

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209128Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

## Risk Evaluation and Mitigation Strategy (REMS) Memorandum

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

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**NDA:** 209128  
**Products:** DSUVIA (sufentanil sublingual tablet)  
**APPLICANT:** AcclRx Pharmaceuticals, Inc.  
**FROM:** Judith A. Racoosin, MD, MPH  
**DATE:** *see DARRTS date stamp*

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

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

Based on data included in the NDA, we have become aware of the risk of respiratory depression resulting from accidental exposure to persons for whom DSUVIA is not prescribed due to the tablet size coupled with its potency. Accidental exposure to a person for whom DSUVIA is not prescribed can occur when someone other than the patient places the tiny DSUVIA tablet in their mouth, which may have dropped when the healthcare provider (HCP) tried to administer it into the patient's sublingual space using the single-dose applicator (SDA) placement aid.

In the first review cycle for DSUVIA, the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the results of a simulated-use human factors validation study that was conducted to demonstrate the safe and effective administration of DSUVIA using the SDA by intended users (HCPs). Among 38 mock patients and 45 untrained HCPs who had access to the directions for use, there were two instances of dropped tablets. DMEPA concluded that DSUVIA's proposed user interface of the Directions for Use (DFU) did not support the safe and effective use of the product by intended users for intended uses and environments. The difficulties seen in the human factors studies could contribute to the risk of accidental exposure to a person for whom it is not prescribed. Following the implementation of the recommendations of DMEPA to add a distinct separate task for visual confirmation of the tablet placement to ensure that the tablet is observed in the patient's sublingual space, the applicant conducted a second simulated-use human factors study. No failures or close calls occurred during the simulated use task portion of the second study. Additionally, there were no dropped tablets. Based on the data from this study, DMEPA 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. As such, a REMS is needed to ensure that DSUVIA is utilized only in its intended use environments.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use (ETASU) is necessary for DSUVIA (sufentanil sublingual tablet) to ensure that the benefits of the drug outweigh the risk of respiratory depression resulting from accidental exposure. The goal of the REMS is to mitigate the risk of respiratory depression resulting from accidental exposure by ensuring that DSUVIA is dispensed only to patients in certified medically supervised healthcare settings.

In reaching this determination, we considered the following:

- A. Acute pain due to surgery or trauma in the inpatient and outpatient setting is very common, and most patients in those settings would need at least some pain management with opioid analgesics. Rapidly acting opioid analgesics that do not require administration through the intravenous route may be advantageous.
- B. DSUVIA is indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments. In the development program, DSUVIA was studied in moderate-to-severe acute postoperative pain or pain due to trauma that required opioid analgesia.
- C. DSUVIA provides an alternate route of delivery to intravenous opioids and is expected to treat post-operative and other acute pain in a medically supervised setting.
- D. It is expected that patients will use DSUVIA on a short-term basis for acute pain. The maximum recommended cumulative daily dose of DSUVIA is 720 mcg or 24 tablets (24 hours x 30 mcg/dose; with at least one hour between doses).
- E. DSUVIA poses serious risks involving respiratory depression because improper handling by HCPs and patients could result in accidental exposure to DSUVIA.<sup>1</sup>
- F. DSUVIA contains sufentanil, which is not a new molecular entity.

In accordance with section 505-1 of FDCA, FDA has determined that a REMS with ETASU is necessary to ensure the benefits outweigh the risk of respiratory depression resulting from accidental exposure to DSUVIA.

The elements of the REMS will be ETASU B (healthcare settings that dispense DSUVIA are specially certified), ETASU C (DSUVIA is only dispensed to patients in certified medically

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<sup>1</sup> DRISK review in DARRTS. NDA 209128, 9/22/17.

supervised healthcare settings), an implementation system, and a timetable for submission of assessments.

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**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.**  
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/s/  
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ALLISON MEYER  
11/02/2018

JUDITH A RACOOSIN  
11/02/2018

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management  
RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW**

Date: November 1, 2018

Reviewer(s): LaShaun Washington-Batts, Pharm.D.,  
Risk Management Analyst  
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H.,  
Health Communications Analyst, DRISK

Team Leader: Selena Ready, Pharm.D, DRISK

Division Director: Cynthia LaCivita, Pharm.D, DRISK

Drug Name(s): Dsuvia (sufentanil)

Therapeutic Class: Opioid Agonist

Dosage and Route: 30 mcg sublingual tablet

Application Type/Number: NDA 209128

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## EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) provides an evaluation of the proposed risk evaluation and mitigation strategy (REMS) for sufentanil sublingual (SL) tablet 30 mcg (Dsuvia), new drug application (NDA) 209128. AcclRx Pharmaceutical, Inc. (Applicant) resubmitted the NDA for Dsuvia with the proposed indication for the 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 healthcare setting. Dsuvia is a small tablet housed in a single dose applicator (SDA). The risks associated with Dsuvia are consistent with other opioids analgesics; however, the Agency is particularly concerned about accidental exposure due to Dsuvia's potency and small tablet size.

Based on the concern for accidental exposure resulting from dropped or misplaced tablets, the Agency determined that the use of Dsuvia should be limited to certain certified medically supervised healthcare settings, such as hospitals, surgery centers, and emergency departments, to reduce the risk of accidental exposure in the home and ensure that the product is administered by a HCP who will safely administer the product.

DRISK and DAAAP determined that a REMS with elements to assure safe use (ETASU) was necessary to ensure the benefits of Dsuvia outweigh its risks. The ETASU will consist of a one-time certification of healthcare settings that dispense Dsuvia to ensure that it is administered by healthcare providers and not dispensed directly to patients for use in the home. Certified medically supervised healthcare settings must have HCPs who can manage acute opioid overdose, including respiratory depression.

The Applicant's proposed REMS consists of ETASU B (dispensing only in a specially certified healthcare settings and ETASU C (dispensed only to patients in a certified medically supervised healthcare setting), an implementation system, and a timetable for submission of assessments.

DRISK has reviewed the Applicant's REMS proposal to mitigate the risk of respiratory depression resulting from accidental exposure by ensuring that Dsuvia is dispensed only to patients in a certified medically supervised healthcare setting. The Applicant's amended REMS submission received November 1, 2018 is acceptable. DRISK is recommending approval of the Dsuvia REMS.

## 1 INTRODUCTION

This review by the Division of Risk Management (DRISK) provides an evaluation of the proposed risk evaluation and mitigation strategy (REMS) for sufentanil sublingual (SL) tablet 30 mcg (Dsuvia), new drug application (NDA) 209128. On May 3, 2018, AcclRx Pharmaceutical, Inc. (Applicant) resubmitted the NDA for Dsuvia with the proposed indication for the 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. The NDA was submitted with a proposed REMS and amended on October 23 and 31, 2018, and November 1, 2018. This application is under review in the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

In the initial REMS submission on May 3, 2018, the Applicant proposed a REMS to mitigate the risk of respiratory depression resulting from *inappropriate administration* by

dispensing only within certified healthcare *facilities or services* and informing healthcare providers (HCP) about the safe use of Dsuvia, including proper administration and monitoring. The Agency had previously communicated in the Complete Response Letter<sup>1</sup> from the first review of the NDA that the risk we identified with the use of Dsuvia was the risk of respiratory depression resulting from accidental exposure. Dsuvia is a very small sublingual tablet in a prefilled single-dose applicator to be administered by a healthcare provider. The risk the Agency is particularly concerned about with Dsuvia is accidental exposure due to Dsuvia's potency and tablet size. After a discussion with the Agency on October 9, 2018 and receiving comments from the Advisory Committee (AC) on October 12, 2018, the Applicant submitted an amended REMS proposal on October 23, 2018 with the goal to mitigate the risk of respiratory depression resulting from accidental exposure by ensuring that Dsuvia is dispensed only in certified medically supervised healthcare settings. The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

DRISK and DAAAP have determined that a REMS with ETASU was necessary to ensure the benefits of Dsuvia outweigh its risks. The ETASU will consist of a one-time certification of healthcare settings that dispense Dsuvia to ensure that it is administered by healthcare providers and not dispensed directly to patients for use in the home.

## 1.1 BACKGROUND

The Applicant is seeking approval of Dsuvia via the 505(b) (2) pathway. The reference listed drug (RLD) for the application is Sufenta (sufentanil citrate injection, NDA 019050), and the application cross references Zalviso (a patient-controlled sufentanil SL 15 mcg tablet system, (b) (4)), which received a Complete Response letter in 2015. Sufenta is not approved with a REMS because it is an IV opioid used primarily in an inpatient setting.

Dsuvia is designed to be administered by a HCP and because the tablet is so small it requires a placement aid. The proposed dosage and administration of Dsuvia is one tablet (30 mcg) administered by a HCP into the sublingual space using the SDA, on an as needed basis, per patient request, with a minimum of one hour between doses and for a maximum of 12 doses.

The Applicant had submitted a human factors validation study in the first review cycle for Dsuvia, which was conducted to demonstrate the safe and effective administration of Dsuvia. Division of Medication Error and Prevention Analysis (DMEPA) reviewed the simulated-use human factors validation study and there were dropped tablets during the study that led DMEPA to conclude that Dsuvia's proposed user interface of the DFU did not support the safe and effective use of the product by intended users for intended uses and environments.<sup>2</sup> The incidences of dropped tablets as seen in the human factors

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<sup>1</sup> Complete Response Letter dated October 11, 2017.

<sup>2</sup> Roosta N. Human Factors Report Review, Label and Labeling Review. August 21, 2017. DARRTS ID 4141954

validation studies could contribute to the risk of accidental exposure to a person for whom it is not prescribed.

DMEPA provided recommendations to the Applicant to improve the user interface.

The Applicant implemented the Agency's recommendations regarding the user interface and conducted a second human factors validation study for review in this NDA submission. After review of the results, DMEPA 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.<sup>3</sup>

In the first review cycle of the NDA, DRISK reviewed the Applicant's proposed REMS and provided our rationale and recommendation for a REMS.<sup>4</sup> DRISK proposed goal of the REMS was to mitigate the risk of respiratory depression resulting from accidental exposure by requiring that Dsuvia is only administered in certified hospitals and surgery centers. However, in this review cycle, the Agency reconsidered the goal for certification of medically supervised healthcare settings to include emergency departments in which it was studied, and potential use on the battlefield. The REMS Oversight Committee concurred with this change.

In the Applicant's resubmission on May 3, 2018, they proposed the same REMS with ETASU that was included in the original NDA submission. The submission included the following proposed REMS goal:

*The goal of the proposed REMS for Dsuvia is to mitigate the risk of respiratory depression resulting from inappropriate administration by:*

- *Ensuring that DSUVIA is dispensed only within certified healthcare facilities or services; and*
- *Informing healthcare providers about the safe use of DSUVIA, including proper administration and monitoring.*

The Agency met with the Applicant via teleconference on October 9, 2018 prior to the AC and explained that, as communicated in the Complete Response Letter, the risk the Agency identified that requires a REMS is respiratory depression resulting from accidental exposure. We determined that additional risk mitigation is not needed for inappropriate administration because the product is intended for administration by a HCP in a medically supervised healthcare setting.

In addition, we informed the Applicant that the other proposed REMS materials were not necessary to support the goal of the REMS. The Applicant had submitted a proposed safety brochure and DHCP letters for prescribers and pharmacists and we determined that these REMS materials are not a necessary as part of the Dsuvia REMS and should be removed, as the Directions for Use (DFU) will support appropriate administration.

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<sup>3</sup> Schlick J. Human Factors Report Review, Label and Labeling Review. August 24, 2018. DARRTS ID 4311683.

<sup>4</sup> Ready, S. NDA 209128 sufentanil SL tablet 30 mcg DRISK evaluation of a need for a REMS. September 22, 2017. DARRTS ID 4156487.

On October 12, 2018, the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) was held to discuss the application for Dsuvia. The AADPAC was also supplemented with 5 members from the Drug Safety and Risk Management (DSaRM) AC. The Agency communicated at the AC<sup>5</sup> that we disagreed with the Applicant's proposed certified use settings (*facilities or services*), which are not well-defined. In particular, there is concern that the reference to "services" could include treatment in the home. The Agency determined if Dsuvia is restricted to the medically supervised healthcare settings in which it was studied, such as a hospital, emergency department, or surgery center, it would reduce the risk of accidental exposure, particularly in the home, and ensure that the product is administered by a HCP who is able to safely administer the product and manage acute opioid overdose, including respiratory depression. Several members of the AC questioned if certified healthcare settings would include nursing homes and/or ambulances. The Agency stated that use in these settings was not studied and these settings would not be included as possible certified healthcare settings.

The Agency disagreed with the risk identified in the applicant's goal (respiratory depression resulting from *inappropriate administration*) and the objective about informing providers about the safe use of Dsuvia, including proper administration and monitoring. Additional risk mitigation is not necessary for inappropriate administration because the proposed labeling includes the DFU for the HCP to reference prior to administration. The REMS will include an attestation in the Healthcare setting enrollment form that the setting will train all relevant staff involved in administration to refer to the DFU prior to administering Dsuvia. This is consistent with the findings of the DMEPA conclusion regarding the second human factors validation study.

The AC reiterated the necessity to restrict the use of Dsuvia to medically supervised healthcare settings to be administered by a HCP who can manage acute opioid overdose, including respiratory depression from accidental exposure.

The AC was asked to vote if the benefits of sufentanil sublingual tablets 30 mcg with the REMS proposed by FDA, outweigh the risks for the management of moderate-to-severe acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised healthcare setting, supported approval of sufentanil sublingual tablets. Ten of the AC members voted yes in favor and 3 members voted against approval of Dsuvia.

Following the AC, the Agency provided preliminary comments to the Applicant. On October 23, 2018, the Applicant submitted an amendment that included a proposed REMS Document, enrollment form, and website screenshots.

The Office of Prescription Drug Promotion (OPDP) reviewed<sup>6</sup> and provided comments on the following proposed REMS materials for DSUVIA:

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<sup>5</sup> FDA Briefing Document for the October 12, 2018 Anesthetic and Analgesic Drug Products Advisory Committee  
<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM622857.pdf>

<sup>6</sup> Lee K. OPDP Review of Dsuvia Risk Evaluation and Mitigation Strategies (REMS) Enrollment Form and Website screen shots October 22, 2018. DARRTS Reference ID 4340903

- Healthcare Setting Enrollment Form
- DSUVIA REMS Website Screenshots

DRISK concurred with OPDP's comments and incorporated them into our comments to the Sponsor.

## 1.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 209128 relevant to this review:

- **12/12/2016:** The Applicant submitted a NDA for Dsuvia (NDA 209128), which included a proposed REMS (Seq. No. 0001)
- **10/10/2017:** REMS Memorandum by the DAAAP was filed in DARRTS
- **10/11/2017:** The Agency sent the Applicant a Complete Response Letter that contained acknowledgment of a REMS requirement and the Agency's REMS goal.
- **05/03/2018:** The Applicant resubmitted NDA 209128 for Dsuvia which included a proposed REMS (Seq No. 0026)
- **10/09/2018:** The Agency and Applicant met via teleconference to discuss the REMS. **10/09/2018:** The Agency and Applicant met via teleconference to discuss the REMS.
- **10/12/2018:** The AADPAC plus supplementation from the DSaRM AC was held to discuss NDA 209128.
- **10/17/18:** Preliminary comments were provided to the Applicant on the REMS Document and REMS materials (Healthcare Setting Enrollment form and Website Screenshots).
- **October 23, 2018:** The Applicant submitted an amended REMS that included the proposed REMS Document, Enrollment form, and Website screenshots. (eCTD Seq. No. 0035)
- **October 25, 2018:** The Agency provided comments on the Applicant's Supporting Document and assessment plan.
- **October 29, 2018:** The Agency provided comments on the Applicant's REMS document, enrollment form and website screenshots.
- **October 31, 2018:** The Applicant submitted an amended REMS that included the proposed REMS Document, enrollment form, and website screenshots. The Agency provided comments on the submission. (eCTD Seq. No. 0037)
- **November 1, 2018:** The Applicant submitted an amended REMS. These materials are the subject of our review. (eCTD Seq. No. 0041)

## 2 MATERIALS REVIEWED

### 2.1 SUBMISSIONS

AcelRx Pharmaceuticals Inc. Proposed Risk Evaluation and Mitigation Strategy for DSUVIA (sufentanil sublingual tablet, 30 mcg) submitted May 3, 2018, October 23, 2018, October 31, 2018, and November 1, 2018.

## **2.2 OTHER MATERIALS INFORMING THE REVIEW**

- Ready, Selena. Dsuvia REMS Rationale Review. September 21, 2017. Reference ID 4156487
- Racoosin, J. REMS Memorandum for NDA 0209128. October 10, 2017
- Washington-Batts L. NDA 209128 DRISK REMS Review-interim comments on the assessment plan. October 25, 2018. Reference ID 4340527
- Ready S. NDA 209128 DRISK REMS Review – interim comments on REMS and materials. October 28, 2018. Reference ID 4341528

## **3 SUMMARY OF THE APPLICANT’S PROPOSED REMS**

### **3.1 REMS GOAL**

The Applicant’s proposed goal is listed below.

The goal of the Dsuvia REMS is to mitigate the risk of respiratory depression resulting from accidental exposure by:

- Ensuring that Dsuvia is dispensed only to patients in certified medically supervised healthcare settings.

*Reviewer Comments: The REMS goal is acceptable.*

### **3.2 ELEMENTS TO ASSURE SAFE USE**

The proposed REMS document submitted by the Applicant mitigates the risk of respiratory depression resulting from accidental exposure by ensuring that relevant staff are trained to manage opioid overdose, trained to administer Dsuvia per the Directions for Use and that Dsuvia is administered only in a certified medically supervised healthcare setting by a healthcare provider. To ensure REMS compliance the Applicant will verify annually the authorized representative, address non-compliance, monitor the certified healthcare settings and distributors, and audit the certified healthcare settings within 6 months of the products first distribution.

The Applicant proposed the REMS Document in the new format.<sup>7</sup>

*Reviewer Comments: DRISK finds the proposed REMS acceptable. Dispensing Dsuvia to patients only in a certified medically supervised healthcare setting (ETASU B) and dispensing only to patients in a certified medically supervised healthcare setting (ETASU C) mitigates the risk of accidental exposure. Distribution is restricted to certified healthcare settings only.*

### **3.3 IMPLEMENTATION SYSTEM**

The Applicant has proposed to include an implementation system including maintenance of validated secure database of certified medically supervised healthcare settings, coordinating center and a Dsuvia REMS website.

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<sup>7</sup> Format and Content for the REMS Document Guidance for Industry October 2017. <https://www.fda.gov/downloads/Drugs/.../Guidances/UCM184128.pdf> (accessed 11.1.2018)

### **3.4 TIMETABLE FOR SUBMISSION OF ASSESSMENT**

The Applicant will submit assessment to the FDA at 6 months and 12 months post approval of the REMS and annually thereafter from the date of the initial approval of the Dsuvia REMS.

### **3.5 REMS SUPPORTING DOCUMENT**

The Applicant submitted a Supporting Document which includes an overview, rationale and proposed implementation system of the REMS program, as well as the REMS assessment, noncompliance and audit plans.

The proposed distribution scheme could ensure that Dsuvia is dispensed only to healthcare settings that will train relevant staff that Dsuvia must be administered by a HCP and not be dispensed for home use. The distributor will have access to the database of REMS certified healthcare settings to verify the setting is certified prior to distribution.

#### **Assessment Plan**

In order to assure that the REMS is meeting its goal, AcclRx will submit REMS Assessment Reports to the FDA at 6 months and 12 months from the initial date of approval of the REMS and yearly thereafter. AcclRx will submit each assessment so that it will be received by the FDA on or before the due date.

The REMS assessment plan will include, but is not limited to, the following elements (to be assessed for the current reporting period and cumulatively):

#### **For the 6-month Assessment only, the following dates:**

- a. DSUVIA REMS program launch
- b. REMS website goes live
- c. REMS Call Center is operational
- d. When healthcare settings are able to initiate the certification in the REMS process
- e. First notification of when a healthcare setting's certification was instated

#### **REMS Program Utilization Data:**

- a. Number and type of certified healthcare settings
  - i. Number and type of certified healthcare settings that received at least one shipment of DSUVIA
  - ii. Number and type of certified healthcare settings that dispensed DSUVIA
- b. Number of enrolled wholesalers/distributors
  - i. Number of wholesalers/distributors that shipped at least one shipment of DSUVIA
  - ii. Number of orders shipped to certified healthcare settings for DSUVIA
  - iii. Estimated number of patients who have received DSUVIA therapy
- c. Number of DSUVIA units shipped to certified healthcare settings

- d. For the reporting period, the number of healthcare setting re-enrollments and the expected number of re-enrollments.

**REMS Non-Compliance:**

- a. The number and type of certified healthcare settings for which non-compliance with the REMS is detected
  - i. Provide the source of the report, a description of the event, the cause of the event, and corrective actions taken
- b. The number of enrolled wholesalers/distributors for which non-compliance with the REMS is detected
  - i. Provide the source of the report, a description of the event, the cause of the event, and corrective actions taken
- c. The number and type of **non-certified** healthcare settings that dispensed DSUVIA and the number of incidents (including dispensing for outpatient use) for each
  - i. Provide the source of the report, a description of the event, the cause of the event, and corrective actions taken
- d. The number of instances where wholesalers/distributors shipped DSUVIA to **non-certified** healthcare settings or other entities (e.g., pharmacies or a patient's home)
  - i. Provide the source of the report, a description of the event, the cause of the event, and corrective actions taken
- e. The number, type, and summary description of instances where wholesalers/distributors denied shipment to healthcare settings because the setting:
  - i. was not certified
  - ii. was de-certified due to non-compliance with the REMS
- f. Number of times DSUVIA was distributed, transferred, or loaned from one healthcare setting to another
  - i. Provide the source of the report, a description of the event, the cause of the event, and corrective actions taken
- g. The number of healthcare settings suspended and/or de-certified for non-compliance with REMS Program requirements and reasons for such actions.
- h. The number of wholesalers/distributors suspended and/or de-enrolled for non-compliance with REMS Program requirements and reasons for such actions.
- i. Refer to the Non-Compliance plan which will be used to determine what are:
  - i. Non-compliance events
  - ii. Consequences of non-compliance
  - iii. What events constitute suspension or de-certification from the REMS

**Annual Healthcare Setting and Wholesaler/Distributor audits:**

- a. The number and percentage of healthcare settings, by type, that were audited, including:
  - i. The number and percentage that lacked training records for relevant staff.

- ii. The number and percentage that lacked immediate-access to equipment, medications, and trained personnel to ensure compliance with the REMS safe use conditions.
  - iii. The number and percentage that lacked documented processes and procedures to verify that DSUVIA is not dispensed for use outside of a certified healthcare setting.
  - iv. The number of times that the authorized representative on file with the REMS was no longer the authorized representative of an audited healthcare setting.
  - v. The number and percentage of healthcare settings identified in 4.4.a.i through iv that successfully completed the required corrective and preventive action (CAPA) plan within one month of audit. For any that did not complete the CAPA within one month of the audit, describe actions taken.
- b. The number and percentage of wholesalers/distributors that were audited to ensure that DSUVIA is distributed in accordance with the program requirements (meaning, only to certified healthcare settings), including:
- i. The number and percentage that lacked documented processes and procedures to ensure compliance with REMS-defined requirements.
  - ii. The number and percentage that lacked records of training of relevant staff.
  - iii. The number and percentage of shipments that were shipped to non-enrolled healthcare settings.
  - iv. The number and percentage of wholesalers/distributors identified in 4.4.b.i. through iii that successfully completed the required CAPA within one month of audit. For any that did not complete the CAPA within one month of the audit, describe actions taken.

**REMS Call Center**

- a. Frequently asked questions and problems identified by the REMS Call Center
  - i. Summary of reasons for calls (e.g., enrollment question, location of a certified healthcare setting) by reporter (authorized representative, Healthcare Setting, patient/caregiver, other)
- b. Number of contacts

**Surveillance for Accidental Exposures and Other Adverse Events**

- a. Quantify the following adverse events, and report all available case descriptions:
  - i. Abuse
  - ii. Misuse
  - iii. Accidental exposure
  - iv. Overdose
  - v. Respiratory depression
  - vi. Medication errors associated with DSUVIA
  - vii. Other serious complications associated with DSUVIA
  - viii. Any adverse events reported from a non-DSUVIA REMS-certified hospital

- b. For each of these adverse events, also quantify the occurrences that resulted in:
  - i. Death or
  - ii. Major medical outcome.
- c. Accidental exposures to DSUVIA are also to be presented stratified by adult (age  $\geq$  18 years) or pediatric exposures (sub-categories: age  $\leq$  5 years and 6-17 years) as well as the setting of the exposure.
- d. A root cause analysis (RCA) of any accidental exposures is to be performed. If an RCA cannot be performed, state the reason(s) for this.
- e. Information about these events is to be obtained through:
  - i. Adverse event reports
  - ii. Literature searches
  - iii. Systematic monitoring of mentions in social media
  - iv. National database(s) that provide data regarding:
    - 1. Drug diversion,
    - 2. Patients entering opioid addiction treatment programs, and
    - 3. Calls to poison control centers.
  - v. Depending on results of monitoring use and adverse events, additional data may be further requested.
  - vi. Relevant auxiliary data may be added to the surveillance data.

### **REMS Assessment of Effectiveness**

Based on the information provided, an assessment and conclusion will be determined regarding whether the REMS is meeting its goals, and whether modifications to the REMS are needed. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

*Reviewer Comments: DRISK agrees that the proposed supporting document contains the rationale for, and supporting information about, the design, implementation, and assessment of the REMS as well as the proposed audit and corrective action plans. DRISK finds this document acceptable.*

### **3.6 DSUVIA HEALTHCARE SETTING ENROLLMENT FORM**

The Applicant submitted a proposed Healthcare setting enrollment form that provides detailed instructions on how to enroll the healthcare setting and who can be an Authorized Representative.

The attestations on the enrollment form were as follows:

1. I am authorized to complete the **Healthcare Setting Enrollment Form** and submit it to the REMS on behalf of this healthcare setting.
2. I acknowledge that this healthcare setting is able to manage acute opioid overdose, including respiratory depression.
3. I will not dispense DSUVIA for outpatient use.

4. I will train all relevant staff that DSUVIA must not be dispensed for use outside of this healthcare setting.
5. I will establish processes and procedures to verify that DSUVIA is not dispensed for use outside of this healthcare setting.
6. I will train all relevant staff involved in administration of DSUVIA to read the ***Directions for Use*** prior to administration.
7. I will not distribute, transfer, loan, or sell DSUVIA.
8. I will maintain records of staff training and of all processes and procedures including compliance with those processes and procedures.
9. I will comply with audits by AcclRx Pharmaceuticals, Inc. or a third party acting on behalf of AcclRx Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed for the DSUVIA REMS. Failure to comply with audits may result in decertification from the DSUVIA REMS.
10. If the Authorized Representative changes, a new Authorized Representative will enroll in the REMS Program by completing the ***Healthcare Setting Enrollment Form***.

*Reviewer Comments:* *The attestations in the form align with the REMS Document. The enrollment form will be available on the REMS website and healthcare settings can submit online, via email, mail, or fax. This material is acceptable.*

### **3.7 DSUVIA REMS WEBSITE**

The Applicant's website proposal included information for the healthcare setting and prescriber. The information aligned with the REMS document and Prescribing Information (PI). The Healthcare setting enrollment form, DFU, and PI are available to download from the site.

*Reviewer Comments:* *The REMS website is acceptable to DRISK.*

## **4 DISCUSSION AND CONCLUSIONS**

The product formulation for Dsuvia differs from the other opioid analgesic products intended for use in the inpatient setting and contributes to a unique risk profile. DRISK and DAAAP has determined that a REMS with ETASU is necessary to ensure the benefits of Dsuvia outweigh its risks of respiratory depression resulting from accidental exposure due to the unique attributes of this opioid analgesic product (extremely small tablet size). DRISK and DAAAP are concerned about dropped or misplaced tablets during administration of Dsuvia and increased the risk of accidental exposure which could lead to respiratory depression and or death.

Based on the concern for accidental exposure resulting from dropped or misplaced tablets, the REMS will ensure that Dsuvia will be limited to certified medically-supervised healthcare settings, such as hospitals, surgery centers, and emergency departments, to reduce the risk of accidental exposure and will not be available for patients in an outpatient setting. Dsuvia will also be administered by a HCP rather than self-administration by the patient to minimize the risk of a dropped or misplaced tablet. The ETASU will consist of a one-time certification of healthcare settings that

dispense Dsuvia to ensure that it is administered by healthcare providers and not dispensed directly to patients for home use. Certified medically-supervised healthcare settings must have HCPs who can manage acute opioid overdose, including respiratory depression.

The Agency determined that limiting the use of Dsuvia to certified medically supervised healthcare settings will prevent this product from being available in the outpatient settings, specifically, use of Dsuvia in the home, stand-alone urgent care centers, nursing homes, ambulances or other first-responder situations, settings in which may accidental exposure may be possible. The risk of respiratory depression resulting from accidental exposure of this potent opioid is concerning in these types of settings because administration could potentially occur in persons for whom Dsuvia is not prescribed, such as children or the elderly who are a particularly vulnerable population. The risk of accidental exposure is possible with ambulance services, due to their ability to administer treatment in a home where accidental exposure is more likely, and therefore Dsuvia will not be available for use in these settings. Dsuvia was studied in hospitals, emergency departments and surgery centers and limiting use to these settings is warranted to mitigate the risk of accidental exposure in the home and outpatient settings.

In the Sponsor's submission, the applicant indicated that the Department of Defense (DoD) supported the development of Dsuvia as they see the need for such a product in battlefield pain management which includes austere conditions. The Agency considered how best to address the potential use of Dsuvia in the battlefield. Use of Dsuvia in combat areas provides an alternative way to deliver analgesia for those injured on the battlefield. The FDA met via teleconference with the DoD to discuss the potential use scenarios for Dsuvia and the DoD stated that they would be able to meet the REMS requirements in these settings.

The Applicant's proposed REMS consists of ETASU B (dispensing only in a specially certified healthcare settings and ETASU C (dispensed only to patients in a certified medically supervised healthcare setting), an implementation system, and a timetable for submission of assessments.

In summary, DRISK has reviewed the Applicant's REMS proposal to mitigate the risk of respiratory depression resulting from accidental exposure by ensuring that Dsuvia is dispensed only to patients in a certified medically supervised healthcare setting. The Applicant's amended REMS submission received November 1, 2018 is acceptable. DRISK is recommending approval of the Dsuvia REMS.

## **5 ATTACHMENTS**

- Dsuvia REMS Document
- Dsuvia REMS Program Website Screenshots
- Dsuvia Healthcare Setting Enrollment Form

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LASHAUN WASHINGTON-BATTS  
11/01/2018

SELENA D READY  
11/01/2018

CYNTHIA L LACIVITA  
11/01/2018

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management  
RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW**

Date: October 28, 2018

Reviewer(s): Selena Ready, Pharm.D  
Team Leader  
Division of Risk Management (DRISK)

Kate Oswell  
Health Communications Analyst  
DRISK

Division Director: Cynthia LaCivita, Pharm.D, DRISK

Drug Name(s): Dsuvia (sufentanil)

Therapeutic Class: Opioid Agonist

Dosage and Route: 30 mcg sublingual tablet

Application Type/Number: NDA 209128

---

## **1 INTRODUCTION**

This review by the Division of Risk Management (DRISK) provides an evaluation of the materials in the proposed risk evaluation and mitigation strategy (REMS) for sufentanil sublingual (SL) tablet 30 mcg (Dsuvia), new drug application (NDA) 209128, submitted on October 23, 2018. On May 3, 2018, AcclRx Pharmaceutical, Inc. (Applicant) resubmitted the NDA for Dsuvia with the proposed indication for the 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. This application is under review in the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

### **1.1 BACKGROUND**

Dsuvia is a drug-device combination product, comprised of an immediate-release formulation of sufentanil SL tablet 30 mcg pre-loaded in a single-dose applicator (SDA). Dsuvia is designed to be administered by a HCP. The proposed dosage and administration of Dsuvia is one tablet (30 mcg) administered by a HCP into the sublingual space using the SDA, on an as needed basis, per patient request, with a minimum of one hour between doses.

The Applicant proposed a REMS to mitigate the risk of respiratory depression resulting from accidental exposure by ensuring that Dsuvia is dispensed only within certified medically supervised healthcare settings. The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

The Applicant submitted an amended REMS on October 23, 2018 that included the proposed REMS Document, supporting document, enrollment form, and website screenshots. This review also considers the recommendations from the Office of Prescription Drug Promotion (OPDP) of the REMS materials provided on October 26, 2018.<sup>1</sup>

## **2 OTHER REVIEWS RELATED TO THE MAY 3, 2018 SUBMISSION**

- Washington-Bates L. NDA 209128 REMS Review-interim comments on the assessment plan, October 25, 2018. Reference ID 4340527

## **3 MATERIALS REVIEWED**

### **3.1 PROPOSED REMS DOCUMENT**

The Applicant submitted a proposed REMS Document that included the draft language provided by the Agency via email on October 16, 2018.

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<sup>1</sup> Lee, K. NDA209128 DSUVIA (sufentanil sublingual tablet 30mcg). Comments of the draft REMS Enrollment Form and DSUVIA REMS Website Screenshots. DARRTS ID 4340903.

*Reviewer Comments: The FDA's most current version of the draft REMS Document removes the words [REDACTED] (b) (4) from the goal. See attached redlined REMS Document.*

### **3.2 PROPOSED HEALTHCARE SETTING ENROLLMENT FORM**

The Applicant submitted a proposed Healthcare Setting Enrollment Form. To guide the Applicant in their development of the enrollment form, the Agency recommended the Applicant review Sublocade REMS on the REMS@FDA website and provided a draft enrollment form via email on October 16, 2018.

*Reviewer Comments: Additional formatting changes were made to the form to improve readability and to separate the content into distinct categories for ease of use. We have also updated the attestations on the form. Recommended edits on the Healthcare Setting Enrollment Form file are included as redlined edits (attached).*

### **3.3 PROPOSED REMS WEBSITE SCREENSHOTS**

The Applicant submitted proposed REMS website screenshots and REMS website content in word format. The Agency provided guidance via teleconference on October 9, 2018 and referred the Applicant to the REMS@FDA website for examples.

*Reviewer Comments: Based on the recommendations from OPDP, we have included the 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 removed some content from the website to streamline it so that key information is included and easier to find. We recommend moving the enrollment information higher up on the page so that it can be found without having to scroll down the page. The website screenshots do not include the functionality of the online enrollment process for healthcare settings. For example, when clicking on the button for online enrollment, another window would open and allow an authorized representative to fill in the data fields of information and read the attestations of requirements and responsibilities. There would also need to be a statement about signing the form electronically. Each step in the process would need to be shown in the screenshots to demonstrate how online enrollment takes place.*

*The Applicant must resubmit screenshots to show the full functionality of online enrollment. The recommended edits on the Dsuvia REMS webpage file are attached.*

## **4 DISCUSSION AND CONCLUSIONS**

The Agency reviewed the Applicant's proposed REMS Document, enrollment form, and website screenshots. The Applicant must make further edits to the REMS Document to remove [REDACTED] (b) (4) from the goal and remove the Directions for Use as a material. Additional edits to the materials must be made to improve readability, functionality, and align all components with the draft REMS Document. DRISK has attached redlined edits to this review.

## **5 COMMENTS TO THE SPONSOR**

The Agency reviewed the proposed REMS Document and materials submitted on October 23, 2018 and made comments and revisions to the clean MS Word version of the

REMS Document and enrollment form and the PDF of the website screenshots. Specific comments are noted on each document attached to the email.

### ***REMS Document***

The REMS Document has completed internal clearance, any additional changes will require additional clearance. The current draft removes the words [REDACTED]<sup>(b) (4)</sup> from the goal. You must align all components of the REMS with the draft REMS Document, remove the *Directions for Use* as a REMS material from your proposed REMS. (See attached)

### ***Healthcare Setting Enrollment Form***

We have made some formatting changes to your form to improve readability and to separate the content into distinct categories for ease of use. We have also updated the attestations on the form, based on the proposed REMS Document. (See attached)

### ***REMS Website:***

We have removed some content from the website so that key information is included and easier to find. We recommend adding the 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 request that the enrollment information be moved higher up on the page so that it can be found without having to scroll down the page.

In addition, the website screenshots do not include the functionality of the online enrollment process for healthcare settings. For example, when clicking on the button for online enrollment, another window would open and allow an authorized representative to fill in the data fields of information and read the attestations of requirements and responsibilities. There would also need to be a statement about signing the form electronically. Each step in the process should be provided in the screenshots to demonstrate how online enrollment takes place. You must resubmit screenshots with the requested edits and additional screenshots to show the full functionality of online enrollment. (See attached with comments.)

### **Resubmission Instructions:**

Submit the following revised REMS materials to your application by **COB, Wednesday, October 31, 2018.**

Accept the track changes with which you agree in the MS Word newly redlined documents and only indicate any new ones you propose as redlined changes in your next submission. The next submission to the Gateway should include Clean MS Word, Tracked MS Word, and pdf formatted versions of the following documents:

- **REMS Document**
- **REMS Supporting Document**
- ***Healthcare Setting Enrollment Form***

- *REMS Website Screenshots*
- *Compiled pdf of REMS Document and final formatted REMS materials (no Supporting Document included in this)*

## **6 ATTACHMENTS**

Agency Redlined REMS Document, enrollment form, and website screenshots

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10/28/2018

CYNTHIA L LACIVITA  
10/28/2018

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management  
RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW**

Date: October 25, 2018

Reviewer(s): LaShaun Washington-Batts, Pharm.D.,  
Risk Management Analyst  
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H.,  
Health Communications Analyst, DRISK

Team Leader: Selena Ready, Pharm.D, DRISK

Division Director: Cynthia LaCivita, Pharm.D, DRISK

Drug Name(s): Dsuvia (sufentanil)

Therapeutic Class: Opioid Agonist

Dosage and Route: 30 mcg sublingual tablet

Application Type/Number: NDA 209128

---

## 1 INTRODUCTION

This review by the Division of Risk Management (DRISK) provides an evaluation of the Assessment Plan in the Supporting Document of the proposed risk evaluation and mitigation strategy (REMS) for sufentanil sublingual (SL) tablet 30 mcg (Dsuvia), new drug application (NDA) 209128, submitted on October 26, 2018. On May 3, 2018, AcelRx Pharmaceutical, Inc. (Applicant) resubmitted the NDA for Dsuvia with the proposed indication for the 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. This application is under review in the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

### 1.1 BACKGROUND

Dsuvia is a drug-device combination product, comprised of an immediate-release formulation of sufentanil SL tablet 30 mcg pre-loaded in a single-dose applicator (SDA). Dsuvia is designed to be administered by a HCP. The proposed dosage and administration of Dsuvia is one tablet (30 mcg) administered by a HCP into the sublingual space using the SDA, on an as needed basis, per patient request, with a minimum of one hour between doses.

The Applicant proposed a REMS to mitigate the risk of respiratory depression resulting from accidental exposure by ensuring that Dsuvia is dispensing only within certified medically supervised healthcare settings. The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

The Agency provided preliminary comments on the REMS to the Applicant following the Advisory Committee on October 16, 2018 (email A. Meyer). The Applicant submitted an amended REMS on October 23, 2018 that included the proposed REMS Document, supporting document, enrollment form, and website screenshots.

## 2 PROPOSED REMS SUPPORTING DOCUMENT

The Applicant submitted a proposed Supporting Document describing their proposed REMS and a detailed section on the implementation system. The Assessment Plan did not contain specific objectives or data sources.

### Reviewer Comments:

*Regarding the Assessment Plan, the Applicant must make edits to the Supporting Document to include specific assessment parameters, an audit protocol, and non-compliance corrective action plan. DRISK has proposed an Assessment Plan, which we will provide, to the Applicant. (See attached) Further edits to the Supporting Document includes aligning the Supporting Document with the Agency's draft REMS Document and removing the Directions for Use as a REMS material.*

### **3 DISCUSSION AND CONCLUSIONS**

The Agency reviewed the Applicant's Supporting Document, which contains the assessment plan. The Applicant must make edits to the Supporting Document to include specific assessment parameters, an audit protocol, a non-compliance corrective action plan, and align all components with the draft REMS Document. DRISK has attached a draft assessment plan to this review. The Agency will email a redlined Supporting Document to the Applicant for their review and comment and, a draft assessment plan.

If required, comments for the other proposed REMS materials will be provided in a future correspondence.

### **4 COMMENTS TO THE SPONSOR**

The Agency has reviewed the proposed REMS Supporting Document submitted on October 23, 2018.

#### ***REMS Supporting Document***

- The Applicant must make edits to the Supporting Document to include specific assessment parameters, an audit protocol, a non-compliance corrective action plan, and align all components with the draft REMS Document, removing the *Directions for Use* as a REMS material. We have attached a redlined Supporting Document and draft Assessment Plan to this email. You must contact the Agency with questions or comments prior to the next submission of final documents.

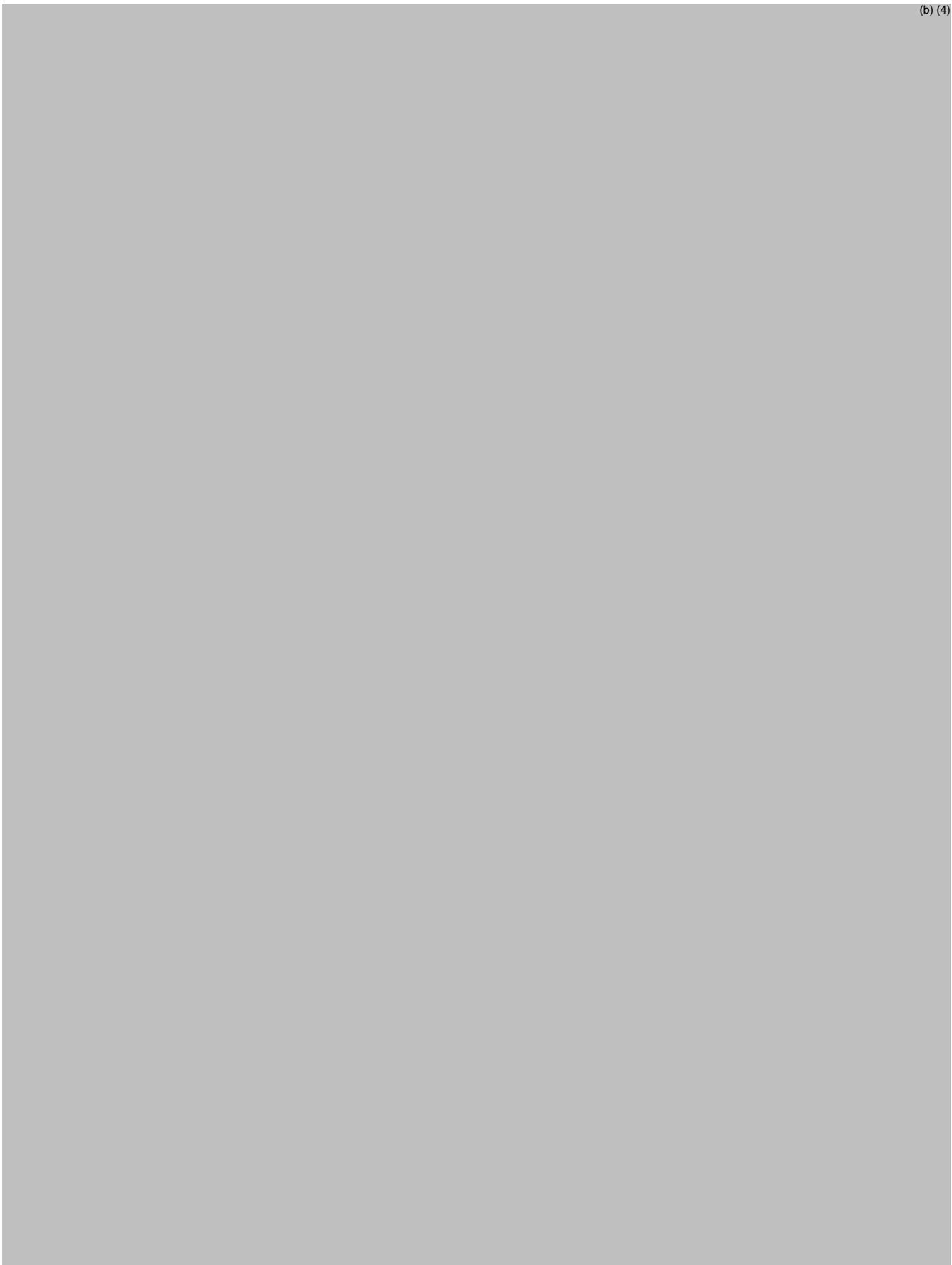
### **5 ATTACHMENTS**

Draft Assessment Plan

The REMS assessment plan must include, but is not limited to, the following elements (to be assessed for the current reporting period and cumulatively):

(b) (4)





7. Based on the information provided, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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LASHAUN WASHINGTON-BATTS  
10/25/2018

SELENA D READY  
10/25/2018

CYNTHIA L LACIVITA  
10/25/2018

## Risk Evaluation and Mitigation Strategy (REMS) Memorandum

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

---

**NDA:** 0209128  
**Products:** Dsuvia (sufentanil sublingual tablet)  
**APPLICANT:** AcclRx Pharmaceuticals, Inc.  
**FROM:** Judith A. Racoosin, MD, MPH  
**DATE:** see DARRTS date stamp

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

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

Based on data included in the NDA, we have become aware of the potential risk of respiratory depression resulting from accidental exposure to persons for whom Dsuvia is not prescribed due to the tablet size coupled with its potency. Accidental exposure to a person for whom Dsuvia is not prescribed can occur in the hospital or surgery center when someone other than the patient ingests the tiny Dsuvia tablet that may have dropped when the healthcare provider (HCP) tried to administer it into the patient's sublingual space using the placement aid (SDA).

DMEPA reviewed the results of the simulated-use human factors validation study that was conducted to demonstrate the safe and effective administration of Dsuvia using the SDA by intended users (HCPs). Among 38 mock patients and 45 untrained HCPs who had access to the directions for use, there were two instances of dropped tablets. DMEPA concluded that Dsuvia's proposed user interface of the Directions for Use (DFU) does not support the safe and effective use of the product by intended users for intended uses and environments. The difficulties seen in the human factors studies could contribute to the risk of accidental exposure to a person for whom it is not prescribed.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use (ETASU) is necessary for Dsuvia to ensure that the benefits of the drug outweigh the risk of respiratory depression resulting from accidental exposure. The goal of the REMS should be to mitigate the risk of respiratory depression resulting from accidental exposure by requiring that

Dsuvia is only dispensed by hospitals and surgery centers that are specially certified (ETASU B), and that Dsuvia is only administered in certified hospitals and surgery centers (ETASU C).

In reaching this determination, we considered the following:

- A. Surgery in the inpatient and outpatient setting is very common, and rapidly acting opioid analgesics that do not require administration through the intravenous route may be advantageous.
- B. Dsuvia is indicated for 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. In the development program, Dsuvia was studied in moderate-to-severe acute postoperative pain or pain due to trauma which required opioid analgesia. It has been estimated that only one in four surgical patients in the US receive adequate relief of acute pain.<sup>1</sup> “Acute postoperative pain” falls under ICD-9 code 338.18 and may be known by a variety of synonyms such as “persistent pain following procedure” or “post-procedural pain” specific to certain areas of the body.<sup>2</sup>
- C. Dsuvia provides an alternate route of delivery to intravenous opioids, and is expected to treat post-operative pain.
- D. It is expected that patients will use Dsuvia on a short-term basis for acute postoperative pain. The maximum cumulative daily dose available of Dsuvia is 720 mcg or 24 tablets (24 hours x 30 mcg/dose; with at least one hour between doses).
- E. Dsuvia poses serious risks involving respiratory depression because improper handling by HCPs and patients could result in accidental exposure to Dsuvia.<sup>3</sup>
- F. Dsuvia contains sufentanil which is not a new molecular entity.

In accordance with section 505-1 of FDCA, FDA has determined that a REMS with ETASU is necessary to ensure the benefits outweigh the serious risks of respiratory depression resulting from accidental exposure associated with Dsuvia. FDA has determined that Dsuvia poses a serious and significant public health concern which cannot be mitigated by labeling alone.

The elements of the REMS will be ETASU B (Dsuvia is only dispensed by hospitals and surgery centers that are specially certified), ETASU C (Dsuvia is only administered in certified hospitals and surgery centers), an implementation system, and a timetable for submission of assessments.

---

<sup>1</sup> Phillips DM. JCAHO pain management standards are unveiled. JAMA. 2000;284(4):428-429.

<sup>2</sup> <http://www.icd9data.com/2012/Volume1/320-389/338-338/338/338.18.htm>

<sup>3</sup> DRISK review in DARRTS. NDA 209128, 9/22/17.

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ALLISON MEYER  
10/10/2017

JUDITH A RACOOSIN  
10/10/2017

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

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<b>Application Type</b>	NDA
<b>Application Number</b>	209128
<b>PDUFA Goal Date</b>	10/12/2017
<b>OSE RCM #</b>	2016-2965
<b>Reviewer/Team Leader</b>	Selena Ready, Pharm.D.
<b>Division Director</b>	Cynthia LaCivita, Pharm.D.
<b>Review Completion Date</b>	September 21, 2017
<b>Subject</b>	Evaluation of Need for a REMS
<b>Established Name</b>	Sufentanil
<b>Trade Name</b>	Dsuvia
<b>Name of Applicant</b>	AcelRx Pharmaceuticals, Inc.
<b>Formulation</b>	Sublingual tablet
<b>Dosing Regimen</b>	30 mcg, on an as needed basis, per patient request, with a minimum of 1 hour between doses

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## EXECUTIVE SUMMARY

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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for Dsuvia® (sufentanil sublingual (SL) tablet 30 mcg) is necessary to ensure the benefits outweigh its risks. AcclRx Pharmaceuticals, Inc. (Applicant) submitted a New Drug Application (NDA 209128) for Dsuvia with the proposed indication for the 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.

The Applicant proposed a REMS to mitigate the risk of respiratory depression resulting from inappropriate administration by dispensing only within certified healthcare facilities or services and informing healthcare providers (HCP) about the safe use of Dsuvia, including proper administration and monitoring. The applicant's proposed REMS consists of Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

DRISK recommends a REMS with ETASU, but does not concur with the Applicant's proposed REMS goal or use setting. The recommended goal of the REMS is to mitigate the risk of respiratory depression resulting from accidental exposure by requiring that Dsuvia is only dispensed by hospitals and surgery centers that are specially certified (ETASU B) and that Dsuvia is only administered in certified hospitals and surgery centers (ETASU C). The REMS must also include an implementation system and timetable for submission of assessments.

## 1 Introduction

---

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for Dsuvia® (sufentanil sublingual (SL) tablet 30mcg) is necessary to ensure the benefits outweigh its risks. AcclRx Pharmaceuticals, Inc. (Applicant) submitted a new drug application (NDA), 209128, for Dsuvia with the proposed indication of the 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. This application is under review in the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). The Applicant's submission included a REMS proposal to mitigate the risk of respiratory depression resulting from inappropriate administration with elements to assure safe use (ETASU). The applicant's proposed REMS consists of Medication Guide, ETASU, an implementation system, and a timetable for submission of assessments.

## 2 Background

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### 2.1 PRODUCT INFORMATION

Dsuvia is drug-device combination product comprised of a new immediate-release formulation of sufentanil SL tablet 30 mcg pre-loaded in a single-dose applicator (SDA) designed to be administered by a HCP. Sufentanil is a synthetic opioid agonist characterized by a high selectivity and affinity for mu-opioid receptors, and is 5 to 10 times more potent than fentanyl. Sufentanil is listed as Schedule II under the Controlled Substances Act and is currently marketed for intravenous (IV) and epidural anesthesia as the listed drug, Sufenta (sufentanil citrate injection). The Applicant is seeking approval for

Dsuvia via the 505(b)(2) pathway for the proposed indication of 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. The reference listed drug (RLD) for the application is Sufenta (sufentanil citrate injection, NDA 019050), and the application cross references Zalviso (a patient-controlled sufentanil SL 15 mcg tablet system, (b) (4)), which received a Complete Response letter in 2015 that included acknowledgment of a REMS requirement and REMS goal. Zalviso is currently marketed in the European Union by Grunenthal, GmbH. Sufenta is not approved with a REMS because it is an IV opioid used primarily in an inpatient setting. Dsuvia is not currently approved in any jurisdiction.

Unlike Zalviso, Dsuvia is not intended for patient self-administration. Once it is determined that the patient needs an opioid analgesic, it is intended that the HCP will retrieve the tamper evident laminate, foil pouch containing the pre-loaded SDA from the pharmacy or automated dispensing safe and will open it immediately prior to the administration of Dsuvia. The HCP will then administer the SL tablet to the patient's sublingual space using the SDA. Subsequently, each dose will be readministered by a HCP as needed for pain control with no less than one hour between doses. The maximum cumulative daily dose available of Dsuvia is 720 mcg or 24 tablets (24 hours x 30 mcg/dose).

Dsuvia was designed as a very small tablet (3 mm in diameter by 0.85 mm) to minimize a salivary response.

### 3 Regulatory History

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The following is a summary of the regulatory history for Dsuvia (NDA 209128) relevant to this review:

- **12/12/2016:** The Applicant submitted a NDA for Dsuvia (NDA 209128), which included a proposed REMS (Seq. No. 0001)

**Internal meetings that helped inform this review:**

- **05/11/2017:** The Mid-cycle meeting was held and DMEPA presented their assessment of the results of the Dsuvia Human Factors Validation Study and recommended that the Applicant conduct another human factors validation study.
- **07/27/2017:** The REMS Oversight Committee (ROC) meeting was convened to discuss the REMS proposal for Dsuvia (NDA 209128). The ROC agreed that a REMS with ETASU is necessary to ensure the benefits outweigh the risks associated with Dsuvia use.

### 4 Therapeutic Context and Treatment Options

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#### 4.1 DESCRIPTION OF THE MEDICAL CONDITION

Pain can be categorized according to its duration, underlying pathophysiology of the original insult, and whether a central sensitization component has developed. Pain can be further classified into acute or chronic, depending upon the duration, and neuropathic or non-neuropathic, depending upon the mechanisms underlying the pain. The proposed treatment population for this product is adults in a medically supervised setting who experience moderate-to-severe acute pain severe enough to require an opioid analgesic.

## 4.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are a variety of oral immediate-release opioids for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The most common are hydrocodone, oxycodone, morphine, or hydromorphone. Each of these immediate-release opioids are available for use in an inpatient and outpatient setting. Each are labeled with a boxed warning for addiction, abuse, and misuse; life-threatening respiratory depression; accidental ingestion; neonatal opioid withdrawal syndrome; cytochrome P450 3A4 interaction; and risks from concomitant use with benzodiazepines or other CNS depressants.

## 5 Benefit Assessment

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The efficacy of Dsuvia was demonstrated in the pivotal Phase 3, adequate and well-controlled study (SAP301) of 161 patients who had outpatient abdominal surgery (abdominoplasty, inguinal hernia repair and laparoscopic abdominal surgery). There was statistically significantly less post-operative pain using the primary endpoint of time-weighted summed pain intensity difference over the 12-hour study period (SPID12) and less rescue medication (morphine 1 mg IV) was used in the Dsuvia group. Patients' ages ranged from 18 to 84 years. The number of doses and duration of treatment was consistent with the expected for management of acute moderate-to-severe pain following surgery.

## 6 Risk Assessment & Safe-Use Conditions

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In controlled and uncontrolled studies, the safety of Dsuvia was evaluated in a total of 363 patients with moderate-to-severe acute postoperative pain or pain due to trauma which required opioid analgesia. An additional 323 postoperative patients were studied with a similar or higher exposure to sufentanil SL tablets, which were the bridged studies from the Zalviso program. There were no deaths in the Dsuvia program and no opioid reversal agents (e.g. naloxone) were used. The most frequently reported adverse events (AEs) > 2% occurring in the Phase 3 studies were nausea, vomiting, headache, dizziness, pruritus, somnolence, hypotension, tachycardia, and dry mouth. Overall, AEs were consistent with the adverse event profile of an opioid treatment given in a postsurgical or other medically supervised setting for acute pain.

### Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Thus, the Dsuvia study protocols required oxygen saturation at 95% and supplemental oxygen was available to patients receiving study treatment. There were two patients (0.6%) who received Dsuvia that discontinued the study due to respiratory rate decreased and one each (0.3%) discontinued following oxygen saturation decreased and hypoventilation. However, respiratory depression would not be unexpected in a postoperative setting where patients are recovering from anesthesia. Overall, changes from baseline in respiration rate and oxygen saturation were generally small. Based on the known risks of respiratory depression with opioids, the risk of respiratory depression has been included as a boxed warning in the proposed labeling for Dsuvia.

## **Accidental Exposure**

Accidental exposure to Dsuvia is an identified risk due to the tablet size coupled with its potency. The Dsuvia tablet is so small that it requires a placement aid (SDA) for administration by a HCP. In addition, the potency of sufentanil is five to ten times greater than fentanyl. Therefore, there is a potential risk of respiratory depression and overdose resulting from accidental ingestion of a potent opioid that is very small in size and may be difficult to find if dropped. In consideration of this risk, Dsuvia will only be administered by a HCP and the proposed labeling includes the Directions for Use (DFU) for the HCP to reference before administration.

The Applicant conducted a simulated-use human factors (HF) validation study in 2016 to demonstrate the safe and effective administration of Dsuvia using the SDA by intended users (HCPs). The study was tested in a simulated health care setting using 38 mock patients and 45 untrained HCPs. The HCPs were required to complete a series of 11 subtasks associated with administration of Dsuvia. This was repeated by each HCP for three full administrations. The DFU was provided to the HCP for guidance, and was available for them to refer to throughout the study. Sixteen task failures were observed, with two task failures resulting in dropped tablets. DMEPA reviewed the results of the study and concluded that Dsuvia's proposed user interface of the DFU does not support the safe and effective use of the product by intended users for intended uses and environments.

## **Addiction, Abuse, and Misuse**

Because Dsuvia is an opioid, it carries the risks of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. Of note, historically, opioids used exclusively in inpatient settings have not required a REMS to mitigate these risks. However, the IR opioids are labeled with a boxed warning for the risk. The proposed indication for Dsuvia is for use in a medically supervised setting and the proposed labeling contains a boxed warning to discontinue the use of Dsuvia prior to discharge and warning for the risk of addiction, abuse, and misuse.

## **7 Expected Postmarket Use**

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Dsuvia is expected to be prescribed by health care providers, with an active DEA license for prescribing Controlled II narcotics, involved in the management of adult patients with acute pain severe enough to require an opioid analgesic. The proposed indication is for the 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.

This product is not proposed for use in children or for use outside of a medically supervised setting.

### **7.1 MEDICALLY SUPERVISED SETTING**

The Applicant proposes to restrict this product use to a medically supervised setting, which is defined as meeting the following criteria:

- a. Healthcare facilities and services with a licensed pharmacy or healthcare provider with DEA registration for CII drugs who will oversee ordering and administration of the medication;

- b. Healthcare facilities and services with access to equipment and personnel trained to detect and manage hypoventilation, including use of supplemental oxygen and opioid antagonists, such as naloxone.

The Dsuvia studies for efficacy and safety were primarily conducted in the postoperative setting where patients are recovering from anesthesia, which were in a hospital or surgery center. There was a small cohort studied in the Emergency Department. However, with the criteria for the medically supervised setting proposed by the Applicant, this product could potentially be used in urgent care clinics, physicians' offices, ambulances, nursing homes, or any setting in which a health care provider is available to prescribe Controlled II substances and detect and manage hypoventilation.

If restricted to the setting in which Dsuvia was studied, such as hospitals and surgery centers, it would ensure the availability of HCPs that routinely monitor postoperative patients and are knowledgeable in the management of respiratory depression, and can safely administer the drug.

## **8 Risk Management Activities Proposed by the Applicant**

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### **8.1 REVIEW OF APPLICANT'S PROPOSED REMS**

The Applicant proposed a REMS with ETASU to mitigate the risk of respiratory depression resulting from inappropriate administration by dispensing only within certified healthcare facilities or services and informing healthcare providers about the safe use of Dsuvia, including proper administration and monitoring. The Applicant developed this REMS proposal based upon Agency feedback from the proposed REMS program for Zalviso. In the proposed REMS Supporting Document, the Applicant referenced Zalviso and the similarities between the products. However, Zalviso and Dsuvia are different products in the following ways: 1) Dsuvia is a single-dose provided in a SDA, 2) Dsuvia is not patient self-administered and, 3) Dsuvia will be administered by a HCP who has the DFU for reference before administering. Therefore, DRISK disagrees with the proposed REMS goal and proposed use setting.

#### **8.1.1 REMS Goals**

The Applicant proposed a REMS with ETASU to mitigate the risk of respiratory depression resulting from inappropriate administration by dispensing only within certified healthcare facilities or services and informing healthcare providers about the safe use of Dsuvia, including proper administration and monitoring.

**Reviewer's Comments:** *The review team disagrees with the Applicant's proposed goal to mitigate the risk of respiratory depression resulting from inappropriate administration. We determined that additional risk mitigation is not needed for inappropriate administration if the product is administered by a HCP. Since the HCP will administer Dsuvia, the need to monitor patients is similar to other opioid analgesics in a hospital setting. Furthermore, the proposed labeling includes the DFU for the HCP to reference prior to administration. Per DMEPA's evaluation of the human factors validation study, Dsuvia's proposed user interface of the DFU could be improved and an additional study is needed to support the safe and effective use of the product by intended users for intended uses and environments. We determined that an improved DFU could allow for safe administration of Dsuvia by a HCP.*

### **8.1.2 Dispensing Only in Certified Healthcare Facilities or Services**

The Applicant proposed the ETASU of dispensing Dsuvia only within certified healthcare facilities or services. The proposed certified healthcare facilities or services will meet the following criteria: a) licensed pharmacy or healthcare provider with DEA registration for CII drugs who will oversee ordering and administration of the medication and, b) access to equipment and personnel trained to detect and manage hypoventilation, including use of supplemental oxygen and opioid antagonists, such as naloxone.

***Reviewer's Comments:** The review team disagrees with the Applicant's proposed certified use settings and has determined that the criteria for certification are too broad to ensure the benefits outweigh the risks of Dsuvia. With the proposed criteria, the Applicant cannot ensure that Dsuvia will not be used in the outpatient setting such as stand-alone urgent care centers, nursing homes, ambulances or other first-responder situations, or any additional settings not explicitly described in labeling. DRISK and DAAAP have concerns about accidental exposure and misuse in these settings.*

### **8.1.3 Administered Only in Certified Healthcare Facilities or Services**

The Applicant proposed to limit the administration of Dsuvia to medically supervised settings.

***Reviewer's Comments:** The review team disagrees with the proposed administration in a medically supervised setting. We have determined that it is too broad to ensure the benefits of Dsuvia outweigh the risks. With the proposed criteria, the Applicant cannot ensure that Dsuvia will not be administered in the outpatient setting such as stand-alone urgent care centers, nursing homes, ambulances or other first-responder situations, or any additional settings not explicitly described in labeling.*

### **8.1.4 REMS Materials & Key Risk Messages**

The Applicant submitted proposed REMS Materials.

***Reviewer's Comments:** A detailed discussion of the proposed key risk messages and the REMS materials will be included in forthcoming review in conjunction with the REMS Document.*

### **8.1.5 REMS Assessment Plan**

The Applicant did not provide a detailed REMS Assessment Plan, but acknowledged that assessments will include an evaluation of the effectiveness of the REMS and any areas for program improvements or modifications.

***Reviewer's Comments:** A detailed REMS Assessment Plan will be included in forthcoming review in conjunction with the REMS Document.*

## **9 Discussion of Need for a REMS**

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The review team determined that a REMS with ETASU is necessary to ensure the benefits of the drug outweigh the risks. Dsuvia is a potent opioid contained in a tiny immediate-released sublingual tablet that requires a placement aid for administration by a healthcare professional. Thus, respiratory depression resulting from accidental exposure to Dsuvia is the identified risk due to the tablet size coupled with its potency. To ensure the benefits outweigh the risk: Dsuvia should not be administered

by the patient or anyone other than a HCP; Dsuvia should not be sent home with a patient; and Dsuvia should not be used in the outpatient setting. Therefore, the goal of the REMS is to mitigate the risk of respiratory depression resulting from accidental exposure by requiring that Dsuvia is only dispensed by hospitals and surgery centers that are specially certified (ETASU B) and that Dsuvia is only administered in the certified hospitals and surgery centers (ETASU C).

If restricted to the setting in which Dsuvia was studied, such as hospitals and surgery centers, it would ensure that Dsuvia is administered by HCPs that routinely monitor postoperative patients and are knowledgeable in the management of respiratory depression. In addition, limiting the use of Dsuvia to certified hospital and surgery centers will help in preventing this product from being available in the outpatient setting and used in stand-alone urgent care centers, nursing homes, ambulances or other first-responder situations, or any additional settings not explicitly described in labeling.

## **10 Conclusion & Recommendations**

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The risk of respiratory depression resulting from accidental exposure associated with Dsuvia is serious and because of this risk, we have determined that requiring a REMS consisting of elements to assure safe use is necessary. DRISK recommends a REMS with ETASU, but does not concur with the Applicant's proposed REMS goal or use setting. The goal of the REMS should be to mitigate the risk of respiratory depression resulting from accidental exposure by requiring that Dsuvia is only dispensed by hospitals and surgery centers that are specially certified (ETASU B) and that Dsuvia is only administered in certified hospitals and surgery centers (ETASU C). The REMS must also include an implementation system and timetable for submission of assessments.

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/s/  
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SELENA D READY  
09/21/2017

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Concur