FDA Briefing Document

Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

October 12, 2018

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought new drug application (NDA) 209128 for sufentanil sublingual tablet 30 mcg 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 setting to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

M E M O R A N D U M

Date:	September 12, 2018
From:	Sharon Hertz, M.D., Director Division of Anesthesia, Analgesia, and Addiction Products Office of Drug Evaluation II Office of New Drugs
To:	Chair, Members, and Invited Guests Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Subject:	Overview of the October 12, 2018, AADPAC Meeting to Discuss NDA 209128

During the October 12, 2018, AADPAC meeting, the committee will discuss the new drug application (NDA) for sufentanil sublingual tablet (proposed trade name DSUVIA), submitted by AcelRx Pharmaceuticals, Inc., 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 setting. The discussion will include benefit-risk considerations and whether this product should be approved.

Adequate control of acute pain after surgery or painful procedure is important for helping patients recover. Prescription opioids are often a component of a multimodal analgesic approach which is standard in many institutions. However, the treatment of acute pain must be balanced with public health considerations related to abuse, misuse, and accidental exposure. While there are multiple drugs approved for treating acute pain, sufentanil sublingual tablet 30 mcg is the

first sublingual sufentanil product proposed for acute pain severe enough to require an opioid analgesic.

The proposed drug-device combination product contains 30 mcg of the potent opioid agonist, sufentanil, for use in a medically supervised setting. The product is intended to be administered by a healthcare provider to a patient's sublingual space using a single-dose applicator (SDA) on an as needed basis with a minimum interval of one hour between doses.

The application is supported by reference to the Agency's previous findings of efficacy and safety for Sufenta (sufentanil citrate for injection; NDA 19050), cross reference to safety data for sufentanil sublingual tablets 15 mcg (proposed tradename Zalviso; NDA 205265), another drug-device combination product that contains 15 mcg of sufentanil and was intended to be administered by a patient using a different device, a Phase 3 placebo-controlled sufentanil sublingual tablet 30 mcg trial (SAP301), and two Phase 3 open-label sufentanil sublingual tablets 30 mcg studies. Of note, the sufentanil sublingual tablets 15 mcg application received a complete response on July 25, 2014, primarily due to issues surrounding the device and inadvertent loss of dispensed tablets.

The efficacy of sufentanil sublingual tablets 30 mcg was evaluated in one placebo-controlled Phase 3 trial in post-surgical adult patients following abdominoplasty, open inguinal hernioplasty, or laparoscopic abdominal surgery with acute pain. This trial was adequate and well-controlled and provided evidence of the efficacy of sufentanil sublingual tablets 30 mcg in treating acute pain, based on the time-weighted summed pain intensity difference from baseline over 12 hours (SPID12).

The safety profile of sufentanil sublingual tablets 30 mcg in acute pain was consistent with the typical safety profile of an opioid agonist, however there were two area of safety concern that required further evaluation: the safety of sufentanil sublingual tablets 30 mcg in patients requiring the maximum dosing proposed for labeling and the risk of misplaced tablets. Given these safety concerns, the application received a complete response and was not approved on October 11, 2017. The focus of this meeting is the Applicant's resubmission to address these concerns. To address the safety of sufentanil sublingual tablets 30 mcg in patients requiring the maximum dosing proposed for labeling, the Applicant reduced the maximum daily dose from 24 to 12 sufentanil sublingual 30 mcg tablets per day and provided new pooled safety analyses. To address the concern of misplaced tablets, the Applicant modified the directions for use and performed another human factors validation study.

The concern regarding misplaced tablets, with associated risks of abuse, misuse, and accidental exposure, will be a significant discussion point at this meeting. The risks associated with sufentanil sublingual tablets 30 mcg include respiratory depression, particularly resulting from accidental exposure, inability to account for the drug due to its small tablet size. In particular, patients and providers may not be aware of a dropped tablet, and when aware, may not be able to recover it. The discussion will include consideration of potential risk mitigation proposals. In addition, a point of discussion for this Advisory Committee Meeting is whether the overall benefit/risk profile is favorable.

Draft Points to Consider:

1. Based on the available efficacy data, discuss the efficacy of sufentanil sublingual tablets 30 mcg 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 setting.
2. Based on the available safety data, discuss the safety profile of sufentanil sublingual tablets 30 mcg. Consider the adequacy of the safety database, in terms of number of patients, to support the proposed dose of 30 mcg every hour as needed, with a maximum of 12 tablets in 24 hours.
3. Discuss any concerns you may have regarding the abuse or misuse of sufentanil sublingual tablets and whether, based on the available data, the benefits to patients are expected to outweigh public health risks related to abuse, misuse, and accidental exposure.
4. Discuss whether data from the human factors studies and the clinical trials support the safe and effective use of the proposed product administered by healthcare professionals in certified settings such as hospitals, emergency departments, and surgical centers. In your discussion, consider whether the REMS proposed by FDA can be expected to mitigate the risks associated with failures resulting from dropped sufentanil tablets and consider the risks of accidental exposure.
5. Overall, do the benefits of sufentanil sublingual tablets 30 mcg with the REMS proposed by FDA outweigh the risks when used 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 setting, supporting approval of sufentanil sublingual tablets 30 mcg?

NDA #	209128
Applicant	AcelRx Pharmaceuticals, Inc.
Date of Submission	May 3, 2018
PDUFA Goal Date	November 2, 2018
Proprietary Name	Sufentanil
Proposed Established or Proper Name	Sufentanil sublingual tablet (SST) 30 mcg
Dosage Form(s)	Sublingual tablets
Applicant Proposed Indication(s)/Population(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
Applicant Proposed Dosing Regimen(s)	A single sufentanil sublingual tablet 30 microgram (SST 30 mcg), on an as needed basis, per patient request, with a minimum of 1 hour between doses. Dosing not to exceed 12 tablets in 24 hours.

1. Introduction

This is a summary review of AcelRx's Pharmaceuticals, Inc (AcelRx's) response to the Complete Response (CR) letter issued on October 11, 2017, for new drug application (NDA) 209128 for sufentanil sublingual tablets (proposed trade name Dsuvia). The application was originally submitted on December 12, 2016, as a 505(b)(2) new drug application (NDA) for sufentanil sublingual tablets (SST), a drug-device combination product containing 30 mcg of the potent opioid agonist, sufentanil. The product is intended to be administered by a healthcare provider to the patient's sublingual space in a medically supervised setting, using the single-dose applicator (SDA), on an as needed basis with a minimum interval of one hour between doses.

AcelRx's proposed indication is 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 setting. If sufentanil sublingual tablets were to be approved, it is anticipated that the indication would be modified to replace "moderate-to-severe acute pain" with acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, consistent with the labeling of other opioids. The exact phrasing of the indication will be reviewed by the Agency and is not an anticipated to be a central discussion point at this Advisory Committee meeting.

The NDA references the Agency's previous findings of efficacy and safety for Sufenta (sufentanil citrate for injection; NDA 19050; Akorn, Inc.), which was approved in 1984 and is indicated for intravenous administration in adults and pediatric patients as an adjunctive and a primary anesthetic and for epidural administration as an analgesic in the setting of labor and vaginal delivery. Sufenta is currently only approved as a solution for injection. The Applicant also cross references their previously submitted NDA 205265 for sufentanil sublingual tablet 15

mcg, another sufentanil sublingual tablet drug-device combination product that, in contrast to sufentanil sublingual tablet 30 mcg, contains 15 mcg of sufentanil and was intended to be administered by the patient using a different device. The sufentanil sublingual tablet 15 mcg application received a complete response on July 25, 2014 primarily due to issues surrounding the device and inadvertent loss of dispensed tablets. The inclusion of selected safety data from the sufentanil sublingual tablet 15 mcg program was determined to be reasonable as the Applicant established a pharmacokinetic bridge between two doses of sufentanil 15 mcg sublingual tablets within 20 to 25 minutes and a single dose of sufentanil sublingual tablet 30 mcg.

The original sufentanil sublingual tablet 30 mcg application was supported by the Agency's previous findings for Sufenta (NDA 19050), a Phase 3 placebo-controlled sufentanil sublingual tablet 30 mcg trial (SAP301), two Phase 3 open-label sufentanil sublingual tablet 30 mcg studies, and selected safety data from the sufentanil sublingual tablet 15 mcg program, as well as CMC/device, pharmacology/toxicology, clinical pharmacology, and human factors data.

There were two deficiencies outlined in the complete response letter. The first deficiency was an inadequate number of patients dosed at the maximum amount described in the proposed labeling to assess the safety of sufentanil sublingual tablet 30 mcg. To address this deficiency, the Applicant was asked to collect additional data in at least 50 patients with postoperative pain sufficient to evaluate the safety of sufentanil sublingual tablet 30 mcg for a period following the maximum proposed dosing. The second deficiency was the possibility of misplaced tablets, which pose a risk for accidental exposure and improper dosing. To address this deficiency, the Applicant was asked to develop mitigation strategies to address the risk of dropped sufentanil tablets and to conduct another human factors validation study. See the Appendix for the cross-discipline team leader (CDTL)/Division Director review from the first cycle. Of note, in this previous review, the names "Dsuvia" and "Zalviso" are used, while sufentanil sublingual tablets, 30 mcg and 15 mcg, respectively, are used in the current review.

In this complete response submission, the Applicant did the following to address the deficiencies described in the complete response letter:

- Decreased the maximum daily dose to 12 tablets from 24 tablets and submitted new pooled safety analyses to support the safety of the proposed maximum daily dose
- Performed a new human factors study
- Submitted a risk assessment following accidental exposure to a sufentanil sublingual tablet 30 mcg

This review will be focus on the Applicant's complete response submission. The CDTL/Division Director review from the original NDA review is included in the Appendix.

2. Background

Sufentanil is a synthetic opioid analgesic that is five to ten times more potent than its analog, fentanyl.

Sufenta (NDA 19050) is the only listed sufentanil product and is for intravenous and epidural use. If approved, sufentanil sublingual tablet 30 mcg would be the first sufentanil analgesic product for sublingual use.

The proposed indication is 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. A variety of immediate-release opioid analgesics and combination opioid/non-opioid products are approved for management of acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate. Available opioid products include meperidine, tramadol, codeine, hydrocodone, oxycodone, morphine, oxymorphone, hydromorphone, and fentanyl. The available products can be given via various routes of administration, such as oral, transdermal, intramuscular, subcutaneous, intravenous, transmucosal, and epidural/intrathecal.

Key regulatory interactions since the original NDA was submitted on December 12, 2016, are listed below by date. Points of discussion or Agency recommendations are provided as a bulleted list for each meeting or interaction. The development program for sufentanil sublingual tablet 30 mcg occurred under IND 113059.

October, 11, 2017 – Complete Response letter issued

January 26, 2018 – Post-action meeting

- The Applicant proposed a revised maximum daily dose from 24 tablets in 24 hours to 12 tablets in 24 hours. In addition, the Applicant proposed pooled analyses from the sufentanil sublingual tablet 30 mcg and sufentanil sublingual tablet 15 mcg programs. The Agency agreed on this approach, but noted that the adequacy of the data would be a review issue.
- The Applicant stated that they incorporated the Agency's recommendations for the Directions for Use (DFU) and planned an additional human factors study to evaluate the effectiveness of the changes to the DFU in addressing the risk of dropped tablets. The Agency reiterated its concern regarding sufentanil sublingual tablet 30 mcg's small tablet size.

3. Product Quality

See the CDTL/Division Director review from the original NDA submission in the Appendix for details regarding the product quality considerations.

In summary, the drug component of this drug-device combination product consists of an immediate-release sublingual tablet containing 30 mcg of sufentanil. The tablet measures 3 mm in diameter and 0.85 mm in thickness with a nominal tablet weight of 7.40 mg. The tablet is blue. Each disposable single dose applicator (SDA) contains one tablet and is intended for single use.

Device
The device constituent of this product consists of the SDA, which is intended for storage and to deliver sufentanil to the sublingual space. The health care provider is directed to remove the SDA lock, place the SDA tip under the patient's tongue, and depress the green pusher to administer the sufentanil tablet to the sublingual space.

Figure 1: Single Dose Applicator Container Label—Front

Source: 3.2.P, page 1, submitted on 05/03/2018

Human Factors
The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the human factors (HF) validation study results from the original NDA and the human factors study in the resubmission. See Section 8 for a discussion of the HF validation studies.

4. Nonclinical Pharmacology/Toxicology

See the CDTL/Division Director review from the original NDA submission in the Appendix for details regarding the nonclinical pharmacology/toxicology considerations. No new nonclinical data were included in the complete response submission.

5. Clinical Pharmacology

See the CDTL/Division Director review from the original NDA submission in the Appendix for details regarding the clinical pharmacology considerations.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Efficacy of this product was based on the results from a single Phase 3 clinical trial, SAP301. See the CDTL/Division Director review from the original submission for a detailed discussion of this study (Appendix).

The following is a summary of the efficacy review of SAP301 that was previously reviewed in the initial NDA. Study SAP301 was a multicenter, randomized, double-blind, and placebo-controlled study. Randomization was stratified by sex and investigational site. Patients were randomly assigned to treatment with sufentanil sublingual tablets 30 mcg or placebo at a 2:1 ratio within each stratum. Study medication was administered by a health care professional using the single-dose applicator on an as needed basis with a minimum of one hour between doses. The study period was up to 48 hours. Efficacy was assessed by patient-reported pain intensity (PI) on an 11-point numerical rating scale. Prior to randomization, a patient was required to have a minimum postoperative PI score of 4 (baseline PI) and a minimum PI score of 4 to continue treatment beyond 24 hours. Rescue medication, 1 mg IV morphine, was allowed if the patient requested additional medication for pain beyond the use of the study medication.

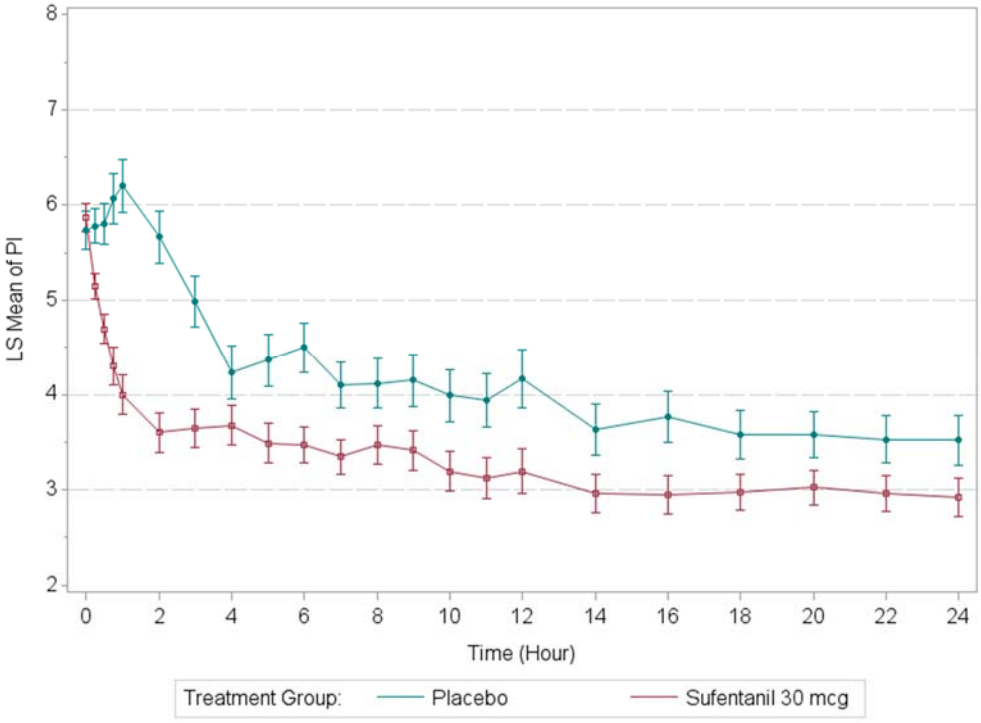
The primary efficacy endpoint was time-weighted summed pain intensity difference from baseline over 12 hours (SPID12). As supportive evidence, the following secondary efficacy endpoints were also examined:
• Time to first use of rescue medication
• Total number of study medication and rescue medication doses used over 12-hour study period
• Time to onset of meaningful pain relief

The efficacy analyses were performed on the intent-to-treat (ITT) population, which included all randomized patients who received study drug. The primary efficacy analysis was an analysis of covariance (ANCOVA) model that used treatment, center, and sex as factors and baseline PI score as a covariate. A pre-rescue PI score was carried forward for one hour following the dosing of rescue medication. For intermittent missing data, a linear interpolation method was used to impute the missing values between two observed pain scores. A modified Brown's method was adopted by the Applicant to impute post-dropout missing values. Since it was a single imputation method, a sensitivity analysis using multiple imputation with baseline distribution was performed to evaluate the impact of missing data. Time to first use of rescue medication and time to onset of meaningful pain relief were summarized using Kaplan-Meier product-limit estimates and were compared between treatment groups using a log-rank test. The number of study medication and rescue medication doses used was analyzed using an ANCOVA model that included treatment, center, and sex as factors. Since there was no adjustment for multiplicity for any of the secondary endpoints, these endpoints were considered supportive of the primary efficacy endpoint and would not be suitable for inclusion in section 14 of the product label.

A total of 161 patients were randomized and received study medication. There was a statistically significant difference ($p < 0.001$) between treatment groups with respect to the primary endpoint SPID12 (mean difference of 12.7, 95% CI of [7.2, 18.2]). The estimated mean of PI and its 95% confidence interval (CI) at each analysis time point were plotted in Figure 2. During this study period, the least squares mean PI scores were significantly lower in the sufentanil group than in the placebo group at all time points except for Hour 4 and after Hour 20 (p-values > 0.05). Given the results of sensitivity analysis and the small number of early dropouts, the impact of missing data was minimal. The efficacy noted with the primary efficacy endpoint, SPID12, was supported by the results from clinically relevant secondary endpoints, time to first use of rescue mediation and amount of rescue medication used over the first 12 hours (p-values < 0.001, see Figure 3 and Table 1). There was no statistically significant difference between sufentanil and

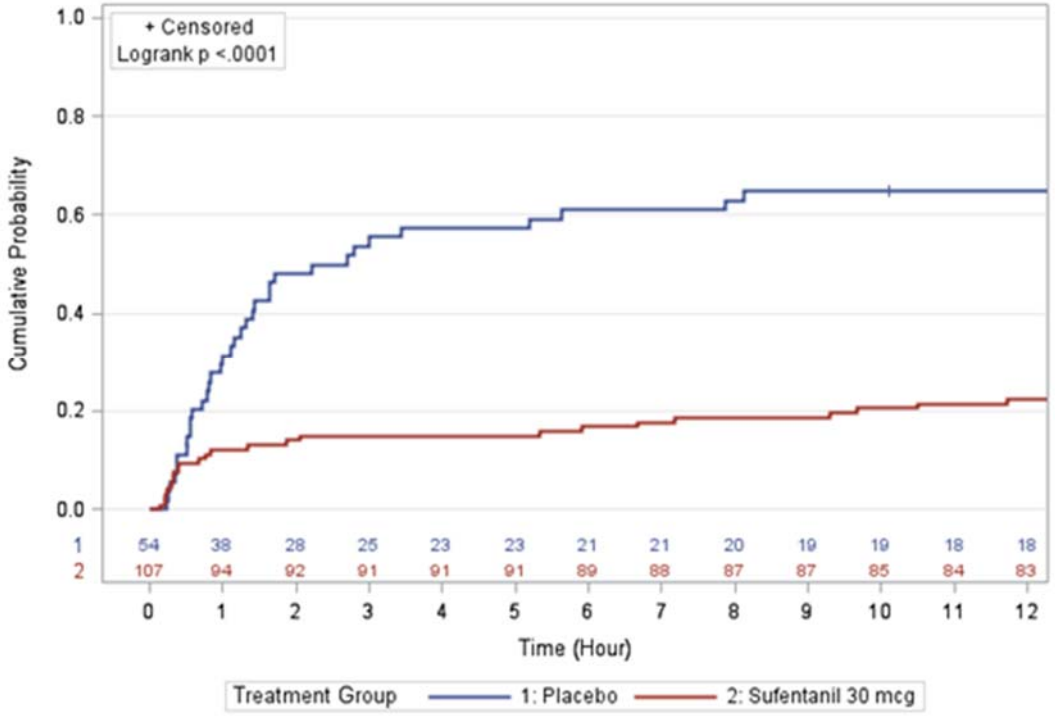
placebo groups for the total number of study medication doses used (p = 0.4). The time to meaningful pain relief was shorter for sufentanil compared to placebo over the first 12 hours but that the difference was not statistically significant (p = 0.5).

Figure 2: Least Squares Mean (95% CI) of Pain Intensity over the 24-Hour Study Period



Source: Reviewer

Figure 3: Kaplan-Meier Curves for Time to First Use of Rescue Medication over the 12-Hour Study Period



Source: Reviewer
Numbers of subjects at risk are listed at the bottom.

Table 1: Number of Rescue Medication Doses Used over the 12-Hour Study Period

Number of Doses Used over 12 Hours	SST 30 mcg (n = 107)	Placebo (n = 54)	P-value
Mean (SD)	0.4 (1.0)	1.6 (1.8)	
Median	0	1	
Range	(0, 7)	(0, 8)	
LS mean difference	-1.2 (-1.6, -0.8)		<0.001
Number (%) by Category			
0	83 (77.6)	19 (35.2)	<0.001
1-2	21 (19.6)	23 (42.6)	
3-4	1 (0.9)	8 (14.8)	
>4	2 (1.9)	4 (7.4)	

Source: Reviewer
P-value for total number of doses is based on the ANOVA model including treatment, center, and gender; P-value for number by category is based on Fisher's exact test.
Abbreviations: SST: sufentanil sublingual tablet; SD: standard deviation

Since sufentanil sublingual tablet 30 mcg was only compared to placebo in the one completed Phase 3 clinical study, there are no data available on the efficacy of sufentanil sublingual tablet 30 mcg compared to other therapies.

In summary, the primary and secondary analyses support the efficacy of sufentanil sublingual tablets 30 mcg for the management of moderate-to-severe acute pain.

8.Safety

8.1 Summary of safety review from 1st review cycle

Studies contributing to integrated safety analyses

A summary of the studies contributing to the safety analyses in the first review cycle is shown in Table 2. The safety database in the original NDA included data from the sufentanil sublingual tablet 30 mcg and sufentanil sublingual tablet 15 mcg programs. From the sufentanil sublingual tablet 30 mcg program, there were three Phase 3 studies (SAP301 [Phase 3 efficacy trial] and SAP302 and SAP303 [open-label safety studies]). SAP301 was a randomized, double-blind, placebo-controlled trial in adults with moderate-to-severe pain following outpatient abdominal surgery. Patients could receive sufentanil sublingual tablet 30 mcg every hour as needed for up to 48 hours. SAP302 was an open-label study in patients 18 years of age and older who were being treated in the emergency department for moderate-to-severe acute pain due to obvious trauma or injury. Patients could receive up to four doses in the five-hour treatment period. SAP303 was a multicenter, open-label study in patients 40 years of age and older who underwent a surgical procedure requiring general anesthesia or spinal anesthesia that did not include intrathecal opioids and who were experiencing acute postoperative pain of at least 4 on an 11-point numeric rating scale (NRS).

There were two additional clinical studies in the sufentanil sublingual tablet 30 mcg program (SAP101 and SAP202) that were not included in the pooled safety analyses. SAP101 was a Phase 1 study conducted in healthy subjects who received naltrexone to block the opioid agonist effects of sufentanil. SAP202 was a Phase 2 study in a bunionectomy population using a different formulation and the in vitro data were not sufficient to bridge the formulation used to the final to-be-marketed formulation.

Sufentanil sublingual tablet 15 mcg (proposed tradename Zalviso) is another sufentanil sublingual tablet drug-device combination product that, in contrast to sufentanil sublingual tablet 30 mcg, contains 15 mcg of sufentanil and is administered by a patient with a different device that has a 20-minute lockout between doses. The sufentanil sublingual tablet 15 mcg application received a complete response, primarily due to issues surrounding the device and inadvertent loss of dispensed tablets. In the sufentanil sublingual tablet 30 mcg NDA, the Applicant provided safety data from the sufentanil sublingual tablet 15 mcg program. From the sufentanil sublingual tablet 15 mcg program, the Applicant provided safety data from selected patients who received the first dose of sufentanil tablet 15 mcg followed by a second dose of sufentanil sublingual tablet 15 mcg within 20 to 25 minutes. This included data from six sufentanil sublingual tablet 15 mcg studies in patients with postoperative pain after open abdominal surgery, total knee arthroplasty, or total hip arthroplasty. While there were differences in the sufentanil sublingual tablet 15 mcg and sufentanil sublingual tablet 30 mcg clinical programs, including different

devices, study designs, and patient populations, it was determined that it was reasonable to use data from the sufentanil sublingual tablet 15 mcg program to support the safety of sufentanil sublingual tablet 30 mcg given that both programs administered sufentanil. In addition, in the original NDA review, the Applicant established a pharmacokinetic bridge between two sufentanil sublingual tablet 15 mcg doses of sufentanil 15 mcg tablets administered within 20 to 25 minutes and a single sufentanil sublingual 30 mcg tablet.

Table 2: Summary of Studies Contributing to Sufentanil Safety Analyses

Study	Overview	Patient Population	Treatment/ Duration	Number of subjects (treated/completed/in pool)	Rescue
Sufentanil sublingual tablet (SST) 30 mcg clinical program					
SAP301 (pivotal efficacy study)	MC, R, DB, PC	Post-surgical adult patients following abdominoplasty, open inguinal hernioplasty, or laparoscopic abdominal surgery	SST: 30 mcg Placebo Up to 48 hours	SST 30 mcg: 107/102 Placebo: 54/41	Morphine IV
SAP302	MC, OL	Emergency room setting – adult patients 18 years of age and older with pain due to trauma or injury	SST 30 mcg Up to 4 doses Up to 5 hours	76/65 (2-hour period)	Morphine IV or oral oxycodone
SAP303	MC, OL	Post-surgical patients 40 years or older following any type of surgery	SST 30 mcg Up to 12 hours	140/132	Morphine IV
Selected patients* in the following studies from sufentanil sublingual tablet (SST) 15 mcg clinical program					
IAP310 Phase 3	MC, R, DB, PC	Open abdominal surgery, with postoperative pain of at least 4 on an 11-point NRS	SST 15 mcg Placebo Up to 72 hours	SST: 114/78/51 Placebo: 58/27/27	Morphine IV
IAP311 Phase 3	MC, R, DB, PC	Total knee or hip replacement	SST 15 mcg Placebo Up to 72 hours	SST: 315/215/142 Placebo: 104/43/54	Morphine IV
IAP309 Phase 3	MC, R, OL, AC	Open abdominal surgery or knee or hip replacement	SST 15 mcg Morphine 1 mg SL Up to 72 hours	SST: 177/146/94 Morphine: 180/136	Morphine IV
ARX-COO1 Phase 2	MC, R, DB, PC	Total knee replacement	SST 5 mcg, 10 mcg, and 15 mcg Placebo Up to 12 hours	SST 15 mcg: 20/13/12 Placebo: 24/7/15	No rescue
ARX-COO5 Phase 2	MC, R, DB, PC	Open abdominal surgery	SST 10 and 15 mcg Placebo Up to 12 hours	SST 15mcg: 29/25/6 Placebo: 30/9/8	No rescue
ARX-COO4 Phase 2	MC, OL; no control	Knee replacement	SST 15 mcg Up to 12 hours	SST 15mcg: 30/26/18	No rescue

* The selected sufentanil sublingual tablet 15 mcg population includes patients who self-administered sufentanil sublingual tablet 15 mcg (SST 15 mcg) or placebo with the second dose administered within 20 to 25 minutes after the first dose.
Abbreviations: AC=active controlled; DB=double blind; MC=multicenter; PC=placebo-controlled; R=randomized
Source: Adapted from Integrated Summary of Safety Table 1 and Table 3, pages 17-19, submitted 5/3/2018 and Clinical Summary of Safety, Table 2.7.4:3, pages 9-10, submitted 12/12/16

Adequacy of the drug exposure experience

During clinical development, the Division agreed that an overall safety database of at least 500 patients would be required with at least 350 subjects exposed to at least one dose of sufentanil sublingual tablets 30 mcg and 100 of these subjects exposed to multiple doses of sufentanil sublingual tablets 30 mcg over the anticipated duration of use.

As shown in Table 3, between 0-12 hours, a total of 646 patients were treated with sufentanil sublingual tablets (sufentanil sublingual tablet 30 mcg: 323 and sufentanil sublingual tablet 15 mcg: 323).[1] Of the 323 patients exposed to sufentanil sublingual tablet 30 mcg, 86% used fewer than six doses in the first 12 hours of the study, and the remaining 14% used between 6 to 12 doses. Between 0-24 hours, 107 patients received sufentanil sublingual tablet 30 mcg and they were all from study SAP301 as the other sufentanil sublingual tablet 30 mcg studies (SAP302 and SAP303) were less than 24 hours. Between 0-24 hours, only 9 patients received more than 12 doses of sufentanil sublingual tablet 30 mcg. The mean number of sufentanil sublingual tablet 30 mcg doses was 3.2 during the first 12 hours and 7 during the first 24 hours. In comparison, the mean number of sufentanil sublingual tablet 15 mcg doses was 13 during the first 12 hours and 25.1 during the first 24 hours. Thus, data from the sufentanil sublingual tablet 15 mcg program provided information on longer duration of exposure (to 48 hours and longer) and with higher mean number of doses. In the sufentanil sublingual tablet 30 mcg program, the more limited exposure to sufentanil was due to the short duration of the studies and the nature of the patient populations evaluated.

During the initial review, it was determined that an adequate number of patients had been exposed to sufentanil sublingual tablet 30 mcg given that 323 were exposed, which was close to the previously discussed requirement of 350 patients. However, the experience with repeated dosing of sufentanil sublingual tablet 30 mcg was not adequate since the maximum cumulative daily dose proposed in the label was 720 mcg or 24 tablets (24 hours x 30 mcg/dose). In addition, there were inadequate safety data at steady-state sufentanil levels from sufentanil sublingual tablet 30 mcg. It takes seven doses of sufentanil sublingual tablet 30 mcg, administered one hour apart to reach steady state. With multiple dosing, the exposure to sufentanil accumulates with increases in AUC (AUC0-60 min) and Cmax of 3.7-fold and 2.3-fold, respectively. This means that most of the safety database from sufentanil sublingual tablet 30 mcg clinical trials represents the adverse event profile of a less than steady-state exposure to sufentanil from sufentanil sublingual tablet 30 mcg. Thus, the adverse effects of the exposure of sufentanil following multiple dosing was not adequately evaluated.

[1] The Applicant notes that over half of the patients who received two doses of sufentanil sublingual tablet 20 to 25 minutes apart also received a third dose within the hour (i.e., 45 mcg/hour), which exceeds the total hourly dose received with sufentanil sublingual tablet 30 mcg.

Table 3: Total Number of SST Doses Used in SST 30 mcg Studies and selected SST 15 mcg Studies (Pool 1N)

	Treatment group				Total
	SST 15 mcg (n=323)	SST 15 mcg placebo (n=104)	SST 30 mcg (n=323)	SST 30 mcg placebo (n=54)	(n=804)
Number of doses used (0-12 hours) - n (%)	323 (100%)	104 (100%)	323 (100%)	54 (100%)	804 (100%)
< 6	31 (9.6%)	32 (30.8%)	277 (85.8%)	37 (68.5%)	377 (46.9%)
6-12	121 (37.5%)	23 (22.1%)	46 (14.2%)	17 (31.5%)	207 (25.7%)
13-24	145 (44.9%)	38 (36.5%)	0	0	183 (22.8%)
>24	26 (8.0%)	11 (10.6%)	0	0	37 (4.6%)
Mean (SD)	14.1 (6.9)	12.6 (8.3)	3.2 (2.1)	4.7 (2.3)	8.9 (7.6)
Median	13.0	11.5	3.0	4.0	6.0
(Min, Max)	(2, 33)	(3, 34)	(1, 9)	(1, 11)	(1, 34)
Number of doses used (0-24 hours) - n (%)	287 (100%)	81 (100%)	107 (100%)	54 (100%)	529 (100%)
< 6			42 (39.3%)		
6-12	16 (5.6%)	20 (24.7%)	56 (52.3%)	25 (46.3%)	103 (19.5%)
13-24	40 (13.9%)	10 (12.3%)	9 (8.4%)	25 (46.3%)	131 (24.8%)
>24	84 (29.3%)	14 (17.3%)	0	4 (7.4%)	111 (21.0%)
Mean (SD)	147 (51.2%)	37 (45.7%)	7.0 (3.6)	0	184 (34.8%)
Median	25.1 (12.9)	22.1 (15.8)	7.0	6.4 (3.8)	19.0 (14.1)
(Min, Max)	25.0	19.0	(1, 15)	6.0	15.0
	(2, 55)	(3, 55)		(1, 18)	(1, 55)

Abbreviation: SST = sufentanil sublingual tablet; SD: standard deviation; Max=maximum; Min=minimum
Source: Adapted from Applicant's Response to Information Request (5/18/17), Table 3, page 8, submitted 6/8/17

Safety review from available drug exposure data

In the first cycle, it was concluded that sufentanil sublingual tablet 30 mcg has a safety profile consistent with an opioid agonist. See the CDTL/Division Director review from the first cycle for additional details of the analyses and safety findings (Appendix). While data from both the sufentanil sublingual tablet 30 mcg and sufentanil sublingual tablet 15 mcg programs were analyzed to support the safety of sufentanil, this review will provide a summary of the safety data from SAP301, which was the only placebo-controlled study with sufentanil sublingual tablet 30 mcg.

Deaths
There were no deaths in Study SAP301.

Serious Adverse Events
Two patients experienced a nonfatal serious adverse event (SAE)—one case of syncope and one case of hemiparesis. Both cases occurred in the placebo group and there were no SAEs in the sufentanil sublingual tablet 30 mcg-treatment group.

Discontinuations due to Adverse Events
As shown in Table 4, in Study SAP301, a higher proportion of patients in the placebo group (3.7%) discontinued due to adverse events compared to the sufentanil sublingual tablet 30 mcg

group (0.9%). The adverse event leading to discontinuation in the sufentanil sublingual tablet 30 mcg group was oxygen saturation decreased, which is an anticipated adverse event for an opioid.

Table 4: Adverse Events Causing the Discontinuation of Study Drug (Study SAP301)

Preferred term	Treatment group		Total n=161
	Sufentanil n=107	Placebo n=54	
Number (%) of Patients With At least One Adverse Event Causing Discontinuation of Study Drug	1 (0.9%)	2 (3.7%)	3 (1.9%)
Oxygen saturation decreased	1 (0.9%)	0	1 (0.6%)
Dizziness	0	1 (1.9%)	1 (0.6%)
Hemiparesis	0	1 (1.9%)	1 (0.6%)
Somnolence	0	1 (1.9%)	1 (0.6%)
Syncope	0	1 (1.9%)	1 (0.6%)

Source: Adapted from SAP301 Clinical Study Report, Table 30, page 106, submitted 12/12/16

Common Adverse Events

The most frequently reported AEs were nausea (sufentanil, 35 [32.7%]; placebo, 16 [29.6%]) and headache (sufentanil, 21 [19.6%]; placebo, 10 [18.5%]). The adverse events in the sufentanil sublingual tablet 30 mcg treatment group were consistent with an opioid's safety profile, such as dizziness and vomiting.

Table 5: Most Frequent Adverse Events in SAP301

	Treatment group		Total n=163
	Sufentanil n=107	Placebo n=54	
Number (%) of Patients With At least One Adverse Event	62 (57.9%)	34 (63.0%)	96 (59.6%)
Nausea	35 (32.7%)	16 (29.6%)	51 (31.7%)
Headache	21 (19.6%)	10 (18.5%)	31 (19.3%)
Vomiting	8 (7.5%)	1 (1.9%)	9 (5.6%)
Dizziness	6 (5.6%)	2 (3.7%)	8 (5.0%)
Hypotension	5 (4.7%)	2 (3.7%)	7 (4.3%)
Flatulence	4 (3.7%)	4 (7.4%)	8 (5.0%)
Tachycardia	3 (2.8%)	0	3 (1.9%)
Procedural nausea	3 (2.8%)	3 (5.6%)	6 (3.7%)
Somnolence	3 (2.8%)	2 (3.7%)	5 (3.1%)
Pruritus	2 (1.9%)	2 (3.7%)	4 (2.5%)
Procedural vomiting	2 (1.9%)	0	2 (1.2%)
Presyncope	1 (0.9%)	1 (1.9%)	2 (1.2%)
Pruritus generalized	1 (0.9%)	1 (1.9%)	2 (1.2%)
Hypertension	1 (0.9%)	1 (1.9%)	2 (1.2%)

Source: Reviewer and adapted from SAP301 Clinical Study Report, Table 26, page 100, submitted 12/12/16

Respiratory

In study SAP301, the proportions of patients who had oxygen saturation levels < 93% or < 95% during the study were higher in the sufentanil sublingual tablet 30 mcg group than in the placebo

group (< 93%: 7.5% vs. 0%; < 95%: 23.4% vs. 7.4%). Two sufentanil sublingual tablet 30 mcg-treated patients had oxygen saturations less than 92% during the study.

8.1.a Safety concern associated with dropped tablets – 1st cycle review

A significant safety concern in the review of the NDA was the risk of dropped sufentanil sublingual tablet 30 mcg tablets, which could lead to accidental exposure, or improper dosing.

In the sufentanil sublingual tablet 30 mcg Phase 3 program, there were three dropped tablets (2 sufentanil and 1 placebo) or 0.15% of the total 1782 single-dose applications (SAP301 = 1,223, SAP302 = 88, and SAP303 = 471) in the Phase 3 studies. The details of these cases were reviewed in the first cycle:

SAP301:

- Patient (b) (6) (placebo):
  The first patient to be dosed at the clinical site. It was determined by the Applicant that the SDA tip was being aimed at the underside of the patient's tongue (instead of the floor of the patient's mouth) as they were lying down, resulting in the tip of the SDA being pointed upwards. The tablet had bounced off the tongue and out of the patient's mouth and was sequestered appropriately by the health care provider (HCP). No further misplaced doses at the site.

- Patient (b) (6) (sufentanil):
  The patient was aware that the dose was not properly administered into the sublingual space. The HCP did not follow the Directions for Use and failed to confirm presence of the tablet after dose administration (Directions for Use step #6). The patient had located the tablet and placed in the room's trash can and told the morning shift HCP who then properly sequestered the tablet and documented the event.

SAP303:

- Patient (b) (6) (sufentanil):
  The HCP prematurely actuated the SDA prior to placing the SDA tip under the patient's tongue. This was a user error of not placing the tip in the correct location prior to actuation. The HCP was aware of the error, and picked up the dropped tablet and properly secured it for accountability.

Although no specific adverse events were associated with these instances of dropped tablets, these are serious errors with potentially serious consequences. These safety concerns precluded approval in the first review cycle.

Human factors validation study:

In the original NDA, the Applicant conducted a human factors validation study in 45 untrained participants that included 15 Post-Anesthesia Care Unit (PACU)/floor nurses, 15 emergency room (ER) nurses, and 15 paramedics. Participants were provided the directions for use (DFU)

and were instructed to read the DFU prior to attempting the tasks. Each participant was asked to administer the medication four times. Three of the scenarios involved administration to three different mock patients, and, in the fourth scenario, participants were given torn packaging and asked to administer the medication to a mock patient to see how this situation may be handled with real-world use. At the end of the session participants responded to questions regarding important warnings and precautions or critical safety information in the DFU.

Failures were identified related to both essential and critical tasks. The most concerning were eight failures associated with a critical task to confirm tablet placement in the patient's sublingual space. Failures related to this task are of critical importance because, if a HCP does not confirm accurate placement of the tablet in the sublingual space, a dropped tablet may go undetected. Sufentanil is a highly potent opioid, and dropped tablets pose significant risks to both the patient and others who may knowingly or unknowingly come in contact with the tablet. These risks include overdose and death due to accidental exposure in contacts, improper dosing in patients (i.e., over- or under-dosing and their associated risks)and associated public health consequences. As a result, the Division of Medication Error Prevention and Analysis (DMEPA) recommended changes to the DFU so that visual confirmation of the tablet placement is a distinct separate task[2].

DMEPA recommended the applicant conduct another human factor validation study to evaluate the effectiveness of the changes to the DFU to address the observed use-related errors. DMEPA also noted additional failures involving critical and essential tasks for which they did not have any recommendations and found the residual risk to be acceptable.

Summary of safety review in 1st review cycle:

Overall, although sufentanil sublingual tablet 30 mcg appears to have a typical safety profile of an opioid agonist, there were two areas of safety concern with this product that required further evaluation: the safety of sufentanil sublingual tablet 30 mcg in patients requiring the maximum dosing proposed for labeling and the risk of misplaced tablets.

A complete response letter was issued on October 11, 2017, outlining these deficiencies and the information needed to address the deficiencies.

8.2. Summary of safety review from 2nd review cycle

Overview of safety review from 2nd cycle
To address the safety database deficiency in terms of an inadequate number of patients dosed with sufentanil sublingual tablet 30 mcg at the maximum dosing proposed, the Applicant provided the following information in the resubmission:

[2] DMEPA recommended 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. Step 7: Visually confirm tablet placement in the patient's sublingual space."

1. A reduced maximum daily dose from 24 sufentanil sublingual 30 mcg tablets (720 mcg sufentanil) to no more than 12 sufentanil sublingual 30 mcg tablets (360 mcg sufentanil) per day.

2. Pooled safety data from all studies of the sufentanil sublingual tablet (SST) with treatment periods of at least 24 hours (Pool 8). Pool 8 was analyzed and presented based on sufentanil dose received (<300 mcg or ≥300 mcg) and maximum measured sufentanil plasma concentration achieved (≤150 pg/mL or >150 pg/mL) from sparse sampling during the first 24-hour study period.

In terms of the reduced total daily dose in the proposed labeling, the Applicant noted that it is likely sufentanil sublingual tablet 30 mcg will be used in short-term settings, such as surgical centers or emergency rooms. Further, in the sufentanil sublingual tablet 30 mcg trials of short-duration, most patients required less than 6 sufentanil sublingual 30 mcg tablets and no patients required more than 10 tablets. In the one sufentanil sublingual tablet 30 mcg trial that extended to 48 hours (SAP301), the maximum number of tablets administered in a 24-hour period was 15. The patients treated with sufentanil sublingual tablet 15 mcg who provided supporting safety data were generally treated for longer durations (48-72 hours), and had increased sufentanil exposure compared to patients treated with sufentanil sublingual tablet 30 mcg because sufentanil sublingual tablet 15 mcg drug-device combination allowed 45 mcg/hr of sufentanil on a patient-controlled basis.

In terms of the safety analyses, the Applicant selected a dose cutoff of 300 mcg (equivalent to 10 sufentanil sublingual 30 mcg tablets), rather than 12 because this provides more patients exposed at higher doses and given that the sufentanil sublingual tablet 15 mcg patient exposures are as high as 825 mcg/24 hours (equivalent to 27.5 sufentanil sublingual 30 mcg tablets). The Applicant selected a plasma concentration cutoff of 150 pg/mL sufentanil concentration as it is the mean plasma sufentanil maximum concentration (Cmax) observed at steady-state with repeated hourly dosing of 12 sufentanil sublingual 30 mcg tablets in Study SAP101.

These analyses by dose and concentration were performed on safety data from Pool 8, which included all sufentanil sublingual tablet 30 mcg and sufentanil sublingual tablet 15 mcg studies that were at least 24 hours in duration.

Table 6 summarizes the studies included in Pool 8. The one study included from the sufentanil sublingual tablet 30 mcg program (SAP301) had a duration of treatment of up to 48 hours, while the three studies from the sufentanil sublingual tablet 15 mcg program (IAP310, IAP311, and IAP309) had durations of up to 72 hours. There were differences in the sufentanil sublingual tablet 15 mcg and sufentanil sublingual tablet 30 mcg clinical programs. The programs had different devices, sufentanil doses, and deliverers (patient for sufentanil sublingual tablet 15 mcg vs. health care professional for sufentanil sublingual 30 mcg tablet). In addition, the sufentanil sublingual tablet 15 mcg and sufentanil sublingual tablet 30 mcg clinical programs had different study designs and patient populations (Table 6). Generally, patients in the sufentanil sublingual tablet 15 mcg studies were older, had higher body mass index (BMI), and had undergone major surgeries compared to the patients in the sufentanil sublingual tablet 30 mcg studies. Further, patients in sufentanil sublingual tablet 15 mcg studies were generally treated for longer durations

(Table 6) and had more extensive sufentanil exposure. Despite these differences, it is reasonable to utilize data from the sufentanil sublingual tablet 15 mcg program to support the safety of the sufentanil sublingual tablet 30 mcg given that both programs administered sufentanil, the Applicant linked the PK of sufentanil sublingual tablet 15 mcg and sufentanil sublingual tablet 30 mcg, and the sufentanil sublingual tablet 15 mcg program included patients who were exposed to higher doses and longer durations of sufentanil in the setting of additional comorbidities.

Table 6: Overview of Studies Included in the Pooled Analysis Supporting Maximal Dosing (Pool 8)

Study	Study Design	Dosing Regimen; SL	Number of Subjects		Patient population	Duration / Rescue Analgesia
			All Subjects	Subjects in Pooled Analyses*		
Sufentanil sublingual tablet 30 mcg program (SST 30 mcg)						
SAP301	MC, R, DB, PC	SST 30 mcg Placebo	SST 30 mcg: treated 107; completed 102 Placebo: treated 54; completed 41	SST 30 mcg: treated 107; completed 102 Placebo: treated 54; completed 41	Post-surgical adult patients following abdominoplasty, open inguinal hernioplasty, or laparoscopic abdominal surgery	Up to 48 hours/ Morphine IV
Sufentanil sublingual tablet 15 mcg program (SST 15 mcg)						
IAP310	MC, R, DB, PC	SST 15 mcg Placebo	SST 15 mcg: treated 114; completed 78 Placebo: treated 58 completed 27	SST 15 mcg: 51 Placebo: 27	Open abdominal surgery	Up to 72 hours/ Morphine IV
IAP311	MC, R, DB, PC	SST 15 mcg Placebo	SST 15 mcg: treated 315; completed 215 Placebo: treated 104; completed 43	SST 15 mcg: 142 Placebo: 54	Total knee or hip replacement	Up to 72 hours/ Morphine IV
IAP309	MC, R, OL, AC	SST 15 mcg Morphine 1 mg over 6 minutes IV	SST 15 mcg: treated 177; completed 146 Morphine: treated 180; completed 136	SST 15 mcg: 94 Morphine: None	Open abdominal surgery or knee or hip replacement	Up to 72 hours/ N/A

All drugs administered SL and PRN, except morphine which was administered IV and PRN
Abbreviations: AC=active control; DB=double-blind; IV = intravenous; MC=multicenter; OL=open-label; PD = pharmacodynamics; PK = pharmacokinetics; PRN = as needed; R=randomized; SST = sufentanil sublingual tablet.

* For studies of the SST 15 mcg, pooled analyses included patients who received their first 2 SST 15 mcg tablets dosed within 20-25 minutes of each other in the first hour of dosing. Inclusion of these patients in pooled analyses with SST 30 mcg (ARX-04) is based on the establishment of bioequivalence of 1 SST 30 mcg tablet with 2 SST 15 mcg tablets dosed within 20 to 25 minutes of each other and PK modeling.
Source: Adapted from ISS Amendment 3, Table 1, page 9, submitted 5/3/2018.

Data from Pool 8 were analyzed and presented based on sufentanil dose received during the first 24 hours and maximum measured sufentanil plasma concentration achieved with sparse sampling during the first 24 hours. The number of patients treated in each study stratified by sufentanil dose (<300 mcg or ≥300 mcg) and included in Pool 8 is presented in Table 7. The one study from the sufentanil sublingual tablet 30 mcg program (SAP301) included 26 patients with sufentanil doses of at least 300 mcg. In contrast, there were three studies included in Pool 8 from the sufentanil sublingual tablet 15 mcg program, with 180 patients with sufentanil doses of at least 300 mcg. Thus, from the sufentanil sublingual tablet 30 mcg and sufentanil sublingual

tablet 15 mcg programs, there were a total of 206 patients with sufentanil doses of at least 300 mcg during the first 24 hours of study treatment.

Across the studies in the sufentanil sublingual tablet 30 mcg and sufentanil sublingual tablet 15 mcg programs, 50 patients had sufentanil concentrations >150 pg/mL during the first 24 hours based on sparse PK sampling, including 3 patients from the sufentanil sublingual tablet 30 mcg study and 47 patients from the sufentanil sublingual tablet 15 mcg studies.

Table 7: Analysis Population Summary by Study, Treatment, and Dose Group: Sufentanil-treated Patients Enrolled in Sufentanil sublingual tablet 30 mcg study SAP301 and Sufentanil sublingual tablet 15 mcg Studies IAP309, IAP310, and IAP311

Study	Control	Treatment Group				Total (n = 394)
		SST 15 mcg		SST 30 mcg		
		< 300 mcg (0-24 hrs)	≥ 300 mcg (0-24 hrs)	< 300 mcg (0-24 hrs)	≥ 300 mcg (0-24 hrs)	
Sufentanil sublingual tablet 30 mcg program (SST 30 mcg)						
SAP301	PC	0	0	81	26	107
Sufentanil sublingual tablet 15 mcg program (SST 15 mcg)						
IAP309 IAP310 IAP311	AC, OL PC PC	34 23 50	60 28 92	0 0 0	0 0 0	94 51 142
Total for sufentanil sublingual tablet 15 mcg studies		107	180	-	-	287
Overall Total		107	180	81	26	394

Abbreviations: AC=active control; hrs=hours; OL=open label; PC=placebo-controlled; SST: sufentanil sublingual tablet
Source: Adapted from ISS Amendment 3, Table 4, page 18, submitted 5/3/2018.

It is important to note that there are significant limitations to the safety analyses based on dose received and sufentanil concentration. As is typical for an opioid, sufentanil sublingual tablets 30 mcg were administered as needed, and while this was reasonable, it complicates the safety analyses by dose and plasma concentration. Specifically, safety analyses based on dose received and plasma concentration are difficult to interpret since the dose received is influenced by a variety of factors, such as the amount of pain experienced and the occurrence of adverse events. Further, the analyses performed were based on total sufentanil dose and sufentanil concentration during the first 24-hour study period, but exposure, disposition, and safety data are presented for the entire study period. Recognizing these limitations, the analyses were felt to be reasonable in the context of supporting the maximum daily dose proposed.

This review will focus on the safety analyses presented by dose received, rather than sufentanil concentration. The dose groups will be referred to as the lower dose group (<300 mcg) and the higher dose group (≥300 mcg). The dose groups are shown stratified by clinical program (sufentanil sublingual tablet 15 mcg or 30 mcg) given differences in the study design and patient populations.

Demographics

Table 8 presents the demographics and baseline characteristics by sufentanil dose for Pool 8. Overall, the mean age was 58 years (SD 15.6) and most patients were female (66%) and white (82%).

For patients receiving sufentanil sublingual tablet 30 mcg, patients in the higher dose group compared to the lower dose group were slightly younger (mean age 38 versus 42 years) and more likely to be male (38.5% vs. 29.6%). For patients receiving sufentanil sublingual tablet 15 mcg, the lower and higher dose groups had similar demographics in terms of age and sex.

Across the sufentanil sublingual tablet 30 mcg and sufentanil sublingual tablet 15 mcg groups, all but one patient with a measured maximum sufentanil concentration >150 pg/mL during the first 24-hour study period received a total sufentanil dose >300 mcg during the first 24-hour study period. For patients in the higher dose sufentanil sublingual tablet 30 mcg group, 7.7% had a maximum sufentanil concentration >150 pg/mL during the first 24-hour study period. For patients in the higher dose sufentanil sublingual tablet 15 mcg group, 28.5% had a maximum sufentanil concentration >150 pg/mL during the first 24-hour study period. Therefore, patients with maximum sufentanil concentrations >150 pg/mL during the first 24-hour study period primarily represent a subset of the higher dose sufentanil sublingual tablet (SST) patients, while the patients with less than maximum sufentanil concentrations ≤150 pg/mL during the first 24-hour study period represent a combination of higher and lower dose SST patients. Since the patients had only sparse sampling, it is possible that additional patients at some point achieved sufentanil concentrations >150 pg/mL but were not included in the higher concentration group. Given these limitations and considerations, the focus of these safety analyses is based on sufentanil dose, rather than concentration.

Table 8: Demographics and Baseline Characteristics of Safety Population by Treatment and Dose Group: Sufentanil Sublingual Tablet 30 mcg Study and Sufentanil Sublingual Tablet 15 mcg Studies

	Treatment group				Total (n = 394)
	SST 15 mcg		SST 30 mcg		
	< 300 mcg (0-24 Hours)	≥ 300 mcg (0-24 Hours)	< 300 mcg (0-24 Hours)	≥ 300 mcg (0-24 Hours)	
	(n = 107)	(n = 180)	(n = 81)	(n = 26)	
Age (years) - n (%)					
≥ 75	27 (25.2%)	32 (17.8%)	0	0	59 (15.0%)
Mean (SD)	65.8 (12.0)	63.3 (12.1)	42.2 (10.9)	38.3 (9.2)	58.0 (15.6)
Median	66.0	64.0	41.0	37.5	60.0
(Min, Max)	(24.0, 86.0)	(19.0, 86.0)	(18.0, 69.0)	(22.0, 62.0)	(18.0, 86.0)
Sex					
Female	72 (67.3%)	115 (63.9%)	57 (70.4%)	16 (61.5%)	260 (66.0%)
Race - n (%)					
American Indian or Alaska Native	0	0	0	0	0
Asian	0	1 (0.6%)	2 (2.5%)	1 (3.8%)	4 (1.0%)
Black or African American	13 (12.1%)	24 (13.3%)	18 (22.2%)	3 (11.5%)	58 (14.7%)
Native Hawaiian or Another Pacific	1 (0.9%)	0	0	0	1 (0.3%)
White	93 (86.9%)	155 (86.1%)	58 (71.6%)	18 (69.2%)	324 (82.2%)
Other	0	0	3 (3.7%)	4 (15.4%)	7 (1.8%)
Surgery Type					
Orthopedic	77 (72.0%)	140 (77.8%)	0	0	217 (55.1%)
Abdominal	30 (28.0%)	38 (21.1%)	81 (100%)	26 (100%)	175 (44.4%)
Other Surgery	0	2 (1.1%)	0	0	2 (0.5%)
Body Mass Index					
Mean (SD) - kg/m^2	29.2 (6.5)	31.1 (7.3)	27.7 (4.9)	26.9 (4.6)	29.6 (6.6)
Maximum sufentanil concentration (pg/ml)					
≤ 150	92 (100%)	118 (71.5%)	79 (98.8%)	24 (92.3%)	313 (86.2%)
> 150	0	47 (28.5%)	1 (1.3%)	2 (7.7%)	50 (13.8%)
Mean (SD)	54.4 (32.9)	128.7 (55.7)	52.9 (26.0)	92.8 (33.3)	90.6 (56.6)

Abbreviations: Max=maximum; min=minimum; SD=standard deviation; SST: sufentanil sublingual tablet
Source: Adapted from ISS Amendment 3, Table 11, page 28, submitted on 5/3/2018.

Key safety results and the comparison of safety results in higher and lower sufentanil dose groups in Pool 8

The following section reviews the key safety findings from Pool 8, including deaths, serious adverse events, discontinuations due to adverse events, and common adverse events.

Deaths in Pool 8

No were no deaths reported in Pool 8.

Serious Adverse Events (SAEs) in Pool 8

Six SAEs were reported in a total of four patients in Pool 8 (Table 9). All the SAEs occurred in sufentanil sublingual tablet 15 mcg-treated patients and no SAEs were reported in sufentanil sublingual tablet 30 mcg-treated patients. The proportion of sufentanil sublingual tablet 15 mcg-treated patients with SAEs was higher in the lower dose group (2.8%) compared to the higher dose group (0.6%). Thus, there did not appear to be a relationship between increased dose and SAEs.

Table 9: Serious Adverse Events by Treatment and Dose Group in Pool 8

	Treatment Group				
	SST 15 mcg		SST 30 mcg		
	<300 mcg (0-24 hours) (n=107)	≥300 mcg (0-24 hours) (n=180)	<300 mcg (0-24 hours) (n=81)	≥300 mcg (0-24 hours) (n=26)	Total (n=394)
Number (%) of Patients With at Least 1 SAE	3 (2.8%)	1 (0.6%)	0	0	4 (1.0%)

Note: Adverse event mapping based on MedDRA Version 11.0.
Abbreviations: SST: sufentanil sublingual tablet; SAE: serious adverse event.
Source: Adapted from ISS amendment 3, Table 19, page 53, submitted on 5/3/2018

Table 10 displays additional details for the six SAEs (oxygen saturation decreased, confusional state, hypoxia, pulmonary embolism, atrial fibrillation, and postoperative ileus) that occurred in the four sufentanil sublingual tablet 15 mcg-treated patients.

Table 10: Treatment-emergent Serious Adverse Events in Selected Sufentanil sublingual tablet 15 mcg Studies IAP310, and IAP311

Patient ID/ Treatment	Adverse Event Preferred Term	Severity	Relationship to Treatment	Action Taken	Outcome
Study IAP311 (Placebo-controlled)					
(b) (6) Lower (< 300 mcg) sufentanil dose group	Oxygen saturation decreased	Severe	Probably Related	Drug withdrawn	Recovered/ resolved
(b) (6) Lower (< 300 mcg) sufentanil dose group	Confusional state	Moderate	Possibly Related	Dose not changed	Recovered/ resolved
	Hypoxia	Moderate	Not Related	Dose not changed	Recovered/ resolved
	Pulmonary embolism	Mild	Not Related	Dose not changed	Recovered/ resolved
(b) (6) Higher (≥ 300 mcg) sufentanil dose group	Atrial fibrillation	Moderate	Not Related	Dose not changed	Recovered/ resolved
Study IAP309 (Open-label)					
(b) (6) Lower (< 300 mcg) sufentanil dose group	Postoperative ileus	Severe	Not Related	Dose not changed	Recovered/ resolved

Source: Adapted from ISS Amendment 3, Table 20, page 54, submitted 5/3/2018.

There were two patients with SAEs related to hypoxia or oxygen saturation decreased in Pool 8. The first patient ((b) (6) was a 65-year-old white female who underwent a total knee arthroplasty under spinal anesthesia on the day of the event. The patient received 14 doses of sufentanil sublingual 15 mcg tablets within seven hours of the event. In addition, she received a total of 11 mg of IV morphine in 4 separate doses within seven hours of the event, along with oxycodone/acetaminophen, fentanyl, meclozine, and propofol. The patient's oxygen saturation decreased to 40 to 50% and resolved with naloxone. She was withdrawn from the study and discharged two days later. The second SAE (patient (b) (6) involved an 80-year-old female who developed aspiration pneumonia and a pulmonary embolism one day after undergoing total knee replacement. She also had hypoxia and encephalopathy with confusion/delirium (confusional state) and wide complex paroxysmal tachycardia/atrial fibrillation. The patient had taken five doses of sufentanil sublingual tablet 15 mcg in the postoperative period on the same day as the surgery. Serious respiratory depression is a known risk of opioids and is included as a Boxed Warning in opioid labeling.

The additional SAEs were atrial fibrillation and postoperative ileus. The event of atrial fibrillation occurred in a 78-year-old white male who underwent a total knee replacement the day before the event. He had received a total of 77 doses of sufentanil sublingual 15 mcg over approximately 47 hours. The SAE of new onset of atrial fibrillation occurred 1 day after the surgery and 28 hours after the first dose. The patient was treated with amiodarone and transferred

to the coronary care unit. The event was considered resolved three days after. There was a temporal relationship between the event and sufentanil, but there were other confounding factors, such as the surgical procedure. The SAE of a postoperative ileus occurred in a 68-year old white male patient with a history of diverticulitis who underwent a laparotomy for sigmoid resection and re-anastomosis.

Discontinuations due to AEs

As shown in Table 11 a total of 22 patients (5.6%) in Pool 8 discontinued due to AEs, and no AEs leading to discontinuation were reported by more than 2% of patients overall. In the sufentanil sublingual tablet 30 mcg study, only one patient discontinued the study due to a AE (decreased oxygen saturation), and this patient received the higher sufentanil dose. In the sufentanil sublingual tablet 15 mcg studies, a higher proportion of patients in the lower dose group (14%) discontinued due to an AE compared to the higher dose group (3.3%). The types of adverse events leading to discontinuation would be anticipated for an opioid (Table 12).

Table 11: Adverse Events Causing the Discontinuation of Study Drug by Sufentanil dose groups in Pool 8

	Treatment Group				Total
	SST 15 mcg		SST 30 mcg		
	< 300 mcg (0-24 Hours)	≥ 300 mcg (0-24 Hours)	< 300 mcg (0-24 Hours)	≥ 300 mcg (0-24 Hours)	
Number of Patients Enrolled in the Study	107	180	81	26	394
Number (%) of Patients With At least One Adverse Event Causing the Discontinuation of Study Drug	15 (14.0%)	6 (3.3%)	0	1 (3.8%)	22 (5.6%)

Abbreviation: SST: sufentanil sublingual tablet
Source: Adapted from ISS Amendment 3, Table 21, page 55-6, submitted 5/3/2018.

Table 12: Adverse Events Causing Discontinuation in Sufentanil Sublingual Tablet 30 mcg and Sufentanil Sublingual Tablet 15 mcg Studies

	Treatment Group				
	SST 15 mcg		SST 30 mcg		
	< 300 mcg (0-24 Hours)	≥300mcg (0-24 Hours)	< 300 mcg (0-24 Hours)	≥300mcg (0-24 Hours)	
Gastrointestinal disorders					
Nausea	2 (1.9%)	3 (1.7%)	0	0	5 (1.3%)
Investigations					
Oxygen saturation decreased	3 (2.8%)	0	0	1 (3.8%)	4 (1.0%)
Hepatic enzyme increased	1 (0.9%)	0	0	0	1 (0.3%)
Respiratory rate decreased	1 (0.9%)	0	0	0	1 (0.3%)
Musculoskeletal and connective tissue disorders					
Back pain	0	2 (1.1%)	0	0	2 (0.5%)
Nervous system disorders					
Sedation	4 (3.7%)	0	0	0	4 (1.0%)
Dizziness	1 (0.9%)	0	0	0	1 (0.3%)
Psychiatric disorders					
Agitation	1 (0.9%)	1 (0.6%)	0	0	2 (0.5%)
Confusional state	2 (1.9%)	0	0	0	2 (0.5%)
Respiratory, thoracic and mediastinal disorders					
Bradypnea	1 (0.9%)	0	0	0	1 (0.3%)
Hypoventilation	1 (0.9%)	0	0	0	1 (0.3%)
Hypoxia	1 (0.9%)	0	0	0	1 (0.3%)

Source: Adapted from ISS Amendment 3, Table 21, page 55-6, submitted 5/3/2018.

Common Adverse Events

As shown in Table 13, overall 74% of patients had an adverse event in Pool 8.

In the sufentanil sublingual tablet 30 mcg study, the proportion of patients with an adverse event (AE) was similar in the lower (58%) and higher (57.7%) dose groups. Some AEs, such as, nausea, pruritus, oxygen saturation decreased, tachycardia and dyspepsia, occurred more frequently in the higher dose group, while other AEs, such as, headache, vomiting, dizziness, hypotension, and hypertension, occurred more frequently in the lower dose group.

In the sufentanil sublingual tablet 15 mcg studies, the proportion of patients with an AE was higher in the higher dose group (82.8%) compared to the lower dose group (76.6%). Similarly to the sufentanil sublingual tablet 30 mcg study, some AEs such as nausea, pyrexia, vomiting, anemia, pruritus, constipation, hypotension, insomnia, leukocytosis, sinus tachycardia, dyspepsia, body temperature increased, hypokalemia, hypertension, and hyponatremia, occurred more frequently in the higher dose group, while other AEs, such as headache, dizziness, decreased oxygen saturation, hypocalcemia, tachycardia, anemia postoperative, hypoalbuminemia, and confusional state, occurred more frequently in the lower dose group. There were no clear trends in terms of dose-response and similar terms (such as anemia/anemia postoperative and sinus tachycardia/tachycardia) did not follow a similar dose-response pattern.

Table 13: Adverse Events (≥ 2% in Total Across All Treatments) and Dose Group in Sufentanil sublingual tablet 30 mcg and Sufentanil sublingual tablet 15 mcg studies

	Treatment Group				Total
	SST 15 mcg		SST 30 mcg		
	< 300 mcg (0-24 Hours)	≥ 300 mcg (0-24 Hours)	< 300 mcg (0-24 Hours)	≥ 300 mcg (0-24 Hours)	
Number of Patients Enrolled in the Study	107	180	81	26	394
Number (%) of Patients Who Received Treatment	107 (100%)	180 (100%)	81 (100%)	26 (100%)	394 (100%)
Number (%) of Patients With At least One Adverse Event	82 (76.6%)	149 (82.8%)	47 (58.0%)	15 (57.7%)	293 (74.4%)
Nausea	43 (40.2%)	93 (51.7%)	24 (29.6%)	11 (42.3%)	171 (43.4%)
Pyrexia	17 (15.9%)	38 (21.1%)	0	0	55 (14.0%)
Headache	13 (12.1%)	21 (11.7%)	18 (22.2%)	3 (11.5%)	55 (14.0%)
Vomiting	10 (9.3%)	20 (11.1%)	7 (8.6%)	1 (3.8%)	38 (9.6%)
Anemia	5 (4.7%)	28 (15.6%)	0	0	33 (8.4%)
Pruritus	7 (6.5%)	15 (8.3%)	1 (1.2%)	1 (3.8%)	24 (6.1%)
Dizziness	8 (7.5%)	8 (4.4%)	5 (6.2%)	1 (3.8%)	22 (5.6%)
Oxygen saturation	9 (8.4%)	11 (6.1%)	0	1 (3.8%)	21 (5.3%)
Constipation	3 (2.8%)	17 (9.4%)	0	0	20 (5.1%)
Hypotension	4 (3.7%)	10 (5.6%)	4 (4.9%)	1 (3.8%)	19 (4.8%)
Hypocalcemia	7 (6.5%)	5 (2.8%)	0	0	12 (3.0%)
Insomnia	3 (2.8%)	9 (5.0%)	0	0	12 (3.0%)
Leukocytosis	4 (3.7%)	7 (3.9%)	0	0	11 (2.8%)
Sinus tachycardia	0	11 (6.1%)	0	0	11 (2.8%)
Tachycardia	4 (3.7%)	4 (2.2%)	2 (2.5%)	1 (3.8%)	11 (2.8%)
Dyspepsia	3 (2.8%)	6 (3.3%)	0	1 (3.8%)	10 (2.5%)
Anemia postoperative	6 (5.6%)	4 (2.2%)	0	0	10 (2.5%)
Body temperature	3 (2.8%)	7 (3.9%)	0	0	10 (2.5%)
Hypoalbuminemia	6 (5.6%)	4 (2.2%)	0	0	10 (2.5%)
Hypokalemia	3 (2.8%)	6 (3.3%)	0	0	9 (2.3%)
Hypertension	1 (0.9%)	7 (3.9%)	1 (1.2%)	0	9 (2.3%)
Hyponatremia	0	8 (4.4%)	0	0	8 (2.0%)
Confusional state	5 (4.7%)	3 (1.7%)	0	0	8 (2.0%)

Abbreviation: SST: sufentanil sublingual tablet
Source: Adapted from Applicant's response to clinical IR, Table 1, pages 3-4, submitted 8/13/2018

Respiratory

Respiratory safety is a key consideration for opioids and all patients in the sufentanil sublingual tablet 15 mcg and sufentanil sublingual tablet 30 mcg studies were monitored with continuous pulse oximetry. Table 14 provides a summary of lowest oxygen saturation by dose group in Pool 8. There was no clear relationship between higher sufentanil dose and decreased oxygen saturation in the sufentanil sublingual tablet 30 mcg or sufentanil sublingual tablet 15 mcg programs.

In the sufentanil sublingual tablet 30 mcg study, the lowest oxygen saturation value recorded was 86% and this occurred in the higher dose group. This was the only incidence of decreased oxygen saturation reported as an adverse event. In the sufentanil sublingual tablet 15 mcg studies, the lowest oxygen saturation value recorded was 40% and this occurred in the lower dose group. Additional details regarding this adverse event are included in the discussion of SAEs.

Table 14: Lowest Oxygen Saturation by Treatment and Dose Group (Pool 8)

	Treatment group				Total (n=394)
	SST 15 mcg		SST 30 mcg		
	< 300 mcg (0-24 hours) (n=107)	≥ 300 mcg (0-24 hours) (n=180)	< 300 mcg (0-24 hours) (n=81)	≥ 300 mcg (0-24 hours) (n=26)	
SPO_2 < 93% -n (%)	17 (15.9%)	15 (8.3%)	7 (8.6%)	1 (3.8%)	40 (10.2%)
SPO2 < 95% -n (%)	35 (32%)	41 (22.8%)	22 (27.2%)	3 (11.5%)	101 (25.6%)
SPO2 (%) -n (%)					
≥ 95%	72 (67.3%)	139 (77.2%)	59 (72.8%)	23 (88.5%)	293 (74.4%)
93-94	18 (16.8%)	26 (14.4%)	15 (18.5%)	2 (7.7%)	61 (15.5%)
90-92	10 (9.3%)	11 (6.1%)	7 (8.6%)	0	28 (7.1%)
< 90	7 (6.5%)	4 (2.2%)	0	1 (3.8%)	12 (3.0%)
Mean (SD)	93.5 (6.2)	94.5 (1.7)	95.2 (1.6)	95.4 (2.2)	94.5 (3.6)
Median	95.0	95.0	96.0	96.0	95.0
(Min, Max)	(40, 100)	(83, 99)	(91, 98)	(86, 98)	(40, 100)

Abbreviation: SST: sufentanil sublingual tablet
Source: ISS amendment 3, Table 23, page 59, submitted on 5/3/2018.

8.2.a Safety concern associated with dropped tablets – 2nd cycle review

As noted in Section 8.1.a, there are significant safety concerns associated with dropped tablets. The overall safety evaluation of sufentanil sublingual tablet 30 mcg must consider the combination of the sublingual tablet and device. The small tablet size (3 mm in diameter and

0.85 mm in thickness) increases the potential risk of tablet dropping and misplacement and increases the risk of accidental exposure, overdose, and death, particularly in children. Sufentanil is a high potency opioid agonist (5 to 10 times more potent than fentanyl).

As described previously in Section 8.1.a, the Applicant reported a total of three dropped tablets in the sufentanil sublingual tablet 30 mcg Phase 3 program and the human factors validation study submitted in the 1st review cycle identified failures related to both essential and critical tasks. The most concerning were the eight failures associated with a critical task to confirm tablet placement in the patient's sublingual space. The Agency recommended changes to the DFU so that visual confirmation of the tablet placement is a distinct separate task. The changes to the DFU were evaluated in a second human factors validation study. The Applicant's proposed DFU is included in the Appendix.

In this resubmission, the Applicant submitted the second human factors validation study. All of the Agency's recommendations made for the DFU in the last review cycle were incorporated and the revised DFU was tested. The human factors validation study was conducted with 45 untrained participants (15 PACU/Floor nurses,15 ER nurses, and 15 Paramedics) that 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.

No failures or close calls occurred during the simulated use task portion of the second study. Additionally, there was no incidence of dropped tablets. However, there was a study protocol deviation that occurred in the knowledge assessment portion of the study. The Applicant provided acceptable response to address the deviations and no additional mitigation strategies were identified.

Based on the data from this study, DMEPA has 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.

HF studies are generally designed to help us identify and minimize (to an acceptable level) anticipated errors but unanticipated errors may still occur after the product is marketed.

8.2.b Risk assessment following accidental exposure to sufentanil sublingual 30 mcg tablets

The Applicant conducted a risk analysis based on simulated pharmacokinetic (PK) data, clinical trial data, and the published literature to evaluate the potential severity levels of harm due to accidental exposure to sufentanil sublingual 30 mcg tablets.

Table 15 Table 15 shows the Applicant's definitions of the various severity rankings. The severity levels ranged from negligible/cosmetic to catastrophic.

Table 15: Severity of Risk Factors

Severity of Effect (S)		
Scale	**Term**	**Definition of Clinical Effects**
1	**Negligible / Cosmetic**	No / virtually no injury to the patient or user; no / virtually no negative effect on the environment. No impact on product performance or user confidence in the product/company; user may or may not even notice the failure.
2	**Minor**	Minor injury to the patient or user; minor negative effect on the environment. Slight decline of product performance or user confidence in the product/company (e.g., customer slightly annoyed and/or inconvenienced). For example, this includes prolonging or delaying a clinical procedure that does not pose a risk of greater injury to the patient or user.
3	**Moderate**	Moderate injury to the patient or user; moderate negative effect on the environment. Decline of product performance or user confidence in the product/company (e.g., customer is very annoyed and/or dissatisfied). For example, this includes actions taken to treat the patient or user within the scope and type of treatment already in progress.
4	**Critical**	Serious injury (reversible) to the patient or user; severe negative effect on the environment. For example, this includes the need for a more invasive procedure such as surgery or increases case complication to fully treat the injury. NOTE: Any labeling issues that could lead to a field action must be ranked at a minimum of 4.
5	**Catastrophic**	Serious injury (irreversible) or death of the patient or user; or very severe negative effect on the environment.

Source: The Applicant's submission Document RSK-7025 Severity Levels of Harm due to Accidental Exposure to SST 30 mcg. Page 2/10, submitted on 5/3/2018

In terms of PK considerations, the Applicant submitted the results of a population pharmacokinetic (popPK) modeling and simulation analysis to assess the risk of accidental exposure of dropped sufentanil tablets in a pediatric population. The adult population pharmacokinetic model developed for sufentanil sublingual tablets during the sufentanil sublingual tablet 15 mcg program (NDA 205265), was used for simulating sufentanil blood levels following accidental exposures to doses of one and two 30 mcg sufentanil sublingual tablets (i.e., two and four sufentanil sublingual 15 mcg tablets, respectively) in a child weighing 12 kg as this is the 50th percentile for weight for an 18-24-month child. The Applicant assumed this would be the minimum age of a toddler likely to be in a hospital setting and independently ambulating. Importantly, it is possible that a younger child could be accidentally exposed to sufentanil sublingual tablet in an inpatient setting. This use of the previous popPK model is acceptable based on the sufentanil sublingual tablet 30 mcg PK study SAP101, which

demonstrated that two 15 mcg sufentanil sublingual tablets were bioequivalent to a single 30 mcg sufentanil sublingual tablet.

Briefly, the steps followed were as follows:

(1) The popPK model developed with sufentanil sublingual tablet 15 mcg data only included data from an adult population. Therefore, the model was supplemented with sufentanil PK data from 19 pediatric patients undergoing cardiovascular procedures (Greeley et al., 1987[3]). The systemic clearance values reported in the literature seem to be in good agreement with the relationship between systemic clearance and body weight derived from the adult popPK model. Therefore, it is acceptable to use the adult popPK model for pediatric simulations.

(2) The adult popPK model was used to simulate the sufentanil blood levels following accidental doses of 30 and 60 mcg in a 2-year-old 'typical' child weighing 12 kg. Additionally, the Applicant made the following assumptions:
   a) Sufentanil's absorption characteristics from the sublingual space in the 'typical' child, such as absorption rate (Ka) and lag time (Tlag) are similar to adults.
   b) Doses are administered simultaneously and retained in the sublingual space. The tablet is absorbed through the sublingual space, and not swallowed.
   c) The relationships between apparent clearance (CL/F) and distributional clearance (Q/F) and body weight in the 'typical' child are similar to that described in the adult popPK model.
   d) The PK parameters are independent of the number of tablets (dose-linearity shown in PK studies of sufentanil sublingual tablets).

The predicted sufentanil blood levels following accidental doses of sufentanil sublingual tablet (30 or 60 mcg) in a typical 2-year-old child weighing 12 kg are shown in Figure 4 below. The predicted peak plasma concentrations were about 208 pg/ml and 416 ng/ml following accidental doses of 30 and 60 mcg sufentanil sublingual tablets respectively, and occurred approximately 1 hour post-dose. These values can be viewed as conservative, as heavier children would have lower plasma concentrations. Also, the assumption that the tablet is absorbed through the sublingual space is conservative, since swallowing results in <10% bioavailability, compared to a bioavailability of approximately 60% following sublingual absorption. The applicant compared these levels to those reported in the literature:

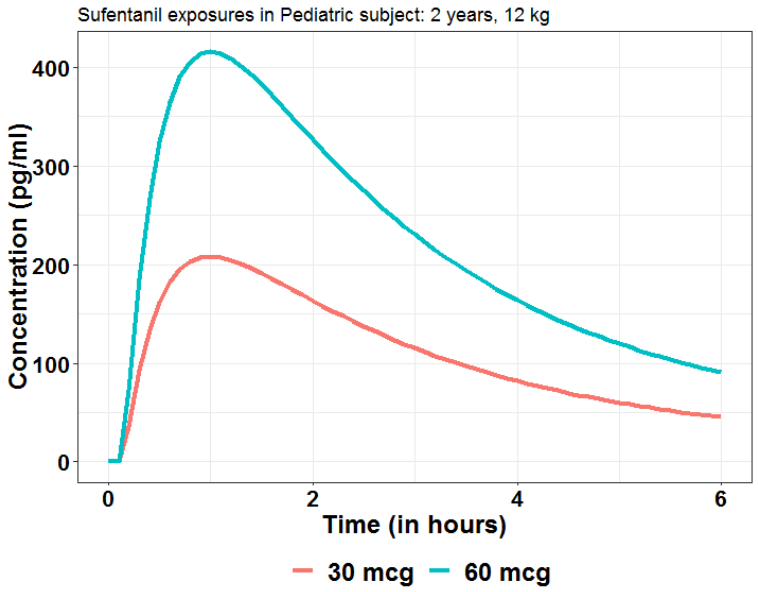
   a) In a correspondence letter to the editor (Haynes et al. 1993)[4], it is reported that intranasal administration of 2 mcg/kg in 15 pediatric outpatients resulted in average peak plasma concentrations of 300 pg/mL and no respiratory depression was reported. It is important to note that the average time to peak sufentanil blood levels occurred at about 15 and 30 min in 8 and 7 subjects respectively, which seems shorter than that predicted following sublingual administration (1 hour).

[3] Greeley WJ, de Bruijn NP, Davis DP. Sufentanil pharmacokinetics in pediatric cardiovascular patients. Anesthesia & Analgesia 1987; 66:1067-1072.
[4] Haynes G, Brahen NH, Hill HF. Plasma sufentanil concentration after intranasal administration to paediatric outpatients. Canadian Journal of Anaesthesia 1993; 40:286.

b) In another study conducted by Zedia et al[5], 2 mcg/kg sufentanil was administered intranasally before anesthetic induction in 60 pediatric outpatient surgery patients, aged 0.5 to 6 years old. It was reported that during a period of 15 to 20 minutes of observation before surgery, the vital signs and oxygen saturation did not change significantly before or after surgery.
c) In the study conducted by Greeley et al., 1987 (referenced above), 10-15 mcg/kg of sufentanil was administered as a rapid bolus intravenously in 28 pediatric patients undergoing cardiovascular procedures, age ranging between neonates (0-1 month) to adolescents (12-18 years). It was reported that the average peak sufentanil concentrations in each age group exceeded 14000 pg/ml. However, it is important to note that the pediatric subjects were closely monitored in an inpatient setting.

Overall, the Office of Clinical Pharmacology (OCP) review team agrees with the Applicant's methodology described above to assess the risk associated with accidental dosing of sufentanil sublingual tablets in a 12-kg child.

Figure 4: Predicted sufentanil blood levels following accidental doses of 1 and 2 sufentanil sublingual tablets 30 mcg in a typical 2-year-old child weighing 12 kg



From a clinical perspective, there are significant limitations in using data from intranasal sufentanil in children as pre-anesthesia to predict the pharmacodynamic effects of an accidental exposure to sufentanil sublingual tablet 30 mcg. Specifically, the context of use of sufentanil in the cited published literature is very different than the context of accidental exposure relevant to sufentanil sublingual tablet 30 mcg's risk assessment. Patients in the cited studies were medically monitored prior to and during surgery and received concomitant medications, including anesthesia, while the context of the risk assessment is accidental exposure in a setting where

[5] Zedie N, Amory DW, Wagner BKJ, O'Hara DA. Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. Clinical Pharmacology and Therapeutics 1996; 59:341-348.

children are not anticipated to be medically monitored. These differences limit the use of data from the published literature to inform risk in the proposed setting. However, they are useful in that they do show the potential for adverse events associated with administration of sufentanil. For example, Henderson et al., 1988[6] showed that sufentanil 4.5 µg/kg nasally can result in detrimental effects in some patients, including "rigidity, postoperative vomiting, perhaps convulsive activity, and occasionally a need for antagonism of its respiratory depressant effect" (page 674). Similarly, in Zedie 1996[7], "two patients were judged to have a mild decrease in chest wall compliance during induction (i.e. rigidity), and another two patients experienced transient apneic episodes with SaO2 values between 92% to 93%. Because all patients were intubated immediately, these adverse effects did not become clinically significant" (page 346). These patients received 2 µg/kg. While there are significant differences in the clinical setting, limiting conclusions, the data indicate that opioid-related adverse events can occur with intranasal sufentanil at doses of 2 and 4.5 µg/kg.

Based on the literature, the Applicant defined the sufentanil plasma concentration of 300 pg/mL to be well-tolerated in young children (12 kg). One sufentanil sublingual tablet 30 mcg could reach peak plasma level of approximately 200 pg/ml and two 30 mcg sufentanil sublingual tablets could reach peak plasma levels of approximately 400 pg/ml. The Applicant graded a toddler (12 kg) with sublingual administration of 1 sufentanil sublingual tablet 30 mcg an "Overdosing" (scale 3 in Table 16) and ≥ 2 sufentanil sublingual 30 mcg tablets a "Serious Injury or Death" (scale 5 in Table 16). Based on predictions from the popPK model, the Applicant graded the severity of harm to toddler, child, and adult due to accidental exposure to sufentanil sublingual tablet 30 mcg, as seen in Table 16.

Table 16: The severity of hard to toddler, child and adult due to accidental exposure to sufentanil sublingual tablet 30 mcg SST

[6] Henderson JM, Brodsky DA, Fisher DM, Brett CM, Herzka RE. Pre-induction of Anesthesia in Pediatric Patients with Nasally Administered Sufentanil. Anesthesiol. 1988;68:671-5.
[7] Zedie N, Amory DW, Wagner BKJ, O'Hara DA. Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. Clinical Pharmacology and Therapeutics 1996; 59:341-348.

PHA Item#	Hazardous Situation [Circumstance in which people, property, or the environment are exposed to one of more hazard(s)]	Harm or Effect [*Physical injury or damage to the health of people*]	Severity
8	Patient receives dose more frequently than hourly	Minor Overdosing	2
11	Non-Patient adult (50kg) takes one dose	Minor Overdosing	2
12	Patient or Non-Patient adult (50kg) takes two doses	Overdosing	3
13	Patient or Non-Patient adult (50kg) takes ≥ 3 doses	Serious Injury or Death	5
14	Non-Patient toddler (12kg) or child (20kg) Takes One Dose	Overdosing	3
15	Non-Patient child (20kg) Takes Two Doses	Moderate to Severe Overdosing	4
15.5	Non-Patient toddler (12kg) Takes Two Doses	Serious Injury or Death	5
16	Non-Patient child (20kg) takes ≥ 3 doses	Serious Injury or Death	5

Source: Applicant's submission document RSK-7025 Severity Levels of Harm due to Accidental Exposure to DSUVIA 30 mcg SST, page 9/10, submitted on 5/3/2018.

Discussion and conclusion of risk analysis

There are limitations in the Applicant's risk analysis given different contexts of use of sufentanil in the cited published literature and in the context of accidental exposure. A topic of discussion at the Advisory Committee will be consideration of the risks associated with accidental exposure to this product which delivers a small sufentanil tablet.

Overall summary of safety review in 2nd review cycle

In this resubmission, the Applicant reduced the maximum daily dose from 24 sufentanil sublingual 30 mcg tablets (720 mcg sufentanil) to no more than 12 sufentanil sublingual 30 mcg tablets (360 mcg sufentanil) per day to address the safety concern of sufentanil sublingual tablet 30 mcg in patients requiring the maximum dosing proposed for labeling. In addition, the Applicant submitted pooled safety analyses comparing the safety of sufentanil sublingual tablets based on dose received (≥ 300 mcg and < 300 mcg) and plasma sufentanil concentration (>150 pg/mL and ≤150 mg/mL). While there are limitations in these analyses by dose and plasma sufentanil concentration, they appeared adequate in the context of the Applicant's proposal to support a maximum daily dose of 12 sufentanil sublingual 30 mcg tablets. Consistent with the first review cycle, overall sufentanil sublingual tablet 30 mcg appeared to have a typical safety profile of an opioid agonist.

Another safety concern considered in this review cycle was the risk of misplaced tablets. Given the potency of sufentanil and the small size of the tablet, there is concern that tablets could be misplaced. The Applicant modified the DFU so that visual confirmation of the tablet placement is a distinct separate task. The changes to the DFU were evaluated in a second human factors

validation study that was reviewed by DMEPA. No failures or close calls occurred during the simulated use task portion of the second study.

Based on the data from this study, DMEPA has 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. However, there remain concerns regarding the risk of misplaced tablets, which could lead to accidental exposure. Potential risk evaluation and mitigation strategies (REMS) are discussed in the next section.

9. Risk Evaluation and Mitigation Strategy (REMS)

The Applicant submitted a proposed REMS during the first review cycle. The complete response letter stipulated that a REMS will be necessary for sufentanil sublingual tablet 30 mcg, if it is approved, to ensure that the benefits of the drug outweigh the risk of respiratory depression resulting from accidental exposure.

REMS Background Information

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food Drug Administration Amendments Act of 2007 (FDAAA), authorizes the FDA to require applicants or application holders to develop and comply with a REMS for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: a Medication Guide or patient package insert (PPI), a communication plan to healthcare providers, elements to assure safe use, and an implementation system. All REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) must have a timetable for submission of assessments of the REMS. These assessments are prepared and submitted by the application holder and reviewed by FDA.

A Medication Guide provides FDA approved patient-focused labeling and can be required as part of the approved labeling if FDA determines one or more of the following apply:

- Patient labeling could help prevent serious adverse events.
- The product has serious risks that could affect a patient's decision to use or continue to use the drug.
- Patient adherence to directions is crucial to product effectiveness.

A communication plan consists of FDA-approved materials used to aid a sponsor's implementation of the REMS and/or inform healthcare providers about the serious risk of a drug. This can include, for example, "Dear Healthcare Professional" letters, collaboration with

professional societies, and education pieces (such as letters, drug fact sheets) to inform prescribers of the risks and the safe use practices for the drug.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and potentially impact patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

Applicant's Risk Mitigation Proposal

The Applicant submitted a proposed 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 about the safe use of sufentanil sublingual tablet 30 mcg, including proper administration and monitoring. The use setting proposed by the Applicant is healthcare facilities or services that 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.

The Applicant asserts that all healthcare facilities and services that order, prescribe or distribute sufentanil sublingual tablet 30 mcg, will be required to become certified in the sufentanil sublingual tablet 30 mcg REMS Program and comply with the program requirements. Healthcare facility certification includes enrollment in the REMS by completion of a *Healthcare Facility/Service Enrollment Form* by an Authorized Representative (AR). The AR will attest that the healthcare facility or service: is a licensed pharmacy or healthcare provider with DEA registration for CII drugs who will oversee ordering and administration of the medication; has access to equipment and personnel trained to detect and manage hypoventilation, including use of supplemental oxygen and opioid antagonists, such as naloxone; and has documented processes and procedures in place to ensure sufentanil sublingual tablet 30 mcg is not dispensed for use outside of the certified setting.

The Applicant has proposed the following materials relevant to their proposed REMS:

- *Healthcare Facility/Service REMS Enrollment Form*;
- *Dear Healthcare Provider (DHCP) Letters*;
- *Sufentanil Sublingual Tablet 30 mcg (proposed tradename Dsuvia) REMS Safety Brochure: Guide for Healthcare Providers and Pharmacists*;
- *Directions for Use (DFU)* – A short guide detailing the appropriate administration of Sufentanil Sublingual Tablet 30 mcg (proposed tradename Dsuvia)
- REMS Website- Sufentanil Sublingual Tablet 30 mcg (proposed tradename Dsuvia) REMS Website.

Agency's Proposed REMS

Because of the small tablet size (3 mm in diameter and 0.85 mm in thickness) of sufentanil sublingual tablet 30 mcg there is a risk of dropping or misplacing the tablet during administration which increases the risk of accidental exposure, overdose, and death, particularly in children. Sufentanil sublingual tablet 30 mcg is an immediate-release (IR) opioid analgesic, and therefore, also carries the risks of abuse and misuse.

In general, we agree with the Applicant's risk mitigation proposal. However, we determined that respiratory depression resulting from inappropriate administration (included in the Applicant's proposed goal) will be mitigated since sufentanil sublingual tablet 30 mcg will be administered by a HCP, not the patient. DMEPA reviewed the second human factors validation study to demonstrate the safe and effective administration of sufentanil sublingual tablet 30 mcg by intended users (HCPs) and concluded that the product-user interface supports the safe and effective use of sufentanil sublingual tablet 30 mcg by the intended users, for its intended uses, and intended use environments.

The FDA proposes the following REMS goal:
The goal of the sufentanil sublingual tablet 30 mcg REMS is to mitigate the risk of respiratory depression resulting from accidental exposure by:

- Ensuring that sufentanil sublingual tablet 30 mcg is dispensed only to patients in certified medically supervised settings.

FDA proposes the following components for the REMS.

1. Elements to assure safe use including:
    A. Healthcare settings that dispense sufentanil sublingual tablet 30 mcg are specially certified.
        i. The *Healthcare Setting REMS Enrollment Form* will list the following requirements. The Healthcare setting must:
            1. Be able to manage an acute opioid overdose
            2. Ensure that healthcare providers, who administer sufentanil sublingual tablet 30 mcg, have read the sufentanil sublingual tablet 30 mcg Directions for Use to ensure proper placement of the tablet.
            3. Ensure that sufentanil sublingual tablet 30 mcg is NOT dispensed to outpatients.
2. Implementation System
    A. Wholesalers/distributors will be required to distribute only to certified medically supervised settings.
3. A timetable for submission of assessments that is at 6 and 12 months from initial approval of the REMS and annually thereafter.

Discussion

FDA has the authority to require a REMS if additional measures beyond the labeling are necessary to ensure the benefits of a drug outweigh the risks. A REMS is necessary for sufentanil sublingual tablet 30 mcg to ensure the benefits outweigh the risk of accidental exposure.

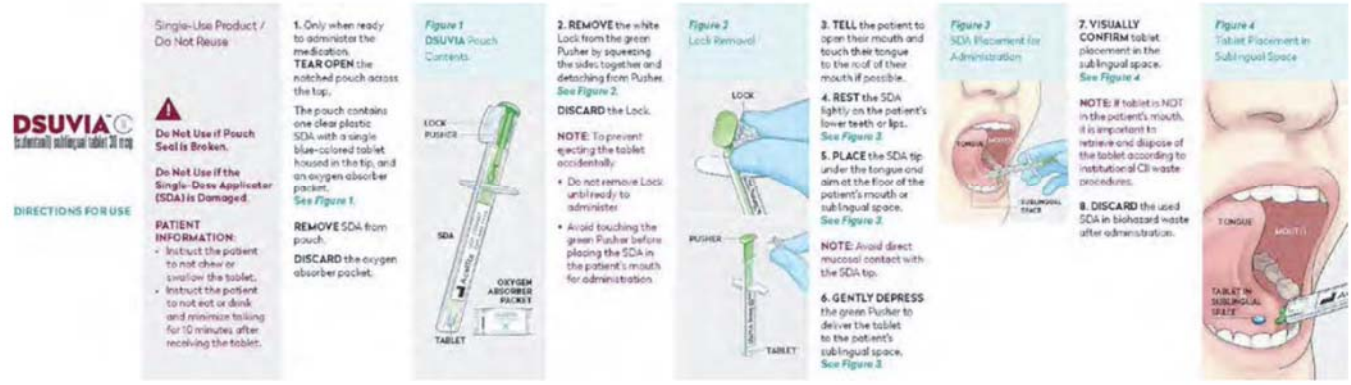
Because of the small tablet size of sufentanil sublingual tablet 30 mcg there is a risk of dropping or misplacing the tablet during administration which increases the risk of accidental exposure, overdose, and death, particularly in children. We determined that the benefit may outweigh the risk of accidental exposure if sufentanil sublingual tablet 30 mcg is administered by a healthcare provider only in certified medically supervised settings. Sufentanil sublingual tablet 30mcg is not intended for outpatient use (e.g., dispensed by a retail pharmacy or in a patient's home). If restricted to medically supervised settings in which sufentanil sublingual tablet 30 mcg was studied, such as hospitals, emergency departments, and surgery centers, it would reduce the risk of accidental exposure and ensure that sufentanil sublingual tablet 30 mcg is administered by a

HCP who is able to manage acute respiratory depression in a setting equipped for opioid overdose. This REMS will not specifically address the risks of abuse, misuse, and addiction because this product will be used exclusively in inpatient settings and other opioids intended for inpatient use have not required a REMS to mitigate these risks.

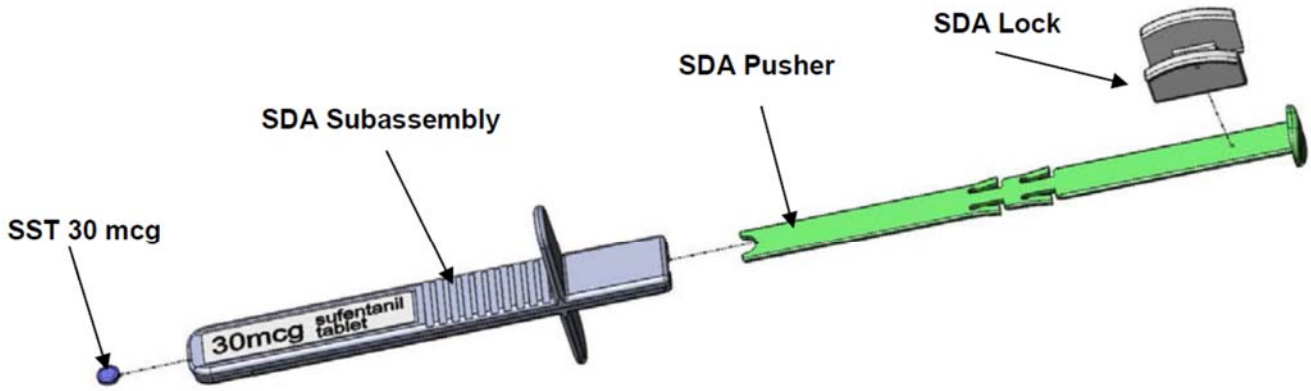
The Agency's proposed REMS may support the safe use of sufentanil sublingual tablet 30 mcg while imposing the minimal burden for prescribers, dispensers, and the targeted patient population.

10 Appendix

10.1. Applicant's Proposed Directions for Use



10.2. Exploded View Figure of Single-dose Applicator



Source: 3.2.P.7.1.2: Page 2. Submitted on December 12, 2016

10.2. CDTL/Division Director Review from First Cycle

Combined Cross-Discipline Team Leader Review And Summary Review for Regulatory Action

Date	(electronic stamp)
Cross-Discipline Team Leader	Joshua Lloyd, MD
Division Director	Sharon Hertz, MD
NDA	209128
Applicant	AcelRx Pharmaceuticals, Inc.
Date of Submission	December 12, 2016
PDUFA Goal Date	October 12, 2017
Proprietary Name / Established (USAN) names	Dsuvia / Sufentanil
Dosage form / Strength	Sublingual tablet / 30 mcg
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
Recommended:	Complete Response

1. Introduction

AcelRx Pharmaceuticals, Inc. submitted this 505(b)(2) new drug application (NDA) for Dsuvia, a drug-device combination product containing 30 mcg of the potent opioid agonist, sufentanil, for use as an analgesic in a medically-supervised setting. The product is intended to be administered by a healthcare provider on an as-needed basis with a minimum interval of one hour between doses.

The NDA references the agency's prior finding of safety and efficacy for Sufenta (sufentanil citrate for injection; NDA 19050; Akorn, Inc.), which was approved in 1984 and is indicated for intravenous administration in adults and pediatric patients as an adjunctive and a primary anesthetic and for epidural administration as an analgesic in the setting of labor and vaginal delivery. Sufentanil is currently only approved as a solution for injection. However, the Applicant previously submitted NDA 205265 for Zalviso, another sufentanil sublingual tablet drug-device combination product that, in contrast to Dsuvia, contains 15 mcg of sufentanil and was intended to be administered by the patient using a different device. The Zalviso application received a complete response, primarily due to issues surrounding the device and inadvertent loss of dispensed tablets.

The application is supported by data from a Phase 3 placebo-controlled trial, two Phase 3 open-label studies[1], and the Zalviso program, as well as CMC/device, pharmacology/ toxicology, clinical pharmacology, and human factors data.

[1] The clinical development program was conducted under IND 113059.

2. Background

Sufentanil is a Schedule II synthetic opioid agonist that is approximately five to ten times more potent than fentanyl at the mu-opioid receptor and, like fentanyl, has low oral bioavailability. Dsuvia was developed as a healthcare professional (HCP)-administered product designed to deliver sufentanil via the sublingual route using a single dose applicator (SDA) to provide acute onset of analgesia without having to establish intravenous (IV) access. The Applicant states that the product may be useful in situations where IV access may be limited or is otherwise not desirable.

The Division held End-of-Phase 2 and Pre-NDA meetings with the Applicant during clinical development where, among other things, agreement was reached on the amount of safety data that would be required for an NDA. Further, agreement was reached that the safety of Dsuvia may, in part, be supported by patients who were administered two doses of Zalviso 15 mcg, given 20 minutes apart, provided that clinical pharmacology data support that similar exposures to sufentanil are observed compared to a single dose of Dsuvia 30 mcg.

3. CMC/Biopharmaceutics/Device

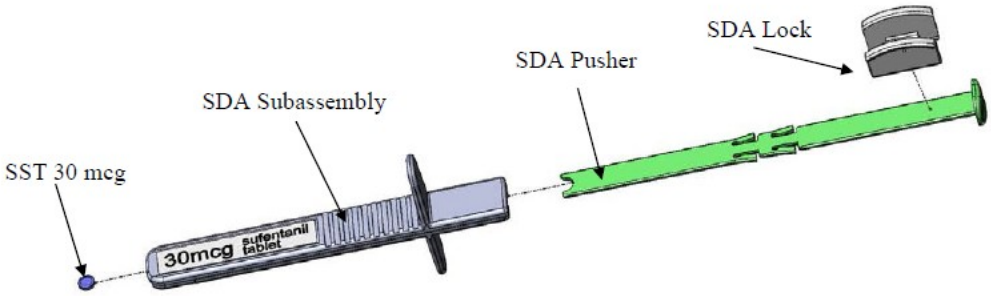
CMC

The drug component of this drug-device combination product consists of an immediate-release sublingual tablet containing 30 mcg of sufentanil. DMF 14505 for the drug substance was found to be adequate.

The tablet measures 3 mm in diameter and 0.85 mm in thickness with a nominal tablet weight of 7.40 mg. All of the excipients are compendial and tested to USP requirements. Each disposable single dose applicator (SDA) contains one tablet and is intended for single use. The primary package consists of the SDA co-packaged with an oxygen absorber –StabilOX– in a labeled, heat-sealed laminate foil pouch.

Figure 3.2.P.7.2: 1 Single Dose Applicator

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



A chipped tablet was found during stability at the initial time point. However, the CMC team found this to be acceptable, as the Applicant has sampling plans in place that will reject a defective batch 90% of the time, which CMC deemed to be an appropriate industry standard.

The drug product specifications will include (b) (4), at the request of the CMC team, until sufficient data are attained to confirm understanding and control of the process. At that point, the Applicant would be able to submit a prior approval supplement to remove this testing from the specifications.

Biopharmaceutics

The proposed dissolution method and acceptance criterion were found to be adequate.

CMC, based on recommendations from drug substance, drug product, process, facilities, and biopharmaceutics reviewers, recommends approval of this application, and I concur with their conclusions. The manufacturing facilities were deemed acceptable. A 24-month expiry at 20° to 25°C with excursions to 15° to 30°C was granted. The request for a categorical exclusion from the requirement to prepare an environmental assessment was determined to be acceptable. The Applicant included a post-approval stability protocol and commitment testing stability out to 36 months.

Device

The device constituent of this product consists of the SDA, which is intended for storage and to deliver sufentanil to the sublingual space. The HCP is directed to remove the SDA lock, place the SDA tip under the patient's tongue, and depress the green pusher to administer the sufentanil tablet to the sublingual space.

CDRH was consulted, and their evaluation included the following areas:

- Design controls, verification/validation, and risk analysis
- Biocompatibility of the SDA with respect to the sublingual space
- Environment of use

CDRH determined that adequate documentation was provided to support the design control process and found the performance requirements to be adequate. The expiry and shelf-life are two years. However, the CDRH reviewer stated that "[t]he [Applicant] has 18-months chemical stability and functional testing of the finished device, including device performance and has conducted 3 year accelerated aging studies. The real-time 3 year aging studies are ongoing and will be requested as a post approval commitment."

The design validation review consisted of an evaluation of device failures in the clinical study; human factors were evaluated separately.[2] The Applicant evaluated clinical device usability and reliability in the context of the Phase 3 clinical study, SAP303. There were three suspected SDA failures, which consisted of two instances of the tablet missing from the SDA or loose within the pouch and one instance of a dropped tablet by the HCP prior to dosing the patient. In the case of the dropped tablet, the tablet was found and secured. In the case involving a tablet missing from the SDA, the Applicant determined that a manufacturing error had occurred. In the case involving a loose tablet in the pouch, the Applicant determined that the HCP unsuccessfully attempted to open the pouch using scissors and subsequently tore open the package, which resulted in actuation of the SDA. The Applicant also evaluated usability through a questionnaire in this study. However, the questionnaire was administered to nine HCPs only. The CDRH device reviewer determined this to be insufficient to establish usability and deferred to the human factors review. However, the CDRH device reviewer noted that device-specific failures were low across all three Phase 3 clinical studies and were eliminated as development continued.

It is worth noting that the original device iteration was used in the two Phase 3 studies (SAP301 and SAP302), and both the original and revised device iterations were used in the third Phase 3 study (SAP303). The revised device iteration incorporated minor changes to optimize usability and manufacturing, and CDRH determined that these changes do not impact the results of the clinical study and were properly evaluated.

[2] The CDRH device review notes that a separate CDRH human factors consult was performed by Xin Feng in CDRH. However, Carolyn Dorgan, the lead CDRH reviewer confirmed over email on 10/6/2017 that a separate CDRH human factors review was not needed.

The Applicant conducted design verification testing under a variety of conditions. In mouth testing demonstrated that 100% of tablets were delivered to the mouth (acceptance criterion ≥99%); however, only 93.1% were delivered to the sublingual space (acceptance criterion ≥95%) with four tablets landing inside the cheek and one on a tooth. The Applicant found these results acceptable because delivery to the areas of the mouth other than the sublingual space will still result in bioavailability in the range observed with sublingual delivery, none were swallowed (which would result in very low bioavailability), and that this study was intended to be a design verification test rather than a validation test. Design validation will occur in the context of human factors testing. The CDRH reviewer noted that "[t]he [Applicant] has identified the critical performance attribute and design requirements per the design control procedures. The attributes were then verified…All device[s] met the product requirement[s] within the predetermined acceptance criteria."

The biocompatibility reviewer noted cytotoxicity, sensitization, intradermal irritation, and oral irritation assessments conducted by the Applicant and found them to be acceptable.

CDRH notes that "[t]he Sponsor's risk analysis and hazard identification processes have adequately captured the use and design risks associated with the device. The lead reviewer concurs with the mitigations for the use and design related risks. All risks have been reduced to as low a level as possible. Therefore [this] is acceptable." CDRH found the batch release criteria for the SDA to be acceptable. The CDRH device and biocompatibility review teams recommended approval for the device constituent of the product with the following post-marketing commitment:

> Provide real time stability data for the SDA Dispensing Test according to the protocols described in the Post-approval Stability Protocol and Stability Commitment located in Seq 0000/3.2.P.8.2 of NDA 209128.

The CDRH Office of Compliance has recommended post-approval inspections of AcelRx Pharmaceuticals and Patheon Pharmaceuticals, Inc., and recommended approval from the perspective of the applicable quality system requirements described under the 21 CFR Part 820 regulations.

I concur with the conclusions reached by the CDRH review team that there are no outstanding CDRH issues that preclude approval.

Human Factors

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the human factors validation study results. The human factors validation study was conducted in 45 untrained participants that included 15 PACU/floor nurses, 15 ER nurses, and 15 paramedics. Participants were provided the directions for use (DFU) and were instructed to read the DFU prior to attempting the tasks. Each participant was asked to administer the medication four times. Three of the scenarios involved administration to three different mock patients, and, in the fourth scenario, participants were given torn packaging and asked to administer the medication to a mock patient to see how this situation may be handled with real-world use. At

the end of the session participants responded to questions regarding important warnings and precautions or critical safety information in the DFU.

DMEPA identified failures related to both essential and critical tasks. DMEPA noted eight failures associated with a critical task to confirm tablet placement in the patient's sublingual space. Failures related to this task are of critical importance because, if an HCP does not confirm accurate placement of the tablet in the sublingual space, a dropped tablet may go undetected. Sufentanil is a highly potent opioid, and dropped tablets pose significant risks to both the patient and others who may knowingly or unknowingly come in contact with the tablet. These risks include overdose and death due to accidental exposure in contacts, improper dosing in patients (i.e., over- or under-dosing and their associated risks), and the risk of diversion and its associated public health consequences. As a result, DMEPA recommended changes to the DFU that will require another human factors validation study to evaluate the effectiveness of the changes to address the observed use-related errors. DMEPA also noted additional failures involving critical and essential tasks for which they did not have any recommendations and found the residual risk to be acceptable.

I concur with the conclusions reached by the DMEPA review team; the outstanding human factors issues preclude approval at this time.

4. Nonclinical Pharmacology/Toxicology

To support a change in route of administration from the reference product, the Applicant conducted repeat-dose buccal irritation/toxicity studies in hamsters. The Applicant also submitted results from genetic toxicity studies for sufentanil impurities.

Dr. Lee notes that:

> The repeat-dose cheek pouch studies in hamsters demonstrated that buccally administered sufentanil showed no local tissue reactions in the cheek pouch. Genetic toxicology studies were conducted for the drug product degradants. Both the cis and trans isomers of (b) (4) tested negative in the in vitro bacterial reverse mutation assays and therefore, these impurities may be regulated as non-genotoxic impurities. Additionally, the Applicant has conducted in silico assessments using the DEREK and Leadscope programs on two other degradants NPPA and NHPA, and these analyses did not identify any potential mutagenic/genotoxic activity for either compound. CDER Office of Transitional Science evaluation confirmed the results of the Applicant's in silico analyses.
>
> Therefore, the proposed drug substance and drug product specifications are acceptable, the excipients have been adequately qualified for safety, and the nonclinical local tissue toxicity study results do not raise any safety concerns for the proposed indication.

I concur with the nonclinical review team that there are no pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology

The Applicant submitted the results of one clinical pharmacology study—SAP101—using the final to-be-marketed formulation. SAP101 was a randomized, open-label, crossover, comparative bioavailability study conducted in healthy adult volunteers who received naltrexone to block the pharmacodynamics effects of the opioid. The treatment groups consisted of:

- Sufentanil IV (Sufenta; 50 mcg/ml); 30 mcg infused over 1 minute
- Sufentanil sublingual tablet 30 mcg; single dose (Dsuvia)
- Sufentanil sublingual tablet 15 mcg; 2 doses administered 20 minutes apart (Zalviso)
- Sufentanil sublingual tablet 30 mcg; 12 doses administered 1 hour apart (Dsuvia)

SAP101 was conducted to establish a pharmacokinetic (PK) bridge between Dsuvia and the reference product, Sufenta, as the basis for relying on the agency's previous finding of safety and efficacy for Sufenta. The study was also intended to describe the multiple-dose PK for Dsuvia and to serve as the basis for referencing a select group of Zalviso-treated patients in support of the safety of Dsuvia.

The results of SAP101 demonstrated that the systemic exposure to sufentanil was lower with a single dose of Dsuvia than with Sufenta IV and that the absolute bioavailability of Dsuvia was 53%. A single dose of Dsuvia was bioequivalent to two doses of Zalviso administered 20 minutes apart, and the Tmax was comparable. The results are summarized in the table and figures below.

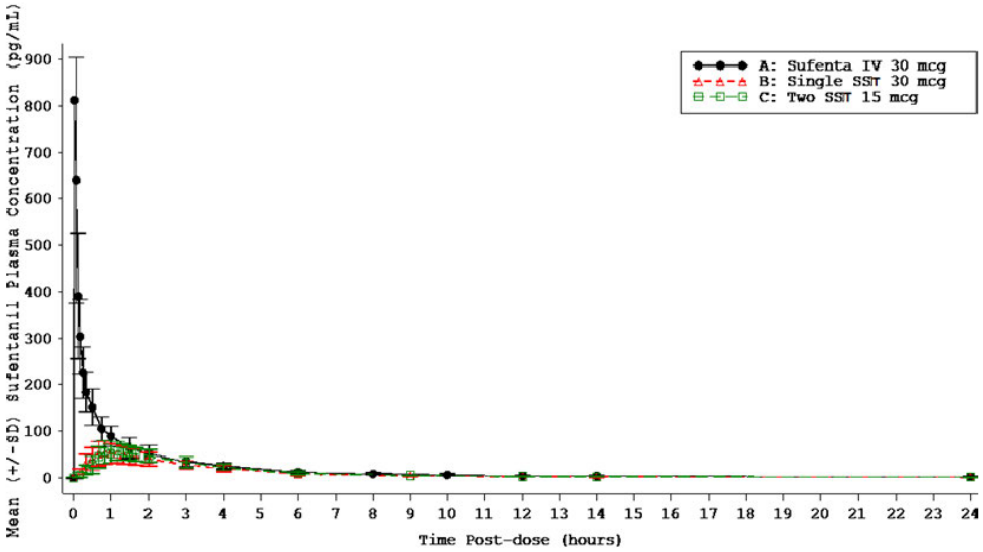
Mean ± SD (%CV) Sufentanil Pharmacokinetic Parameters for a Single Dose of Sufenta IV 30 mcg, a Single Sublingual Dose of Sufentanil Sublingual Tablet (SST) 30 mcg (Dsuvia), and Two Sublingual Doses of SST 15 mcg dosed 20 minutes apart (Zalviso) in Healthy Subjects under Naltrexone Block

PK Parameter	Sufenta IV 30 mcg (n = 35)	Dsuvia 30 mcg (n = 35)	Zalviso 2 x SST 15 mcg (n = 35)
AUCinf (pg.h/mL)	539.68 ± 112.12 (20.96%)	277.68 ± 84.36 (30.38%)	307.30 ± 79.08 (25.73%)
Cmax (pg/mL)	1073.94 ± 968.17 (90.15%)	63.14 ± 23.49 (37.21%)	66.00 ± 20.38 (30.88%)
T1/2 (h)	13.72 ± 6.12 (44.6%)	13.37 ± 8.89 (66.5%)	15.66 ± 9.38 (59.9%)
Tmax (h)[a]	0.07 (0.02, 0.17)	1.00 (0.50, 2.00)	1.17 (0.67, 2.00)
CL (mL/h)	57878 ± 11446 (20%)	--	--
Amount Absorbed (mcg)	30 mcg	15.9 ± 5.2 (32.7%)	17.6 ± 5.2 (29.5%)
F (%)	--	52.86 ± 17.22 (32.6%)	58.76 ± 17.50 (29.8%)
Geometric Mean Ratio (1 x SST 30 mcg/2 x SST 15 mcg) % (90% CI)			
AUCinf		0.89 (0.81, 0.97)	
Cmax		0.93 (0.84, 1.03)	

[a] tmax reported as median (min, max)

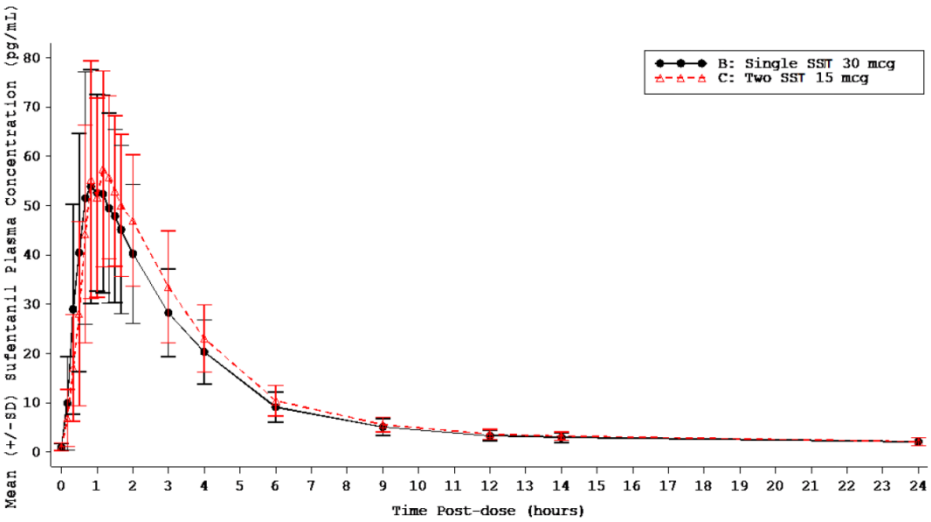
Adapted from Dr. Qiu's review, pg. 3

Mean (± SD) Sufentanil Plasma Concentration Versus Time for Treatments A (Sufenta IV 30 mcg), B (Sufentanil Sublingual Tablet [SST] 30 mcg; Dsuvia), and C (2 doses of SST 15 mcg dosed 20 minutes apart; Zalviso)



Adapted from Dr. Qiu's review, pg. 10

Mean (± SD) Sufentanil Plasma Concentration Versus Time for Treatments B (Sufentanil Sublingual Tablet [SST] 30 mcg; Dsuvia) and C (2 doses of SST 15 mcg dosed 20 minutes apart; Zalviso)

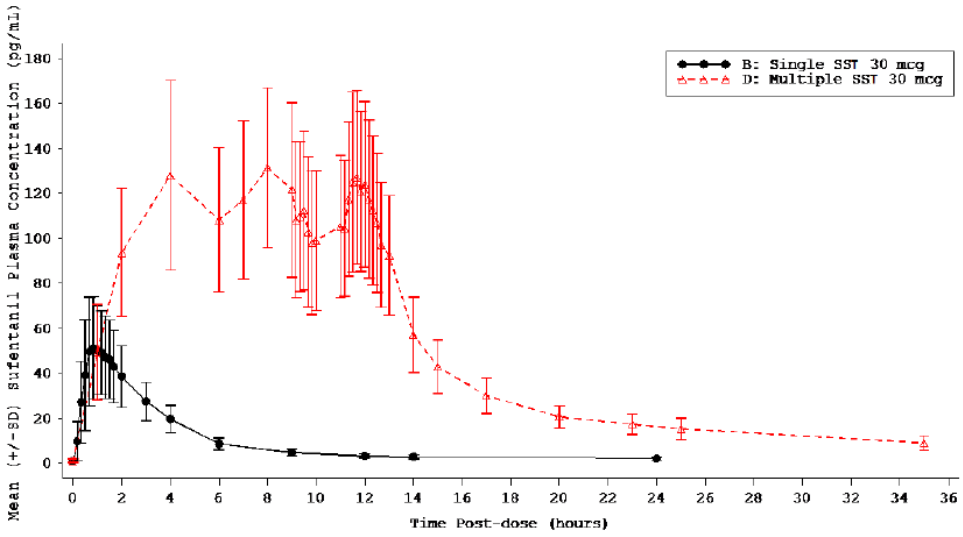


Adapted from Dr. Qiu's review, pg. 10

The Applicant also submitted PK modeling/simulation data, and, taken together with the above PK results, the clinical pharmacology review team concluded that these findings provide support to bridge the systemic safety results for two doses of Zalviso administered 20 to 25 minutes apart to Dsuvia.

Steady state was reached after seven doses of Dsuvia that were administered one hour apart (i.e., after 360 minutes) with the AUC within a dosing interval (i.e., AUC0-60 min) and Cmax values increased by 3.7 and 2.3 fold, respectively, after multiple dosing. Multiple dose PK results are summarized in the table and figure below.

Mean (± SD) Sufentanil Plasma Concentration versus Time for Treatments B (single dose Sufentanil Sublingual Tablet [SST] 30 mcg; Dsuvia) and D (12 x SST 30 mcg administered every hour; Dsuvia)



Abbreviations: SD = standard deviation; SST = sufentanil sublingual tablet.
Treatment B: single dose of SST 30 mcg.
Treatment D: multiple (12 consecutive) doses of SST 30 mcg administered 1 hour apart.

Adapted from Dr. Qiu's review, pg. 13

Sufentanil Pharmacokinetic Parameters for Single Dose Sufentanil Sublingual Tablet (SST) 30 mcg (Treatment B; Dsuvia) and Multiple Dose SST 30 mcg (Treatment D: 12 x SST 30 mcg administered every hour; Dsuvia)

Parameter	Single SST 30 mcg (n = 32)	12th Dose of SST 30 mcg (n = 32)
AUCinf (pg h/mL)	269.82 ± 79.51 (29.47%)	--
AUC0-60min (pg h/mL)	33.71 ± 16.23 (48.15%)	118.25 ± 34.45 (29.13%)
AUC0-720min (pg h/mL)	196.26 ± 61.76 (31.47%)	--
Cmax (pg/mL)	60.55 ± 22.65 (37.40%)[a]	134.12 ± 39.51 (29.46%)
T1/2 (h)	14.12 ± 9.09 (64.3%)	12.68 ± 4.31 (34.0%)
Tmax (h)[a]	1.00 (0.50, 2.00)	0.67 (0.33, 1.33)
Geometric Mean Ratio (Last Dose (12th) of SST 30 mcg Q1H/Single Dose SST 30 mcg) (90% CI)		
AUC0-60min	3.74 (3.25 – 4.31)	
Cmax	2.27 (2.01 – 2.56)	

[a] tmax reported as median (min, max)

Adapted from Dr. Qiu's review, pg. 13

The Applicant also submitted a population PK analysis, and the clinical pharmacology review team concluded that no dosage adjustments are required based on age or weight. Insufficient data are available in moderate or severe kidney or hepatic impairment. The Applicant did not evaluate the impact of hot, cold, and various pH liquids or the impact of mucositis on sufentanil PK. The Applicant has proposed to address this by restricting these conditions in labeling, and the Division agreed to this approach during clinical development.

I concur with the conclusions reached by the clinical pharmacology review team that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The Applicant submitted the results of one Phase 3, randomized, double-blind, placebo-controlled trial that used the final to-be-marketed sufentanil formulation. Dr. Galati and Dr. Ren conducted a full review of this study, as it is the pivotal trial intended to demonstrate efficacy in acute pain for Dsuvia. I will review the salient study design features and describe the key efficacy results below.

Study SAP301

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of the Sufentanil Sublingual Tablet 30 mcg for the Treatment of Post-Operative Pain in Patients after Abdominal Surgery

Primary objective: To compare the analgesic efficacy of Dsuvia to placebo in patients with acute moderate-to-severe pain following outpatient abdominal surgery

Duration of treatment: 48 hours

Population: Adults with moderate-to-severe acute postoperative pain following outpatient abdominal surgery, including abdominoplasty, open tension-free inguinal hernioplasty (Lichenstein repair with mesh), or laparoscopic abdominal surgery

Treatment: Patients were randomized in a 2:1 fashion to receive Dsuvia 30 mcg or placebo administered using the SDA as needed with a minimum of one hour between doses

Rescue medication: Morphine 1 mg IV, no sooner than 10 minutes after study drug administration and as long as the patient was not otherwise eligible to receive another dose of study drug

Design: The study was a multicenter (conducted at four sites in the U.S.), randomized, double-blind, placebo-controlled trial that consisted of a screening visit, an admission for surgery visit, and an up to 48-hour treatment period. Patients were allowed standard-of-care postoperative pain management but needed to have a postoperative pain intensity of ≥4 on an 11-point numeric rating scale (NRS) to be randomized. Patients who did not meet that criterion within 8 hours were discontinued. Patients who remained in the study for 24 or more

hours were considered completers. Patients were required to have a pain intensity of ≥4 on an NRS to continue treatment beyond 24 hours.

Primary efficacy endpoint: Time-weighted summed pain intensity difference (SPID) over 12 hours[3] based on an 11-point NRS (0-10)

Secondary efficacy endpoints: The Applicant included several secondary efficacy endpoints (refer to Dr. Galati's review), including the following:

- SPID24 and SPID48
- Pain intensity and pain intensity difference at each time point
- Proportion of patients requiring rescue
- Time to first use of rescue
- Total number of study medication and rescue medication doses used over the 48-hour study period
- Time to onset of perceptible and meaningful pain relief

Statistical analysis plan: The efficacy analyses were performed on the intent-to-treat (ITT) population, which included all randomized patients who received study drug. The primary efficacy analysis was an analysis of covariance (ANCOVA) model that used treatment, center, and sex as factors and baseline pain intensity score as a covariate. A pre-rescue pain intensity score was carried forward for one hour following the dosing of rescue medication. Regarding missing data, Dr. Ren noted that the Applicant's method was designed to not attribute a favorable pain score to a subject who discontinued early due to an adverse event or lack of efficacy, however, that it was a single imputation method, which is not desirable. Therefore, Dr. Ren performed a sensitivity analysis using a multiple imputation method.

Results: A total of 161 patients were randomized and received study drug. Most of the patients were under 65 and female; however, treatment groups were balanced with respect to baseline characteristics and demographics. Half of the surgeries were abdominoplasty with the remaining 30% laparoscopic abdominal surgery and 21% hernioplasty. Most Dsuvia-treated subjects completed the 12- and 24-hour treatment periods. As expected, fewer placebo-treated subjects completed those same periods due, in large part, to discontinuation due to lack of efficacy. Overall very few patients discontinued due to an adverse event. As the study progressed into the 24 to 48 hour treatment period, the vast majority of discontinuations were due to patients no longer requiring treatment. Patient disposition is summarized in the table below.

[3] Although a SPID24 or SPID48 are more typical for an acute pain setting, the Division agreed to a SPID12 in this particular outpatient surgery acute pain setting provided the Applicant continued to evaluate pain intensity for 48 hours.

Patient Disposition

	Sufentanil 30 mcg	Placebo	Total
Randomized	109	54	163
Did not receive treatment	2	0	2
Included in the ITT population for efficacy analyses	107 (100%)	54 (100%)	161 (100%)
12-Hour Study Period			
Completed the 12-hour study period	104 (97.2%)	43 (79.6%)	147 (91.3%)
Discontinued during the 12 hours	3 (2.8%)	11 (20.4%)	14 (8.7%)
Reason for discontinuation:			
Lack of efficacy	3 (2.8%)	8 (14.8%)	11 (6.8%)
Adverse event	0	2 (3.7%)	2 (1.2%)
Protocol Violation	0	1 (1.9%)	1 (0.6%)
24-Hour Study Period			
Completed the 24-hour study period	102 (95.3%)	41 (75.9%)	143 (88.8%)
Discontinued between 12 and 24 hours	2 (1.9%)	2 (3.7%)	4 (2.4%)
Reason for discontinuation:			
Lack of efficacy	1 (0.9%)	2 (3.7%)	3 (1.8%)
Withdrawal by subject	1 (0.9%)	0	1 (0.6%)
36-Hour Study Period			
Completed the 36-hour study period	22 (20.6%)	9 (16.7%)	31 (19.3%)
Completed 24 hours but did not enter the 36-hour study period	62 (57.9%)	28 (51.9%)	90 (55.9%)
Reason for not entering			
Patient discharged	49 (45.8%)	18 (33.3%)	67 (41.6%)
Recovery	13 (12.1%)	8 (14.8%)	21 (13.0%)
Lack of efficacy	0	2 (3.7%)	2 (1.2%)
Discontinued between 24 and 36 hours	18 (16.8%)	4 (7.4%)	22 (13.7%)
Reason for discontinuation:			
Recovery	15 (14.0%)	4 (7.4%)	19 (11.8%)
Lack of Efficacy	2 (1.9%)	0 (0.0%)	2 (1.2%)
Adverse event	1 (0.9%)	0 (0.0%)	1 (0.6%)
48-Hour Study Period			
Completed the 48-hour study period	10 (9.3%)	8 (14.8%)	18 (11.2%)
Completed 36 hours but did not enter the 48-hour study period	1 (1.9%)	0	1 (0.6%)
Reason for not entering			
Recovery	1 (0.9%)	0 (0.0%)	1 (0.6%)
Discontinued during the 48 hours	11 (10.3%)	1 (1.9%)	12 (7.5%)
Reason for discontinuation:			
Recovery	11 (10.3%)	0	11 (6.8%)
Withdrawal by subject	0	1 (1.9%)	1 (0.6%)

Source: Dr. Ren's Review, pp. 10-11

There was a statistically significant difference ($p < 0.001$) between treatment groups on the primary endpoint, time-weighted SPID12, as shown in the table below.

Primary Efficacy Analysis Results for SPID12

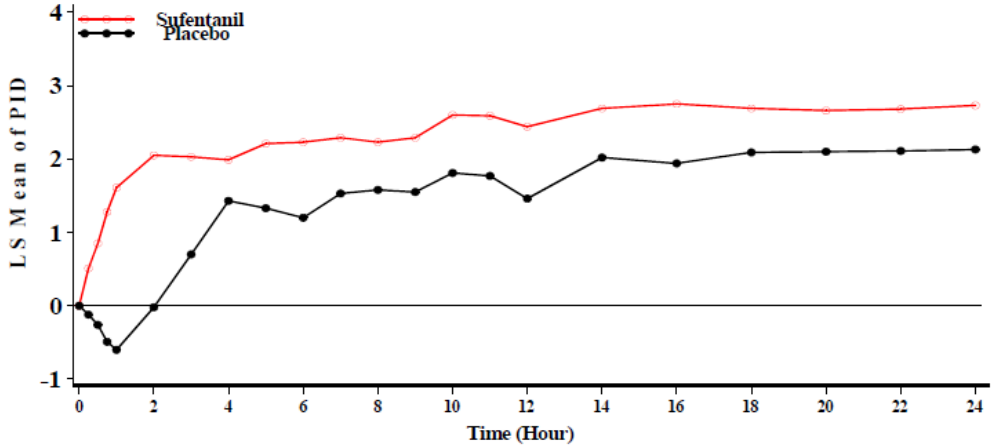
	Sufentanil (n=107)	Placebo (n=54)	P-value
Baseline Pain Intensity			
Mean (SD)	5.79 (1.75)	5.59 (1.56)	
Range	(3.00, 10.00)	(4.00, 9.00)	
LS mean (SEM)	5.87 (0.15)	5.73 (0.20)	
95% CI	(5.58, 6.17)	(5.34, 6.13)	
Difference			
LS mean (SEM)	0.14 (0.23)	NA	0.543
95% CI	(-0.31, 0.59)		
SPID12			
Mean (SD)	25.93 (20.25)	11.88 (19.47)	
Range	(-42.15, 71.87)	(-34.96, 64.37)	
LS mean (SEM)	26.36 (1.83)	13.66 (2.44)	
95% CI	(22.74, 29.98)	(8.83, 18.48)	
Difference			
LS mean (SEM)	12.70 (2.80)	NA	<0.001
95% CI	(7.17, 18.24)		

Source: Dr. Ren's review, pg. 12
SD: standard deviation
SEM: standard error of the LS mean

The results of Dr. Ren's sensitivity analysis to address the lack of a multiple imputation strategy were consistent with the primary analysis.

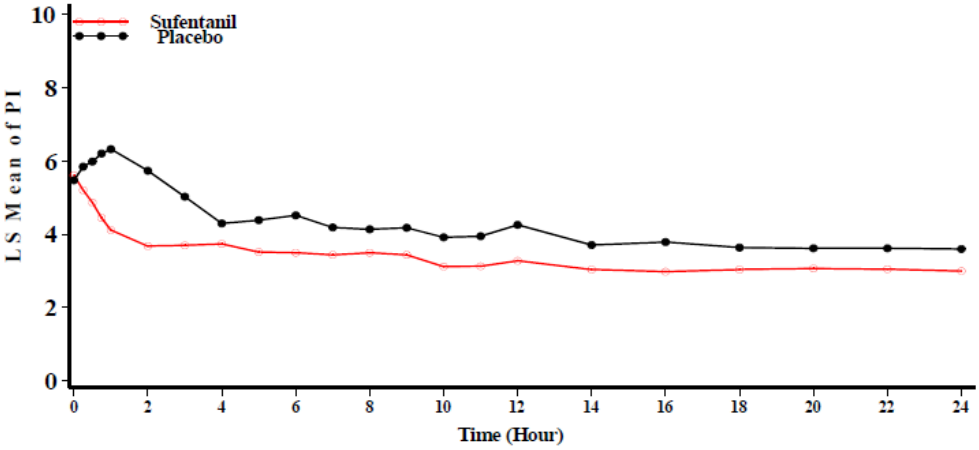
Pain intensity difference and pain intensity over the first 24 hours are summarized in the figures below, respectively.

Least Squares Mean of Pain Intensity Difference by Evaluation Time Point Over the 24-Hour Study Period: ITT Population



ITT: intent-to-treat; LS: least squares; PID: pain intensity difference.
Source: Applicant's Clinical Study Report for SAP301, pg. 67

Least Squares Mean of Pain Intensity by Evaluation Time Point Over the 24-Hour Study Period: ITT Population



ITT: intent-to-treat; LS: least squares; PI: pain intensity.
Source: Applicant's Clinical Study Report for SAP301, pg. 67

Dsuvia-treated patients required less rescue analgesics and had a longer time to first rescue use compared to placebo, which is consistent with a treatment effect favoring Dsuvia. Approximately 27% of patients required rescue medication in the Dsuvia group compared to approximately 65% in the placebo group in the first 24 hours. Dr. Ren performed a Kaplan-Meier analysis for time to first rescue and found that there was a statistically significant difference between Dsuvia and placebo over the first 12 hours and over the entire 48-hour treatment period. Dsuvia-treated patients consistently required less rescue doses over the course of the study compared to placebo, as summarized in the table below.

Number of Rescue Morphine Doses Used by Study Period: ITT Population

Number of Doses Used	Sufentanil 30 mcg (n = 107)	Placebo (n = 54)	p-value [1]
0 - 6 Hours: n (%)			< 0.001
0	89 (83.2%)	21 (38.9%)	
1 – 2	15 (14.0%)	27 (50.0%)	
3 – 4	3 (2.8%)	5 (9.3%)	
> 4	0	1 (1.9%)	
Mean (SD) number of doses used	0.3 (0.7)	1.1 (1.1)	< 0.001
Median	0.0	1.0	
(Min, max)	(0.0, 4.0)	(0.0, 5.0)	
0 - 12 Hours: n (%)			< 0.001
0	83 (77.6%)	19 (35.2%)	
1 – 2	21 (19.6%)	24 (44.4%)	
3 – 4	1 (0.9%)	6 (11.1%)	
> 4	2 (1.9%)	5 (9.3%)	
Mean (SD) number of doses used	0.4 (1.0)	1.6 (1.8)	< 0.001
Median	0.0	1.0	
(Min, max)	(0.0, 7.0)	(0.0, 8.0)	
0 - 24 Hours: n (%)			< 0.001
0	78 (72.9%)	19 (35.2%)	
1 – 2	24 (22.4%)	18 (33.3%)	
3 – 4	2 (1.9%)	8 (14.8%)	
> 4	3 (2.8%)	9 (16.7%)	
Mean (SD) number of doses used	0.5 (1.4)	2.1 (2.9)	< 0.001
Median	0.0	1.0	
(Min, max)	(0.0, 11.0)	(0.0, 14.0)	
Total No. of Doses Used for Entire Study Period: n (%)			< 0.001
0	78 (72.9%)	19 (35.2%)	
1 – 2	23 (21.5%)	18 (33.3%)	
3 – 4	2 (1.9%)	8 (14.8%)	
> 4	4 (3.7%)	9 (16.7%)	
Mean (SD) total number of doses used	0.6 (1.6)	2.4 (3.7)	0.001
Median	0.0	1.0	
(Min, max)	(0.0, 13.0)	(0.0, 19.0)	

ITT: intent-to-treat; SD: standard deviation
Source: Applicant's Clinical Study Report for SAP301, pg. 81

The median time to meaningful pain relief was 54 minutes for the Dsuvia group and 84 minutes for the placebo group. Dr. Ren's Kaplan-Meier analysis revealed that the time to meaningful pain relief was shorter for Dsuvia compared to placebo over the first 12 hours but that the difference was not statistically significant.

In the first 12- and 24-hour study periods, the mean duration between doses was approximately 3 to 3.5 hours for the Dsuvia group, as summarized below.

Mean Duration of the Inter-dosing Interval During the 12-Hour and 24-Hour Study Periods: ITT Population

	Sufentanil 30 mcg (n = 101)	Placebo (n = 52)	p-value [1]
12-Hour Study Period			
Mean (SD)	181.40 (85.24)	143.12 (83.11)	
LS mean (SEM)	185.41 (8.80)	146.55 (11.97)	0.008
95% CI	(168.02, 202.80)	(122.90, 170.19)	
Difference†			
LS mean (SEM)	38.87(14.39)	NA	
95% CI	(10.44, 67.29)		
24-Hour Study Period			
Mean (SD)	217.78 (95.78)	185.85 (120.68)	
LS mean (SEM)	220.81 (10.87)	189.82 (14.78)	0.083
95% CI	(199.33, 242.29)	(160.61, 219.03)	
Difference†			
LS mean (SEM)	30.99 (17.77)	NA	
95% CI	(-4.12, 66.10)		

†Sufentanil minus placebo.
CI: confidence interval; ITT: intent-to-treat; LS: least squares; SD: standard deviation; SEM: standard error of the LS mean.
Source: Applicant's Clinical Study Report for SAP301, pg. 79

Dr. Ren was able to reproduce the results of all primary and secondary analyses and concluded that there is sufficient evidence to support the efficacy of Dsuvia 30 mcg for management of moderate-to-severe acute pain. Dr. Galati also concluded that the primary and supporting secondary efficacy results demonstrated superior efficacy for Dsuvia compared to placebo.

I concur with the conclusions reached by the statistical and primary clinical reviewers that there are no outstanding efficacy issues that preclude approval.

8. Safety

Dr. Galati conducted a review of the safety of Dsuvia, which was based on four clinical studies in the Dsuvia program and selected patients from the Zalviso program that received the first dose of sufentanil sublingual tablet 15 mcg followed by a second dose of sufentanil sublingual tablet 15 mcg within 20 to 25 minutes.[4] Subsequent dosing in the Zalviso-treated patients was on an as needed basis with a 15 mcg dose of sufentanil sublingual tablet and a 20 minute lockout between doses. As stated above in Section 5 of this review, the clinical pharmacology team determined that the Applicant provided sufficient support to allow these Zalviso-treated patients to contribute to the evaluation of safety for Dsuvia.

The Applicant conducted three Phase 3 clinical studies—SAP301 (the pivotal Phase 3 efficacy trial) and SAP302 and SAP303 (open-label safety studies)—and one Phase 1 relative

[4] This included data from six Zalviso studies in patients with postoperative pain after open abdominal surgery, total knee arthroplasty, or total hip arthroplasty; refer to Dr. Galati's review for more details.

bioavailability study (SAP101) using the final to-be-marketed sufentanil formulation. The designs of SAP301 and SAP101 have been discussed previously. SAP302 was a multicenter, open-label study in patients 18 years of age and older who were being treated in the emergency department for moderate-to-severe acute pain due to obvious trauma or injury. Patients could receive up to four doses in the five hour treatment period. SAP303 was a multicenter, open-label study in patients 40 years of age and older who underwent a surgical procedure requiring general anesthesia or spinal anesthesia that did not include intrathecal opioids and who were experiencing acute postoperative pain of at least 4 on an 11-point NRS. The study included a 12-hour treatment period.

The Applicant additionally conducted a Phase 2, randomized, double-blind study in a bunionectomy pain population (SAP202). However, this study was conducted using a different formulation, and the Applicant's submitted in vitro data were not sufficient to bridge the formulation used to the final to-be-marketed formulation. Therefore, the safety data from this study do not support the safety of Dsuvia.

During clinical development, the Division agreed that an overall safety database of at least 500 patients would be required with at least 350 of those treated with Dsuvia and at least 100 patients treated with multiple doses. An assessment of the clinical safety of Dsuvia requires an understanding of the safety of the proposed dosing for sufentanil (i.e., systemic exposure to sufentanil) and the safety of the product as a whole, that is, the safety of sufentanil in combination with the SDA device. Overall, 646 patients were treated with sufentanil sublingual tablets, with 323 of those exposed to Dsuvia and 323 exposed to Zalviso.[5] Very few patients were treated with Dsuvia for 24 hours and beyond, which is expected given the design of the studies and the nature of the patient populations studied. The value of the Zalviso-treated patients is that they provide experience with a duration of exposure to sufentanil of up to 48 hours or more.[6] There were also a greater number of Zalviso-treated patients that were elderly and who underwent major surgery, as compared to Dsuvia.[7] Dr. Galati concluded that the submitted safety database was adequate to inform the safety of Dsuvia, despite the Applicant having not provided 350 overall exposures to Dsuvia. I concur with this assessment given the indication and planned restricted setting of use, the prior findings for Sufenta, and the overall size of the safety database when the Zalviso-treated patients are included.

Deaths and non-fatal Serious Adverse Events (SAEs)

There were no deaths in the Dsuvia program. There was one death in a 69 year-old female with a history of hypertension, hypercholesterolemia, and gout who underwent a unilateral total knee replacement patient and received Zalviso postoperatively. The patient received six doses of sufentanil for postoperative pain in the 24 hours after surgery and was taking OxyContin and ibuprofen at the time of discharge from the study. Six days after her last dose, she was re-hospitalized with pancolitis and acute renal failure and ultimately died of the renal

[5] The Applicant notes that over half of the patients who received two doses of Zalviso 20 to 25 minutes apart also received a third dose within the hour (i.e., 45 mcg/hour), which exceeds the total hourly dose received with Dsuvia.

[6] Refer to Dr. Galati's review, Table 17, pg. 47.

[7] Refer to Dr. Galati's review, Table 23, pg. 52.

failure 30 days after the knee surgery. Dr. Galati determined this case to be unlikely related to study drug, and I concur.

Two patients experienced a nonfatal serious adverse event (SAE)—one case of syncope and one case of hemiparesis—in the placebo-controlled Dsuvia study (SAP301); however, both cases occurred in the placebo group. One SAE occurred in the open-label Dsuvia studies. This was a case of chest pain in a 65 year-old female with a history of coronary artery disease/myocardial infarction, diabetes mellitus, and congestive heart failure who presented to the emergency department with a femur fracture and was treated with Dsuvia for pain. The patient subsequently developed chest pain that responded to nebulized albuterol. The study staff were then informed by the healthcare providers that the patient also experienced similar symptoms prior to having received Dsuvia, and the patient was subsequently diagnosed with a myocardial infarction.

In the Zalviso placebo-controlled group, there were three patients who experienced SAEs. The first case involved a 65 year-old female who developed a decreased oxygen saturation to 40 to 50% with periods of apnea, excess sedation, diaphoresis, and tachycardia in the evening after undergoing a total knee replacement under spinal anesthesia. She had received 14 doses of Zalviso over approximately 7 hours in the postoperative period, along with 11 mg of IV morphine over the same period, fentanyl in the context of her procedure, and oxycodone/acetaminophen. The patient responded to naloxone and study medication was discontinued. This case highlights the very real and all-too-frequent risk of opioid overdose in this setting. The second case involved an 80 year-old female who developed aspiration pneumonia and pulmonary embolism one day after undergoing total knee replacement. Her signs and symptoms related to this event included hypoxia and encephalopathy with confusion/delirium (confusional state) and wide complex paroxysmal tachycardia/atrial fibrillation. The patient had taken five doses of Zalviso in the postoperative period on the same day as the surgery. The third SAE was new onset atrial fibrillation in a 78 year-old male with a history of hypertension who underwent total knee replacement.

In the Zalviso open-label group, a 68 year-old male patient with a history of diverticulitis who underwent an open sigmoid resection experienced an SAE of postoperative ileus associated with hypoxia (oxygen saturation of 84%). He received no additional doses of Zalviso after this event. The patient underwent repeat laparotomy and his postoperative course was subsequently complicated by axillary vein thrombosis and clostridium difficile sepsis.

Discontinuations due to an Adverse Event (AE)

There was 1 (0.9%) patient who discontinued due to an adverse event (AE) in in the placebo-controlled Dsuvia study (SAP301). The AE that led to discontinuation was an oxygen saturation decrease from a baseline of 98% to 93-95%. Two (3.7%) additional patients discontinued due to adverse events in the placebo group (due to the SAEs noted above). In the open-label Dsuvia studies, 4 (1.9%) patients discontinued due to an AE. Two of the patients discontinued due to intermittent oxygen desaturations down to the low 90's that responded to supplemental oxygen. One patient discontinued due to dizziness that was accompanied by a systolic blood pressure that remained in the normal range but was approximately 30 mmHg lower than baseline. The fourth patient discontinued due to pruritus.

In the Zalviso placebo-controlled group, 11 (5.2%) Zalviso-treated patients discontinued due to an AE compared to 4 (3.8%) in the placebo group. The AEs that led to discontinuation in this group are summarized in the table below.

	Treatment Group		
	Sufentanil 15 mcg[a]	Placebo	Tre p-[
Number of Patients Enrolled in the Study	211	104	
Number (%) of Patients Who Received Treatment	211 (100%)	104 (100%)	
Number (%) of Patients Without Any Adverse Event Causing the Discontinuation of Study Drug	200 (94.8%)	100 (96.2%)	
Number (%) of Patients With at Least One Adverse Event Causing the Discontinuation of Study Drug	11 (5.2%)	4 (3.8%)	
Number (%) of Patients Who Reported Adverse Events Causing the Discontinuation of Study Drug by System Organ Class			
GASTROINTESTINAL DISORDERS	3 (1.4%)	1 (1.0%)	
Nausea	3 (1.4%)	0	
Abdominal Pain	0	1 (1.0%)	
INVESTIGATIONS	2 (0.9%)	1 (1.0%)	
Respiratory Rate decreased	1 (0.5%)	1 (1.0%)	
Oxygen saturation decreased	1 (0.5%)	0	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.5%)	1 (1.0%)	
Back Pain	1 (0.5%)	1 (1.0%)	
NERVOUS SYSTEM DISORDERS	3 (1.4%)	1 (1.0%)	
Sedation	2 (0.9%)	0	
Dizziness	1 (0.5%)	0	
Tremor	0	1 (1.0%)	
PSYCHIATRIC DISORDERS	2 (0.9%)	0	
Anxiety	1 (0.5%)	0	
Confusional State	1 (0.5%)	0	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.5%)	0	
Hypoventilation	1 (0.5%)	0	

Source: Dr. Galati's review, Table 34, pg. 65

Dr. Galati compared the discontinuations due to an AE between the open-label Zalviso and Dsuvia groups in the first hour of dosing, as summarized below.

	Treatment Group		
	Sufentanil 15 mcg[a]	Sufentanil 30 mcg	Treatment p-value[b]
Number of Patients Enrolled in the Study	112	216	
Number (%) of Patients Who Received Treatment	112 (100%)	216 (100%)	
Number (%) of Patients Without Any Adverse Event Causing the Discontinuation of Study Drug	104 (92.9%)	212 (98.1%)	
Number (%) of Patients With at Least One Adverse Event Causing the Discontinuation of Study Drug	8 (7.1%)	4 (1.9%)	0.026
Number (%) of Patients Who Reported Adverse Events Causing the Discontinuation of Study Drug by System Organ Class			
GASTROINTESTINAL DISORDERS	2 (1.8%)	0	NS
Nausea	2 (1.8%)	0	NS
INVESTIGATIONS	2 (1.8%)	2 (0.9%)	NS
Oxygen saturation decreased	2 (1.8%)	2 (0.9%)	NS
NERVOUS SYSTEM DISORDERS	2 (1.8%)	1 (0.5%)	NS
Sedation	2 (1.8%)	0	NS
Dizziness	0	1 (0.5%)	NS
PSYCHIATRIC DISORDERS	2 (1.8%)	0	NS
Agitation	1 (0.9%)	0	NS
Anxiety	1 (0.9%)	0	NS
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (1.8%)	0	NS
Bradypnoea	1 (0.9%)	0	NS
Hypoxia	1 (0.9%)	0	NS
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (0.5%)	NS
Pruritus	0	1 (0.5%)	NS

[a] Patients who received at least 2 SST 15 mcg (Zalviso) tablets dosed within 20-25 minutes of each other in the first hour of dosing. All patients in this group received 30 to 45 mcg of sufentanil in the first hour of Zalviso treatment, followed by prn dosing of 15 mcg/dose (subject to a 20 min lockout) for the duration of the Zalviso study.

Source: Dr. Galati's review, Table 35, pg. 66

Common Adverse Events

The frequency of adverse events that occurred in the placebo-controlled study (SAP301) is summarized in the table below.

		Actual Treatment for Period 01				
		Sufentanil 30 mcg		Placebo		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
Gastrointestinal disorders	Nausea	35	32.7%	16	29.6%	51
	Vomiting	8	7.5%	1	1.9%	9
	Flatulence	4	3.7%	4	7.4%	8
	Diarrhoea	1	0.9%	.	.	1
	Dry mouth	1	0.9%	.	.	1
	Dyspepsia	1	0.9%	.	.	1
	Gastritis	1	0.9%	.	.	1
	Hypoaesthesia oral	1	0.9%	.	.	1
	Retching	.	.	1	1.9%	1
Nervous system disorders	Headache	22	20.6%	10	18.5%	32
	Dizziness	6	5.6%	2	3.7%	8
	Somnolence	3	2.8%	2	3.7%	5
	Presyncope	1	0.9%	1	1.9%	2
	Hemiparesis	.	.	1	1.9%	1
	Syncope	.	.	1	1.9%	1
Vascular disorders	Hypotension	6	5.6%	2	3.7%	8
	Hypertension	1	0.9%	1	1.9%	2
	Orthostatic hypotension	1	0.9%	.	.	1
Injury, poisoning and procedural complications	Procedural nausea	3	2.8%	3	5.6%	6
	Procedural vomiting	2	1.9%	.	.	2
Skin and subcutaneous tissue disorders	Pruritus	2	1.9%	2	3.7%	4
	Pruritus generalised	1	0.9%	1	1.9%	2
Cardiac disorders	Tachycardia	3	2.8%	.	.	3
	Sinus tachycardia	.	.	1	1.9%	1
Psychiatric disorders	Anxiety	.	.	1	1.9%	1
	Hallucination	1	0.9%	.	.	1
	Insomnia	.	.	1	1.9%	1
Renal and urinary disorders	Bladder spasm	.	.	1	1.9%	1
	Dysuria	.	.	1	1.9%	1
	Incontinence	.	.	1	1.9%	1
General disorders and administration site conditions	Non-cardiac chest pain	1	0.9%	.	.	1
	Pyrexia	.	.	1	1.9%	1
Musculoskeletal and connective tissue disorders	Muscle spasms	1	0.9%	.	.	1
	Musculoskeletal pain	1	0.9%	.	.	1
Respiratory, thoracic and mediastinal disorders	Haemoptysis	.	.	1	1.9%	1
	Hypoxia	1	0.9%	.	.	1
Investigations	Oxygen saturation decreased	1	0.9%	.	.	1

Source: Dr. Galati's review, Table 38, pg. 71

The most common adverse events occurring in at least 1% of patients while on treatment and within the 12 hour period after discontinuation of dosing in the open-label Dsuvia studies are summarized in the table below.

	Treatment Group
	Sufentanil 30 mcg
Number of Patients Enrolled in the Study	216
Number (%) of Patients Who Received Treatment	216 (100%)
Number (%) of Patients Without Any Adverse Event	148 (68.5%)
Number (%) of Patients With at Least One Adverse Event	68 (31.5%)
Number (%) of Patients Who Reported Adverse Events by System Organ Class	
CARDIAC DISORDERS	3 (1.4%)
Bradycardia	1 (0.5%)
GASTROINTESTINAL DISORDERS	47 (21.8%)
Nausea	45 (20.8%)
Vomiting	4 (1.9%)
INVESTIGATIONS	6 (2.8%)
Oxygen saturation decreased	5 (2.3%)
NERVOUS SYSTEM DISORDERS	19 (8.8%)
Headache	8 (3.7%)
Dizziness	7 (3.2%)
Somnolence	4 (1.9%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	6 (2.8%)
Pruritus	5 (2.3%)
VASCULAR DISORDERS	6 (2.8%)
Hypotension	3 (1.4%)
Hypertension	2 (0.9%)

Source: Applicant's ISS amendment, Table 21, pg. 39

Dr. Galati found that the analysis of common adverse events in the Zalviso-treated patients were consistent with the known safety profile of an opioid. It is worth noting that many of the common AEs in the open-label Zalviso group occurred at a higher frequency than that of the Dsuvia open-label group.[8] The Applicant noted that this finding may, in part, be due to over half of the Zalviso-treated patients having received three doses (i.e., 45 mcg) in the first hour of treatment rather than two (i.e., 30 mcg). However, the Applicant performed an analysis of common AEs between those Zalviso-treated patients that received two doses and those that received three doses in the first hour,[9] and there were no consistent trends to support that the patients who received a higher hourly dose of Zalviso meaningfully contributed to the observed increase in AEs for the Zalviso-treated patients compared to Dsuvia. The Zalviso-treated patients, on average, were older and underwent major surgery, and, therefore, the safety data from the Zalviso-treated patients may actually be a more accurate reflection of the anticipated safety of Dsuvia in older populations or in patients undergoing major surgeries. Therefore, if the Applicant is able to address the deficiencies in the application, this information should be included in labeling along with the relevant safety information from the Dsuvia program.

Additional Respiratory Safety Findings

Dr. Galati evaluated changes in oxygen saturation between treatment arms in the Dsuvia placebo-controlled study. From his review:

[8] Refer to Applicant's Integrated Summary of Safety (ISS), Table 41, pg. 112.
[9] Refer to Applicant's ISS, Table 42, pg. 114.

Oxygen Saturation:

> There were small, but statistically significant differences between treatment groups for mean changes from baseline at 1 hour (-0.88% vs. -0.24%; p = 0.007) and 20 hours (-1.32% vs. -0.71%; p = 0.032), with greater decreases in the sufentanil group than in the control group at these times. For the sufentanil group, the mean decreases from baseline ranged from -0.19% at 15 minutes to -1.47% at 44 hours. For the placebo group, mean decreases from baseline ranged from -0.17% at 30 minutes to -1.22% at 36 hours. The proportions of patients who had SpO2 levels < 93% or < 95% during the study were higher in the sufentanil group than in the placebo group (< 93%: 7.5% vs. 0%; p = 0.052; <95%: 23.4% vs. 7.4%; p = 0.016). Additionally, two sufentanil-treated patients had SpO2 less than 92% during the study. A summary of oxygen saturation is shown in [the table below].

Summary of Oxygen Saturation – SAP301

SPO_2	Sufentanil (n=107)	Control (n=54)
Less than 95%	25 (23.4%)	4 (7.4%)
Less than 93%	8 (7.5%)	0 (0%)
Less than 90%	1 (0.9%)	0 (0%)
Mean (SD)	95.3 (1.7)	96.1 (1.3)

Source: Dr. Galati's review, Table 46, pg. 80.

Additional Safety Concern Associated with Dropped Tablets

The safety profile observed in the clinical development program is typical for an opioid analgesic. However, the small tablet size creates additional risk for accidental exposure associated with dropped tablets. The human factors evaluation noted eight failures associated with a critical task to confirm tablet placement in the patient's sublingual space, and because the tablet is very small, there is potential that an improperly administered tablet will go undetected. The potential risks associated with dropped tablets are of great consequence and include accidental exposure, overdose, death, improper dosing, and diversion for misuse and abuse, as described in the human factors section of this review (Section 3).

The Applicant reported a total of three dropped tablets in the Dsuvia Phase 3 program. In one case, a tablet bounced off the patient's tongue and landed out of the mouth. The HCP located and accounted for this dropped tablet. A second case involved an SDA that was prematurely actuated. The HCP located and secured the tablet. In the last and most worrisome case, the patient was aware that the dose was not properly administered, but the HCP did not follow the Directions for Use and failed to confirm presence of the tablet after dose administration (Directions for Use step #6). The patient subsequently located the tablet and placed it in the trash can. The patient later notified the morning shift HCP of where the tablet had been placed who then properly secured the tablet and documented the event.

Although no specific adverse events were associated with these instances of dropped tablets, these are serious errors with potentially grave consequences. These safety concerns preclude approval and must be addressed prior to approval.

9. Advisory Committee Meeting

An Advisory Committee (AC) meeting was not held for this application, as the issues that preclude approval did not require additional input. However, if the Applicant addresses these issues in a resubmission and the application may otherwise be approved, an AC meeting will likely be necessary to get additional input on the potential impact of any regulatory decision given the current public health crisis surrounding opioids.

10. Pediatrics

Data from the pediatric population were not included in this application. The agency agreed with the Applicant's pediatric study plan (PSP) on November 2, 2016. The agreed PSP includes a request for waiver in patients birth to <6 years of age because children in this age group would not be able to consistently comply with the dosing instruction to keep the tablet in the sublingual space for approximately ten minutes after administration. Sufentanil has a very low oral bioavailability, and swallowing the tablet would result in subtherapeutic concentrations. The agreed PSP includes a deferral for studies in the remaining pediatric age ranges. If the Applicant is able to address the deficiencies, the following deferred studies will be required:

- An open-label, multiple-dose, pharmacokinetic and safety study in pediatric patients 6 to <12 years of age with acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
- An open-label, multiple-dose, pharmacokinetic and safety study in pediatric patients 12 to <17 years of age with acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate

Efficacy may be extrapolated from adults to the required pediatric age groups provided that the exposures between adults and those pediatric age groups are similar.

11. Other Relevant Regulatory Issues

Risk Evaluation and Mitigation Strategy (REMS)
A REMS is required to mitigate the serious risk of life-threatening or fatal respiratory depression resulting from accidental exposure by requiring that Dsuvia is only dispensed by and administered in inpatient or similarly-resourced healthcare settings that are certified. Although serious, life-threatening or fatal respiratory depression has been observed with all opioids, Dsuvia carries additional risk because sufentanil is a highly potent opioid and the tablet is very small (3 mm by 0.85 mm). Errors involving the critical task of confirming tablet placement in the sublingual space were identified in the human factors study and dropped tablets were noted in the clinical studies. The tablet must be delivered by an HCP, and the HCP must confirm the tablet is in place. Lost tablets will be hard to locate given their size, posing risk to those who may accidentally come in contact with the lost tablet, including children. To ensure the benefits continue to outweigh the risks, the agency is requesting a

REMS 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).

Controlled Substances Staff
CSS concluded that Dsuvia "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" and that the major risks associated with Dsuvia are opioid overdose and unauthorized access to the product for purposes of misuse and abuse. CSS noted that unauthorized access could occur in the medical setting; however, "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."

Clinical Site Inspections
Navid Homayouni, MD, from the Office of Scientific Investigations (OSI) completed the Clinical Inspection Summary for this application. Study SAP301 is the pivotal efficacy study submitted in support of this application. Two clinical investigator sites were selected for audit by the agency. Two additional clinical investigator sites and the contract research organization (CRO), Inventive Health Clinical, for the pivotal study were inspected by the European Medicines Agency (EMA) between August 7 and 5, 2017.

OSI found that "[t]he data for Study SAP301 submitted by the [Applicant] 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 Inventive Health Clinical 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."

I concur with the OSI reviewers that the inspectional findings at the four clinical investigator sites and the CRO are unlikely to impact the interpretation of the pivotal study results.

Financial Disclosures
The Applicant provided certification that there were no financial interests or arrangements to disclose.

505(b)(2) Committee
This application was presented at a meeting of the 505(b)(2) committee on September 25, 2017, and it was cleared for action from their perspective.

12. Labeling

DMEPA found the proposed proprietary name, Dsuvia, to be acceptable. DMEPA also provided comments on the prescribing information, as well as on the directions for use, device labeling, and carton and container labeling. Additionally, the Division of Pediatric and Maternal Health (DPMH) and the Controlled Substances Staff (CSS) provided recommendations on relevant sections of the labeling.

Some of the DMEPA labeling comments were related to deficiencies in the application and will be communicated in the complete response letter. Otherwise, labeling comments will not be provided to the Applicant, and labeling will be addressed in a resubmission because these comments may change as the deficiencies are addressed.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  Complete Response

- Risk Benefit Assessment

  CDTL
  The Applicant submitted this application for Dsuvia, a drug-device combination product containing 30 mcg of sufentanil that is intended to be delivered to the sublingual space by a healthcare professional no more than once an hour for the management of acute pain that requires opioid-level analgesia in an inpatient or similarly-resourced healthcare setting. Although the dose and dosing regimen for sufentanil 30 mcg appear effective in the proposed patient population and reasonably safe in the context of existing opioid therapy, there are safety concerns that must be addressed before this application can be approved.

  An adequate and well-controlled clinical trial in a postoperative pain population demonstrated a statistically superior treatment effect in favor of Dsuvia on the prespecified primary endpoint, SPID12, which was supported by multiple secondary analyses, including rescue analgesic use. The safety evaluation did not identify a risk for the drug component that would not be expected for an opioid analgesic. Additionally, the availability of this product in this particular setting would not be expected to further add to the ongoing opioid epidemic that we are currently experiencing in the U.S. provided that adequate restrictions are in place to confine its use to an appropriate healthcare setting.

  However, the human factors evaluation identified serious concerns regarding the use of the device. Specifically, there were numerous errors related to study participants not being able to correctly confirm the placement of the tablet in the

sublingual space. A dropped tablet poses significant risks, including life-threatening or fatal respiratory depression due to accidental exposure, improper dosing, and diversion. Furthermore, due to the size of the tablet, a dropped tablet may go undetected by the patient and the HCP. The Applicant must address this concern prior to approval. DMEPA recommended modifications to the directions for use to ensure that the risks associated with not confirming placement of the tablet are minimized and that the adequacy of those changes be confirmed through additional human factors evaluation.

Division Director
Dr. Lloyd has provided a thorough summary and review of the individual discipline reviews, and I concur with most of his conclusions.

The efficacy data from Study 301 demonstrate that a 30-mcg sublingual sufentanil tablet is able to provide more analgesia than placebo in postoperative patients. The Applicant has made no attempt to demonstrate that Dsuvia has a role that is superior to traditional oral analgesics in the postoperative period, nor that it is even equivalent.

The patients in Study 301 did not use a lot of postoperative analgesic medication, even in the placebo group. The number of rescue morphine doses used by placebo patients averaged 1.1 doses in the first 6 hours (median 1.0), 1.6 doses (median 1.0) in the 0 to 12 hour interval, and 2.1 doses (median 1.0) in the 0 to 24 hour interval. In the 0 to 12 hour interval, only 15% of placebo patients used 3 to 4 doses of rescue morphine and just 16.7% of placebo patients used more than four doses of rescue morphine. There were some patients with difficult to control pain; the maximum use of rescue doses was 11 in the Dsuvia group and 14 in the placebo group. In the assessment of whether there was sufficient exposure to Dsuvia and Zalviso for a safety assessment, the total number of patients treated with sublingual sufentanil tablets was 646, with 323 of those exposed to Dsuvia and 323 exposed to Zalviso. So while I agree that the number could have been sufficient, the experience with repeated dosing is not. Table 18 of Dr. Galati's review provides the number of doses of sublingual sufentanil used. Of the 323 patients exposed to Dsuvia, 86% used fewer than six doses in the first 12 hours of the study, and the remaining 14% used from 6 to 12 doses. It takes seven doses of Dsuvia, administered one hour apart to reach steady state. With multiple dosing, the exposure to sufentanil accumulates with increases in AUC (AUC0-60 min) and Cmax of 3.7-fold and 2.3-fold, respectively. This means that most of the safety database from Dsuvia clinical trials represents the adverse event profile of a less than steady-state exposure to sufentanil from Dsuvia. The adverse effects of the maximum exposure of sufentanil following multiple dosing have not been adequately evaluated.

The concern about misplaced tablets cannot be understated. The experience with Zalviso demonstrated that patients who self-administered the small sublingual fentanyl tablet were not always aware that the dose was not properly administered

and several were found in bed sheets. In the limited evaluation of Dsuvia, administration errors were made, the nature of which could result in misplaced tablets without the awareness of either the patient or healthcare provider. The risk of unaccounted sufentanil is unacceptable.

Overall, although efficacy was demonstrated, Dsuvia offers no apparent advantage to currently available therapies. There are two areas of safety concern with this product that require further evaluation: the safety of Dsuvia in patients requiring the maximum dosing proposed for labeling because of the accumulation of sufentanil and the risk of misplaced tablets due to the small tablet size, use of an applicator, and inadequate directions for use. These concerns outweigh the possible benefit at this time.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  If the deficiencies can be adequately addressed, a REMS restricting use of Dsuvia to an appropriate healthcare setting will be required.

- Recommendation for other Postmarketing Requirements and Commitments

  If the deficiencies can be adequately addressed, pediatric studies based on the requirements of the Pediatric Research Equity Act will be required

- Recommended Comments to Applicant

  SAFETY
  The safety database, while suitable in number of patients, did not contain a sufficient number of patients dosed at the maximum amount described in the proposed labeling to assess the safety of Dsuvia. This is particularly important as there is a nearly 4-fold increase in the exposure and a more than 2-fold the maximum concentration when Dsuvia is dosed at steady state.

  To address this deficiency:
  Collect additional data in at least 50 patients with postoperative pain sufficient to evaluate the safety of Dsuvia for a period following the maximum dosing proposed.

  HUMAN FACTORS

  We have determined that the human factors (HF) 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, improper dosing, and diversion. Overall, we do not find the risk acceptable and note that you did not propose any additional measures to further mitigate the risk.

To address this deficiency:
We recommend you make the following changes to the user interface and conduct another HF validation study to demonstrate the effectiveness of the recommended mitigation strategies in addressing the use-related errors that were observed in your validation study and to ensure that the changes do not introduce new risks:
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 such as the following:

"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. Pouch Package
1. 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 complete DFU cannot be easily separated from the foil packet prior to use or discarded along with the carton.

Additional comments:

CONTAINER LABEL AND CARTON LABELING COMMENTS
We reserve final comment on the proposed container label and carton labeling until the application is otherwise adequate. The following comments are being shared at this time for your consideration:

A. Single Dose Applicator Container Label

In accordance with the requirements of 21 CFR 201.10(i), the label must include the following information, at a minimum:

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

Include all of the above information on this container label. In addition, we recommend including the expiration date[10].

B. 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. Delete the statements "Not for home use" and "To be administered by an HCP" since this information is redundant. The statement, "For use in a medically supervised settings only" is sufficient.

3. If room permits, 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 after receiving the tablet."

C. Pouch Labeling - Back

1. Revise the statement, "Dispensing Information" to read, "Administration Information" so that it more accurately reflects the information that follows.

2. 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 may help guide users in the proper administration technique.

D. Carton Labeling

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.

[10] United States Pharmacopoeia (USP) General Chapter <7> Labeling

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/s/

JOSHUA M LLOYD
10/11/2017

SHARON H HERTZ
10/11/2017