support changes to the user interface. Please see our recommendations in sections 5.1 and 5.2 below for the Division and AcclRx respectively.

5.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. To separate the recommended dosing information from the information containing the patient selection, use environment, dose and administration of the drug product, consider creating a new subsection (i.e., '2.2 Dosing'), and move dosing information to this new subsection. This will improve readability and clarity of the information presented. See Appendix H.
2. Retain subsection 2.1, but rename it "*Important Dosage and Administration Instructions*" and retain information on patient selection, appropriate use environment, and other special requirements of Dsuvia.
3. In the Directions for Use (DFU), within the Administration subsection (Section 2.2), revise step 6:
"Depress the green Pusher to deliver the tablet to the patient's sublingual space and confirm tablet placement" into two separate steps:
"Step 6: Depress the green Pusher to deliver the tablet to the patient's sublingual space."
"Step 7: Visually confirm tablet placement in the sublingual space."
We have also made this same recommendation for the stand alone DFU to remind users to visually confirm tablet has been appropriately placed in the sublingual space.

4.

(b) (4)

5.2 RECOMMENDATIONS FOR ACELRX PHARMACEUTICALS, INC.

We determined that the human factors validation study data did not demonstrate that the user interface supports safe and effective use of the product by intended users for intended uses and environments. Failures that result in dropped sufentanil tablets pose a risk for accidental exposure, over dosing (more than 1 dose per hour), under dosing the patient, and diversion.

Overall, we do not find the residual risk acceptable and note that you did not propose any additional measures to further mitigate the risk. We have made recommendations for the user interface to further minimize the residual risk. We recommend that you conduct another HF validation study to validate the changes made to the user interface.

We recommend the following:

A. Directions for Use (DFU)

1. Revise step 6 of the DFU: “Depress the green Pusher to deliver the tablet to the patient’s sublingual space and confirm tablet placement” into two separate steps:
“Step 6: Depress the green Pusher to deliver the tablet to the patient’s sublingual space.”
“Step 7: Visually confirm tablet placement in the sublingual space.”
2. Modify the figures that depict the patient’s mouth by labeling parts of the mouth so they represent a more accurate representation of human anatomy. Labeling parts of the mouth within the graphics will help guide users in the proper administration technique.
3. Label each figure (e.g., Figure 1, Figure 2) in the DFU and refer to the figures within the written instructions (e.g. “see Figure 1”).

B. SDA Container Label

Per 21 CFR 201.10(i), the label should include the following information, at a minimum:

1. Proprietary name
2. Established name
3. Lot or control number
4. Name of manufacturer, packer or distributor of the drug

We recommend for the Applicant to include all the above information on this container label. In addition, we would recommend the addition of the expiration date.^c

C. Pouch Labeling- Front

1. To improve readability, consider an alternative presentation for the proprietary name. We recommend the proprietary name “Dsuvia” is presented in all the same color without any intervening matter.
2.  (b) (6)
3. Consider adding the statements, “Instruct the patient to not chew or swallow the tablet. Instruct the patient to not eat or drink and minimize talking for 10 minutes

^c United States Pharmacopoeia (USP) General Chapter <7> Labeling

after receiving the tablet.”

D. Pouch Labeling - Back

1. We recommend that you consider replacing the simplified graphics on the back of the foil pouch with the complete DFU (written instruction with revised and labeled graphics) such that it cannot be easily separated from the foil packet prior to use or discarded along with the carton.
2. Change the statement, [REDACTED] ^{(b) (4)} to read, “Administration Information” so that it more accurately reflects the information that follows.
3. Modify the figures that depict the patient’s mouth by labeling parts of the mouth so they represent a more accurate illustration of human anatomy. Labeling parts of the mouth within the graphics will help guide users in the proper administration technique.

E. Carton Labeling

1. To improve readability, consider an alternative presentation of the proprietary name on the carton labeling. We recommend the proprietary name “Dsuvia” is presented in all the same color without any intervening matter.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Sufentanil citrate that AcelRx Pharmaceuticals, Inc. submitted on January 12, 2017.

Table 2. Relevant Product Information for Sufentanil citrate	
Initial Approval Date	N/A
Active Ingredient	Sufentanil citrate
Indication	Administration by a healthcare professional (HCP) as needed for management of acute moderate-to-severe pain; not to exceed 30 mcg sufentanil per hour.
Route of Administration	Sublingual
Dosage Form	Sublingual tablet
Strength	30 mcg
Dose and Frequency	As needed, not to exceed 30 mcg per hour
How Supplied	The primary container closure system is comprised of ARX-04 SST 30 mcg housed in a SDA and packaged with an oxygen absorber packet; the SDA and oxygen absorber are packaged together in a laminate foil pouch
Storage	(b) (4)
Container Closure	Each tablet is housed in and dispensed from a disposable single-dose applicator (SDA).

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 1, 2017, we searched the L:drive and AIMS using the terms, sufentanil to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews^{d,e}, and we confirmed that one of our previous recommendations was not fully implemented.

OSE RCM #	Review Date	Summary of Recommendations
2016-438	April 28, 2016	We reviewed the human factors protocol. We made one comment to convey to the Applicant in Section 4.1 to add an additional step in the DFU to confirm the placement of the tablet under the tongue.

^d Schlick, J. Human Factors Meeting Package for Sufentanil Sublingual Tablet. IND 113059. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Dec 10. RCM No.: 2015-2469.

^e Schlick, J. Human Factors Protocol Review for Sufentanil Sublingual Tablet. IND 113059. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016, Apr 28. RCM No.: 2016-438.

APPENDIX C. HUMAN FACTORS STUDY

See Human Factors Validation Study results for detailed information on study design and reported results:

<\\cdsesub1\evsprod\nda209128\0001\m3\32-body-data\32p-drug-prod\sufentanilsublingualtablet-devicecomponents\32p7-cont-closure-sys\human-factors-summ-usability-val-rpt.pdf>

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis^f we reviewed the following Sufentanil labels and labeling submitted by AcclRx Pharmaceuticals, Inc. on December 12, 2017 and March 21, 2017.

- SDA container label
- Pouch label- front and back
- Carton labeling
- Prescribing Information

G.2 Label and Labeling Images



4 Pages have been Withheld in Full as Draft Labeling Immediately Following this Page

^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

NASIM N ROOSTA
08/21/2017

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QUYNHNHU T NGUYEN
08/21/2017

QUYNHNHU T NGUYEN on behalf of IRENE Z CHAN
08/21/2017