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RESEARCH**

APPLICATION NUMBER:

209128Orig1s000

NON-CLINICAL REVIEW(S)



FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

PHARMACOLOGY TOXICOLOGY SAFETY REVIEW

NDA number:	209128
Drug Product:	Dsuvia (Sufentanil Sublingual Tablet)
Applicant:	AcelRx Pharmaceuticals, Inc.
Submission Type:	Commercial
Supporting Document:	26
Submission Date/Receipt:	May 3, 2018
Reviewer name:	Grace S. Lee, PhD, DABT
Supervisor:	R. Daniel Mellon, PhD
Division name:	Division of Anesthesia, Analgesia, and Addition Products
Review completion date:	October 24, 2018

AcelRx Pharmaceuticals, Inc. submitted a 505(b)(2) application for Dsuvia (sufentanil sublingual tablet 30 mcg), a drug-device combination product, on December 12, 2016. In this original NDA submission, Dsuvia is intended for the management of moderate-to-severe acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate, in adult patients in a medically supervised setting and the proposed dose regimen was to be administered, as needed for pain management, with a minimum of 1 hour between doses. Thus, the maximum daily dose (MDD) for the Dsuvia product was 720 mcg (30 mcg X 24 tablets). In SD 26 submitted on May 3, 2018, the Applicant provided the response to Complete Response Letter dated October 11, 2017, and in this resubmission, the Applicant proposed the new daily maximal dose of 12 tablets (360 mcg) in 24 hours: "Dosing not to exceed 12 tablets in 24 hours." Accordingly, the safety margins for all animal studies in the drug label needed to be revised, based on the new maximum human daily dose of 360 mcg/60 kg, in replacement of maximum human daily dose of 720 mcg/60 kg. The changes have been made during the internal labeling discussion and is being communicated to the Applicant.

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/s/

GRACE S LEE
10/24/2018

RICHARD D MELLON
10/24/2018

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 209128
Supporting document/s: 1, 5, & 22
Applicant's letter date: December 12, 2016, March 10, 2017, & August 21, 2017
CDER stamp date: December 12, 2016, March 10, 2017, & August 21, 2017
Product: Dsuvia™ (Sufentanil)
Indication: 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: AcclRx Pharmaceuticals, Inc.
Review Division: Anesthesia, Analgesia, and Addiction Products
Reviewer: Grace S. Lee, PhD, DABT
Supervisor/Team Leader: R. Daniel Mellon, PhD
Division Director: Sharon Hertz, MD
Project Manager: Allison Meyer

Disclaimer

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1 Executive Summary

1.1 Introduction

AcelRx Pharmaceuticals, Inc. has submitted a 505(b)(2) application for Sufentanil Sublingual Tablet 30 mcg (Dsuvia), a drug-device combination product, intended for the management of moderate-to-severe acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate, in adult patients in a medically supervised setting. The product consists of 30 mcg tablets of sufentanil and a controller device. The Applicant has referenced the Agency's prior findings of safety and efficacy for Sufenta (sufentanil injectable solution, NDA 19050).

1.2 Brief Discussion of Nonclinical Findings

The Applicant conducted repeat-dose buccal irritation/toxicity studies with local tolerance assessments using the hamster cheek pouch model and several genetic toxicity studies for sufentanil impurities. 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. (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 Leadscape programs on two other degradants (b) (4), 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.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, NDA 209128 may be approved with no post-marketing requirements and with the recommended labeling.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The following labeling recommendations are provided prior to discussion with the review team and the Applicant. For final labeling, the reader is referred to the action letter.

Applicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
<p>8 USE IN SPECIFIC POPULATIONS</p>		
<p>(b) (4)</p>	<p>8.1 Pregnancy Risk Summary</p> <p>(b) (4)</p> <p>[INSERT HUMAN DATA STATEMENTS]</p> <p>In animal reproduction studies, embryoletality and maternal toxicity were noted in rabbits when sufentanil was administered intravenously at (b) (4) times the maximum human daily dose of (b) (4) mcg/60 kg/day, based on a body surface area comparison during organogenesis. Decreased live fetuses and pup survival were noted in rats treated with sufentanil late in gestation and throughout lactation at doses below the human daily dose of (b) (4) mcg. No malformations were observed in either rats</p>	<p>During the NDA review cycle, the referenced drug product label was updated with additional information. The recommended changes reflect the latest Sufenta labeling modified to reflect the appropriate exposure margins for this drug product.</p>

<p>(b) (4)</p>	<p>or rabbits at doses below the human daily dose of (b) (4) mcg [see Data]. [INSERT BACKGROUND INCIDENCE STATEMENTS].</p> <p><u>Data</u> <i>Animal Data</i></p> <p>Pregnant rats were treated with intravenous sufentanil doses of 0.005, 0.02, or 0.08 mg/kg/day (b) (4) (b) (4) times the maximum human daily dose of (b) (4) mcg/60 kg, based on a body surface area, respectively). No malformations or embryotoxic effects were noted despite maternal toxicity (increased mortality in the mid- and high-dose group).</p> <p>Pregnant rabbits were treated with intravenous sufentanil doses of 0.005, 0.02, or 0.08 mg/kg/day ((b) (4) times the maximum human daily dose of (b) (4) mcg/60 kg, based on a body surface area, respectively). Decreased live fetuses per litter and decreased litter size in the high-dose group were noted in the presence of maternal toxicity (decreased body weight gain and mortality in the high-dose group).</p> <p>No evidence of malformations or adverse</p>	
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effects on the fetus was reported in a published study in which pregnant rats were administered 10, 50, or 100 mcg/kg/day sufentanil (b) (4) times the maximum human daily dose of (b) (4) mcg/60 kg, based on a body surface area, respectively) continuously from Gestation Day 5 through Gestation Day 20 via subcutaneously implanted osmotic minipumps.

Pregnant rats were treated intravenously with sufentanil 0.005, 0.02, or 0.08 mg/kg/day (b) (4), (b) (4) times the maximum human daily dose of (b) (4) mcg/60 kg, based on a body surface area, respectively) from Gestation Day 16 through Lactation Day 21. Sufentanil reduced birth weights in the mid- and high-dose groups, decreased live fetuses in the high-dose group, and decreased pup survival in all groups in the presence of maternal toxicity (decreased weight gain and increased mortality in all groups).

(b) (4)

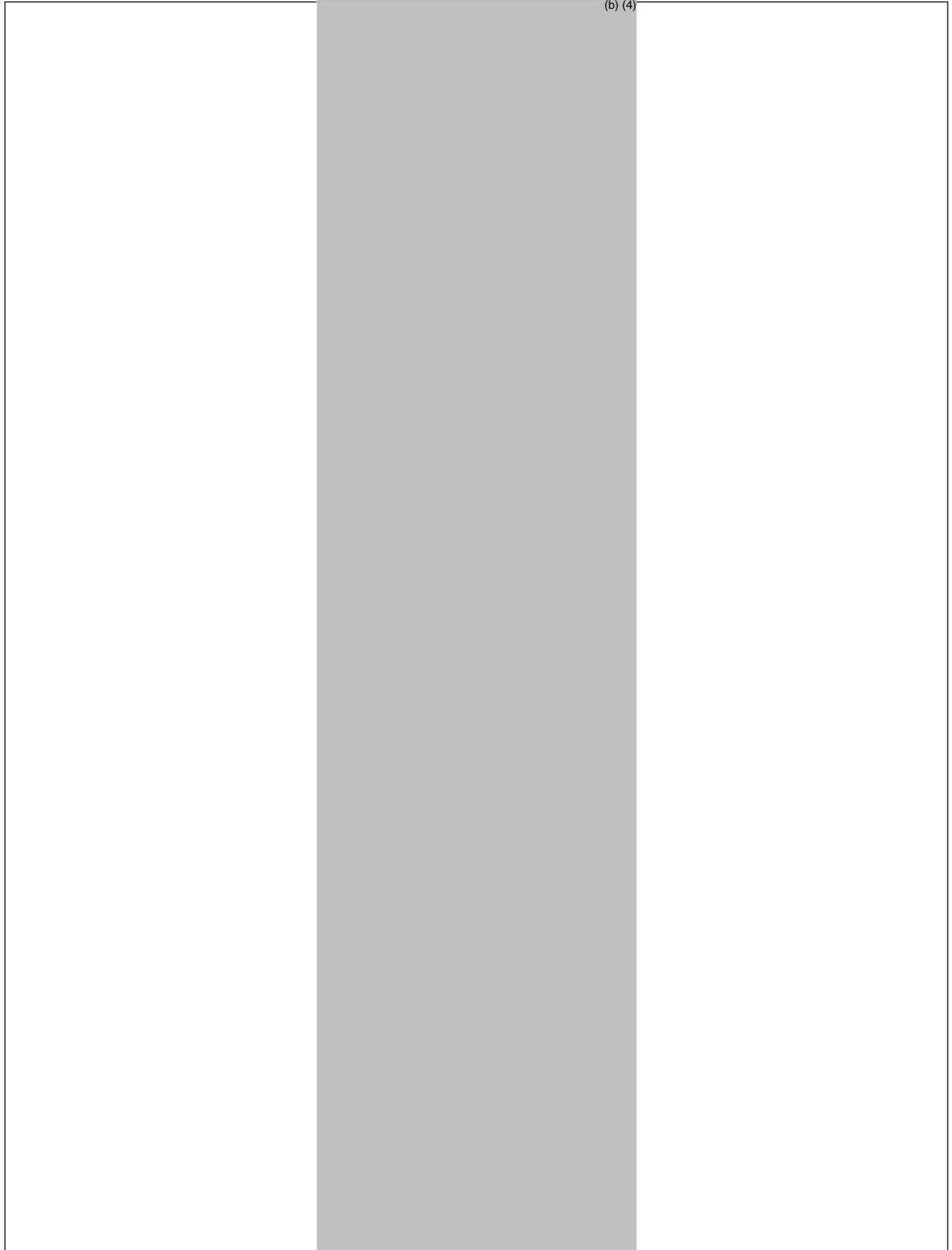
	(b) (4)	
12.1 Mechanism of Action (b) (4)	12.1 Mechanism of Action Sufentanil is an opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The principle therapeutic action of sufentanil is analgesia and sedation, thought to be mediated through opioid-specific receptors throughout the CNS. Like all full opioid agonists, there is no ceiling effect to analgesia. (b) (4)	(b) (4)

12.2 Pharmacodynamics	12.2 Pharmacodynamics	
(b) (4)	<p><u>Effects on the Central Nervous System</u> Sufentanil produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.</p> <p>Sufentanil causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose</p>	<p>Labeling has been edited to reflect class opioid labeling for analgesic drug products and to remove promotional claims and clinical practice information. The recommended changes reflect the latest Sufenta labeling.</p>

<p>(b) (4)</p>	<p>situations.</p> <p><u>Effects on the Gastrointestinal Tract and Other Smooth Muscle</u> Sufentanil causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.</p> <p><u>Effects on the Cardiovascular System</u> Sufentanil produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.</p> <p><u>Effects on the Endocrine System</u> Opioids inhibit the secretion of adrenocorticotrophic hormone (ACTH), cortisol,</p>	

	<p>and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon [see Adverse Reactions (6.2)].</p> <p>Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see Adverse Reactions (6.2)].</p> <p><u>Effects on the Immune System</u></p> <p>Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.</p>	
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(b) (4)



	(b) (4)	
<p>13 NONCLINICAL TOXICOLOGY</p>		
<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>(b) (4)</p>	<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p><u>Carcinogenesis</u> Long-term (b) (4) studies in animals (b) (4) to evaluate the carcinogenic potential of sufentanil have not been conducted.</p> <p><u>Mutagenesis</u> Sufentanil was not genotoxic in the in vitro bacterial reverse mutation assay (Ames assay) or in the in vivo rat bone marrow micronucleus assay.</p> <p><u>Impairment of Fertility</u> Fertility and early embryonic development studies were conducted in male and female rats treated with 0.005, 0.02, or 0.08 mg/kg sufentanil IV for 56 days and 14 days prior</p>	<p>To be consistent with the latest Sufenta label, subheaders have been re-formatted, and several wordings were revised. Exposure margins have been modified for the maximum human daily dose of Dsuvia.</p>

<p>(b) (4)</p>	<p>to mating through gestation respectively. Increased mortality was noted in all treatment groups. Lower pregnancy rates were noted following treatment of males at doses of 0.02 and 0.08 mg/kg ((b) (4) times the maximum human daily dose of (b) (4) mcg/60 kg, based on a body surface area, respectively)</p>	
	<p>(b) (4)</p> <p>suggesting the potential for an adverse effect on fertility in males. Increased resorption of fetuses and reduced litter size was noted in the high dose females ((b) (4) times the maximum human daily dose of (b) (4) mcg/60 kg, based on a body surface area, respectively)</p> <p>(b) (4)</p> <p>suggesting the potential for fetotoxicity, likely due to maternal toxicity.</p>	

2 Drug Information

2.1 Drug

CAS Registry Number: 60561-17-3

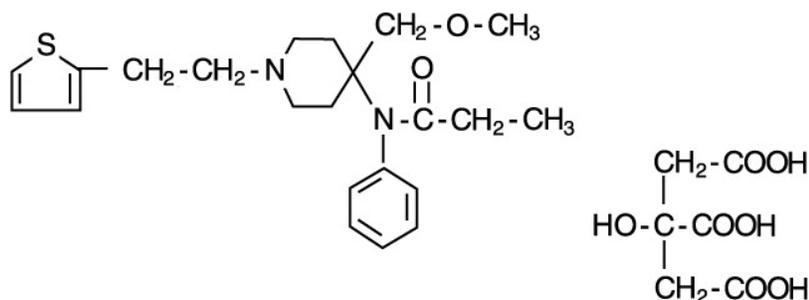
Generic Name: Sufentanil citrate

Code Name: 0672 and AFX-04 (code for drug product)

Chemical Name: N-(4-(Methoxymethyl)-1-(2-(2-thienyl)ethyl)-4-piperidyl)-N-phenylpropionamide citrate

Molecular Formula/Molecular Weight: C₂₂H₃₀N₂O₂S•C₆H₈O₇ / 578.68

Structure or Biochemical Description:



Pharmacologic Class: Opioid agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND#	Drug	Status	Division	Indication	Stamp Date	Sponsor
113059	Sufentanil Sublingual tablet 30 mcg	Active	DAAAP	Moderate-to-severe acute pain in adult patients in the medically supervised setting	10/3/2011	AcelRx Pharmaceuticals

NDA#	Drug	Status	Division	Indication	Approved Date	Applicant
19050	Sufenta (sufentanil citrate) injection	Approved	DAAAP	Adjunct to general anesthesia	05/04/1984	Akorn, Inc.
(b) (4)	Zalviso™ (sufentanil sublingual tablet system)	Complete Response	DAAAP	Management of moderate-to-severe acute pain in adult patients in a hospital setting		AcelRx Pharmaceuticals

The Applicant is relying upon the Agency's previous finding of safety and efficacy for Sufenta to support this application. They are also cross referencing (b) (4).

MF #	Subject of MF	Holder
(b) (4)	Sufentanil citrate	(b) (4)

2.3 Drug Formulation

The Dsuvia single-dose applicator (Figure 1) contains a single sublingual sufentanil 30 mcg tablet, to be administered by a healthcare professional, as needed for pain management, with a minimum of 1 hour between doses. Thus, the maximum daily dose (MDD) for the Dsuvia product is 720 mcg (30 mcg X 24 tablets). The composition of the Dsuvia product is listed in Table 1. Hypromellose (b) (4), mannitol, croscarmellose sodium, and stearic acid have been used in FDA-approved buccal/sublingual drug products at comparable doses and for comparable durations. Although the dicalcium phosphate anhydrous has not been used in an FDA-approved sublingual or buccal dosage form, it has been used in oral drug products at comparable doses and for comparable durations, and the local tolerance of these excipients has been adequately characterized in the 28-day hamster cheek pouch study.

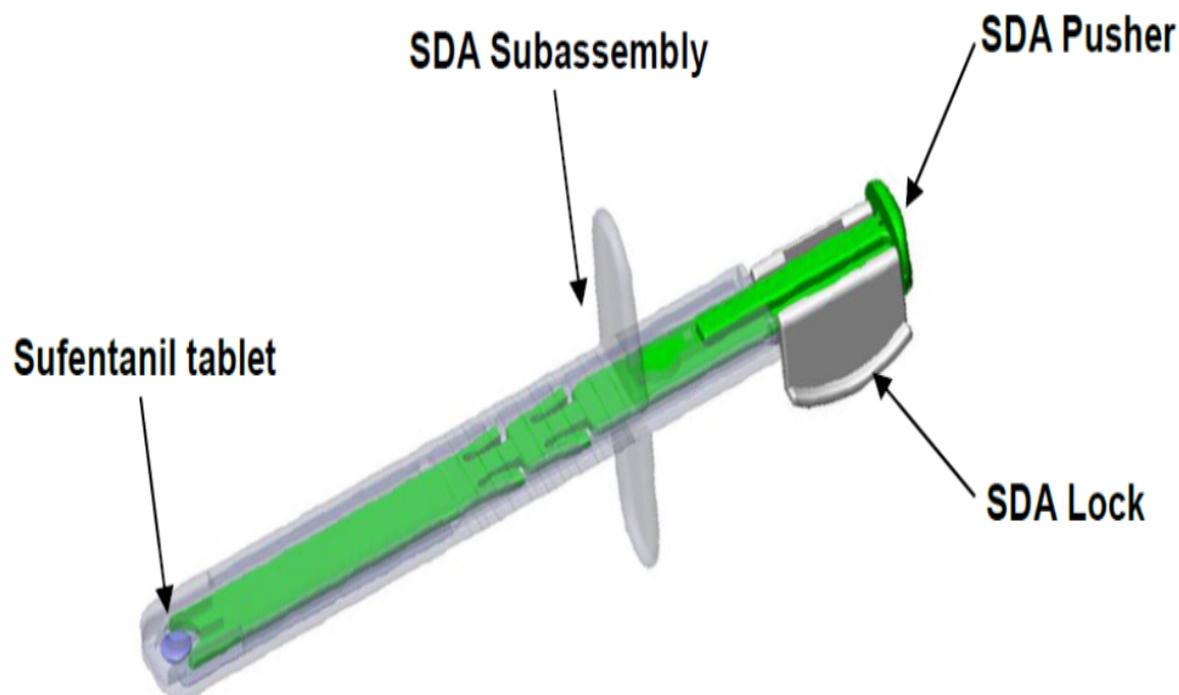


Figure 1 Illustration of single-dose applicator with a Sufentanil Sublingual Tablet 30 mcg [taken directly from 3.2.P.1 Description and Composition of the Drug Product, p 1]

Table 1 Nominal composition of Sufentanil Sublingual Tablet 30 mcg [taken directly from 3.2.P.1 Description and Composition of the Drug Product, p 3]

Components	Quality Reference	Function	Composition per tablet (mg)
Sufentanil Citrate	USP	Active pharmaceutical ingredient	0.0450
Mannitol (b) (4)	USP, EP	(b) (4)	(b) (4)
Dicalcium Phosphate Anhydrous	USP		
Hypromellose (b) (4)	USP, EP, JP		
Croscarmellose Sodium	NF, Ph Eur, JP		
FD&C Blue #2 (b) (4)	FD&C		
Stearic Acid (b) (4)	NF, Ph Eur, BP, JP		
(b) (4)			
Total			(b) (4)
(b) (4)			

2.4 Comments on Novel Excipients

FD&C Blue No. 2 (b) (4) has not been used in FDA-approved sublingual drug products. During the filing review of this NDA, the NDA submission did not appear to contain adequate information to justify the local safety of sublingual FD&C Blue No. 2 in the drug product formulation although the to-be-marketed formulation has been evaluated in clinical studies. Note that FD&C Blue No. 2 (b) (4) was not used in the nonclinical cheek pouch hamster studies. Thus, an information request was sent to the Applicant to submit all available safety information on the sublingual use of FD&C Blue No. 2.

In the response [Supporting Document 5 submitted March 10, 2017], the Applicant stated that the Applicant has not conducted any nonclinical studies using FD&C Blue No. 2 (b) (4), nor was aware of any sublingual dosage form that uses this colorant. Although FD&C Blue No. 2 (b) (4) is not listed in the FDA's Inactive Ingredient Database (IID) for sublingual dosage forms, it is listed for oral products and a buccal product. The maximum potency for the buccal product is 0.008 mg, and no other information can be found for this drug product. Note that the blue colorant in one Dsuvia tablet contains (b) (4) mg, whereas 24 tablets contain (b) (4) mg of FD&C Blue No. 2 (b) (4). The Applicant also stated that color additive lakes are provisionally listed under 21 CFR §81.1, but not specifically for FD&C Blue No. 2 (b) (4). FD&C Blue No. 2 (b) (4) is acceptable for use in foods, drugs, and cosmetics.

In addition, the Applicant provided the summary results from the 4 human clinical studies that used FD&C Blue No. 2 (b) (4) in both active tablets (representing the intended commercial DSUVIA™ formulation) and placebos. In the Phase 1 PK Study SAP101 (single and multiple dose), the examination of the oral mucosa was included during the physical exam at screening and end of study, and 39 subjects received a single dose of 30 mcg and 34 of those subjects received the multiple dose treatment (12 doses at an hourly interval). There was no report of sublingual irritation, redness, or pain based on AE reporting or post-Dsuvia dosing oral mucosal irritation noted based on clinical evaluation. In three Phase 3 studies (SAP301 with 161 patients dosed with a median use of 6-7 doses in 24 hours, SAP302 with 76 patients dosed with a median use of 1 dose in 5 hours, and SAP303 with 140 patients dosed with a median use of 3 doses in 12 hours), there was no report of sublingual irritation, redness, or pain based on AE reporting. Based on these clinical results, the Applicant concludes that FD&C Blue No. 2 (b) (4) does not present a local safety issue to the sublingual mucosa. The Medical Officer also concludes that there is no obvious safety concern with FD&C Blue No. 2 (b) (4) from the clinical data (verbal communication with Dr. Steven Galati).

In addition to 21 CFR §81.1 that was cited by the Applicant, 21 CFR §74.1102 states that FD&C Blue No. 2 may be safely used for coloring ingested drugs in amounts consistent with current good manufacturing practice. Based on the fact that color additive FD&C Blue No. 2 is provisionally listed under 21 CFR §74.1102 for use in ingested drugs and FD&C Blue No. 2 (b) (4) is used in the FDA-approved oral drug products, along with available clinical data of the sublingual use of FD&C Blue No. 2 (b) (4), the Reviewer considers that there is adequate safety information for the sublingual use of FD&C Blue No. 2.

2.5 Comments on Impurities/Degradants of Concern

There are no safety issues with threshold of impurities.

Drug substance: Sufentanil citrate has 3 potential impurities, which are process impurities/related substances generated during synthesis, as following: (b) (4)

(b) (4)

(b) (4). According to ICH Q3A(R2) guidance, the qualification threshold for impurities in the drug substance for a maximum daily dose (MDD) of ≤ 2 g/day is 0.15% or 1 mg/day intake, whichever is lower. The Applicant has set the specification for these impurities in the sufentanil drug substance at not more than (NMT) (b) (4)%, (see Table 2), which results in (b) (4) mcg/day at the maximum daily dose (MDD) of 720 mcg. Additionally, the specification for heavy metal (b) (4) is (b) (4)%. The MDD of 720 mcg could result in up to (b) (4) mcg/day of (b) (4) exposure, which is less than the permissible daily exposure limit for (b) (4) (NMT 5 mcg/day) specified in the ICH Q3D Elemental Impurities guidance.

Overall, the specifications for the sufentanil drug substance impurities/degradants are acceptable from a nonclinical pharmacology toxicology perspective.

Table 2 Proposed Drug Substance Specifications for Sufentanil Citrate, USP [taken directly from 3.2.S.4.1 Specification, p 1]

Test	Method	Acceptance Criteria
Heavy Metals (b) (4)	USP <231> (b) (4)	(b) (4)
Limit of (b) (4) a	USP	
Assay (HPLC) (b) (4)	USP	
Related Substances (HPLC) (b) (4)	USP	
Unknown Related Substances (Each)		
Total Related Substances		

Drug product: Four drug product degradants have been identified as following: (b) (4)

The Applicant has conducted the Ames assays using (b) (4) (b) (4), and the results of the assays were negative. Thus, these impurities may be regulated as non-genotoxic impurities. Additionally, the Applicant has conducted DEREK and Leadscope assessments on (b) (4), and these assessments did not identify any potential mutagenic/genotoxic activity for either compound. CDER Office of Transitional Science evaluation concurred with the Applicant's analysis and also did not identify these degradants as potential genotoxic compounds. According to the ICH Q3B(R2) guidance, the qualification threshold for nongenotoxic degradants in a drug product for a MDD of < 10 mg/day is 1.0% (equivalent to 7.2 mcg/day intake at the MDD of 720 mcg of sufentanil) or 50 mcg/day intake, whichever is lower. The specification of NMT (b) (4) % at the MDD of these impurities results in up to (b) (4) mcg/day (Table 3). Thus, the specifications for the sufentanil drug product impurities/degradants are acceptable from a nonclinical pharmacology toxicology perspective.

Table 3 Proposed Specifications for related substances in the drug product [taken directly from 3.2.P.5.6 Validation of Analytical Procedures (sufentanil tablet), p 2]

Related Substances	Method	
(b) (4)	930204	(b) (4)
Individual unspecified		
Total Related Substances		

Regarding residual solvents, (b) (4) is a solvent in the manufacture of the sufentanil drug product. The Applicant's initially proposal was not to perform any residual (b) (4) testing for commercial lots. The (b) (4) concentrations in developmental and registration lots were less than (b) (4) ppm. Assuming that (b) (4) is present at (b) (4) ppm (b) (4) in a 30 mcg sufentanil tablet, then there would be (b) (4) mcg (b) (4) /tablet. At the MDD of 720 mcg (24 tablets per day), the maximum exposure to (b) (4) is (b) (4) mcg/day. According to the ICH Q3C guidance, (b) (4) is a (b) (4) solvent, and daily doses less than (b) (4) mg/day ((b) (4) mcg/day) are acceptable. However, the CMC review team sent an information request to the Applicant to include residual (b) (4) testing, and the Applicant responded to include testing of residual (b) (4) at lot release for commercial lots until sufficient data has been gathered for submission of a prior-approval supplement to remove this residual (b) (4) from the specification. The specification of residual (b) (4) is < (b) (4) ppm [Supporting Document 22 submitted August 21, 2017]. The specification is acceptable from a pharmacology toxicology perspective.

2.6 Proposed Clinical Population and Dosing Regimen

The indication sought for Dsuvia™ is 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. Dsuvia is not intended for home use or for use in children. Dsuvia is to be administered sublingually to the patient by a healthcare professional in response to pain using the single-dose applicator in which the tablet is housed. The applicator is used as a placement aid for the healthcare professional to deliver a single sufentanil 30 mcg sublingual tablet, on an as needed basis, per patient request, with a minimum of 1 hour between doses.

2.7 Regulatory Background

The current NDA for Dsuvia™ was submitted via the 505(b)(2) pathway with the reference drug sufentanil injection (Sufenta, NDA 19050) held by Akorn, Inc. Sufentanil was synthesized by Janssen Pharmaceuticals in 1974 and was originally approved in 1984. Sufentanil citrate is approved for use via both the intravenous and epidural routes of administration. In adults and pediatric patients, sufentanil is administered intravenously as an analgesic adjunct in the maintenance of balanced general anesthesia in patients who are intubated and ventilated, and as a primary anesthetic agent for the induction and maintenance of anesthesia. Sufentanil citrate is also indicated for epidural administration as an analgesic combined with low dose bupivacaine during labor and vaginal delivery.

The EOP2 and pre-NDA meetings for the Dsuvia product were held for between the Division and AcelRx Pharmaceuticals, Inc. (AcelRx) under IND 113059 on December 18, 2013 and December 9, 2015, respectively. During the EOP2 meeting, there was a discussion on the nonclinical program for the Dsuvia product. The Division stated that

the Applicant's proposal to rely upon the Agency's previous finding of safety for the Sufenta drug product, along with the 4-day hamster cheek pouch irritation study and the 7- and 28-day repeat-dose toxicology studies as bridging studies for the alternative route of administration from the approved routes of administration for Sufenta was acceptable for the acute indication of up to 24-hour treatment. At the pre-NDA meeting, the Division asked whether one of their excipients (b) (4) (b) (4) is FD&C Blue No. 2 (b) (4) and communicated that safety justification for a new excipient needs to be provided as per the FDA guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*.

3 Studies Submitted

3.1 Studies Reviewed

Study #	Title	EDR Location
Pharmacokinetics		
(b) (4) 591001	A pharmacokinetic study comparing sufentanil sublingual nanotabs and intravenous sufentanil administration in dogs.	4.2.2.2
(b) (4) 591002	A pharmacokinetic study comparing administration of sufentanil intravenously, sublingually, and sufentanil nanotabs orally in dogs.	4.2.2.2
Toxicology		
(b) (4) 591014	A 28-day buccal pouch irritation/toxicity study with sufentanil sublingual NanoTabs™ in Golden Syrian hamsters with a 14-day recovery period.	4.2.3.2
Local Tolerance		
692032	A repeat dose cheek pouch irritation study of AR-F01 sublingual sufentanil NanoTabs™ in the hamster.	4.2.3.6
Other Toxicity Studies		
(b) (4) 10-114	(b) (4) impurity B (b) (4): Salmonella- <i>E. Coli</i> /mammalian microsome reverse mutation assay	4.2.3.7.6
(b) (4) 11-143	(b) (4): Salmonella- <i>E. Coli</i> mammalian microsome reverse mutation assay	4.2.3.7.6
(b) (4) Derek	Derek Nexus Report – (b) (4) Impurity A	4.2.3.7.6
(b) (4) Derek	Derek Nexus Report – (b) (4)	4.2.3.7.6
(b) (4) LeadScope	Computational toxicity assessment using the Leadscope model applier – (b) (4) Impurity A	4.2.3.7.6
(b) (4) LeadScope	Computational toxicity assessment using the Leadscope model applier– (b) (4)	4.2.3.7.6

3.2 Studies Not Reviewed

The rest of the submitted studies were not reviewed because 1) they were not relevant for the safety evaluation of this application, 2) similar or more complete studies were available for review, or 3) they do not provide pivotal information in the nonclinical safety evaluation of the application.

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

No primary pharmacology studies were conducted for NDA 209128.

4.2 Secondary Pharmacology

No secondary pharmacology studies were conducted for NDA 209128.

4.3 Safety Pharmacology

No safety pharmacology studies were conducted for NDA 209128.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Non-GLP PK studies to compare the intravenous administration of sufentanil to the sublingual and oral administration of sufentanil in dogs were conducted, and these studies were previously reviewed by Dr. R. Daniel Mellon. The review by Dr. Mellon is included in this section.

The Applicant conducted a non-GLP dog PK study to compare sufentanil IV to sublingual [Study No. (b) (4) 591001].

The study was conducted in 3 male beagle dogs. Two different experimental formulations of 5 mcg Nanotabs (numbered 1 and 2) or IV injection was administered to these animals to determine relative bioavailability. In addition to PK data, animals were observed twice a day for mortality and morbidity. Clinical signs following IV administration included hypoactivity, excessive salivation, pale gums, and diarrhea. No clinical signs were noted following sublingual administration. There were no changes in body weights following either route of administration. Placebo tablet dissolution assessments indicated that 2 of 9 tablets dissolved within 5 minutes, 4 of 9 within 10 minutes and 3 of 9 dissolved within 15 minutes. All nanotab formulations of sufentanil dissolved within 30 minutes. T_{max} values were typically at about 10 minutes for formulation 1 and variable for formulation 2.

The PK data obtained is summarized below indicating that the relative bioavailability via the sublingual route is approximately 60%.

Table 4 Relative Sublingual Bioavailability in Beagle Dogs

MEAN PHARMACOKINETIC RESULTS for SUFENTANIL (5.0 µg)						
	AUC _{0-t} (pg•h/mL)	AUC _{0-∞} (pg•h/mL)	C _{max} (pg/mL)	t _{max} (h)	Half-life (h)	F*
Intravenous	202	220	537	0.028	0.84	-
Sublingual Formulation 1	120	129	278	0.17	0.43	0.57
Sublingual Formulation 2	113	133	294	0.40	0.30	0.60

*F = Bioavailability

In a second non-GLP study [Study No. (b) (4) 591014], IV and sublingual formulations were compared to oral administration of a sufentanil solution (5 mcg). The results suggest that relative oral bioavailability of sufentanil was 11%. The results are summarized in Table 5.

Table 5 Relative Oral and Sublingual Bioavailability in Beagle Dogs

Mean Pharmacokinetic Results For Sufentanil (5.0 µg)						
	AUC _{0-t} (pg•h/mL)	AUC _{0-∞} (pg•h/mL)	C _{max} (pg/mL)	t _{max} (h)	Half-life (h)	F*
Intravenous	118	142	595	0.022	0.33	NA
Sublingual	27.0	50.0	209	0.10	NC	0.58
Oral (NanoTabs, Formulation 1)	7.74	17.4	33.8	0.24	NC	0.11

*F = Bioavailability. NA = Not applicable. NC = Not calculable.

5.2 Toxicokinetics

Toxicokinetic (TK) analysis of sublingual administration of sufentanil was conducted as part of the 28-day irritation/toxicity study in hamsters. See the TK results in the Repeat-Dose Toxicity section.

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity studies were conducted for NDA 209128.

6.2 Repeat-Dose Toxicity

A 28-day buccal pouch irritation/toxicity study in Golden Syrian Hamsters using sufentanil was conducted, and this study report was previously reviewed by Dr. BeLinda Hayes. The review by Dr. Hayes is included in this section.

Study title: A 28-day buccal pouch irritation/toxicity study with sufentanil sublingual NanoTabs™ in Golden Syrian hamsters with a 14-day recovery period.

Study no.:	(b) (4) 591014
Study report location:	EDR/4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 20, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ARX-01 NanoTabs™ CII 15 mcg Sufentanil, Batch № 3097675R, Purity: 98.7%
	ARX-01 Sublingual Sufentanil NanoTabs™ 30 mcg, Lot № 110623, Purity: 100.8%

Key Study Findings

Sufentanil NanoTabs (0, 15, 90, and 180 mcg/day) was administered sublingually via cheek pouch to golden hamsters for 28 days with the following results:

1. Sufentanil was readily absorbed following sublingual administration via the cheek pouch. Sufentanil was rapidly absorbed in the dose range of 15 to 180 mcg/day. T_{max} ranged from 0.5 to 4 hours on Day 0 and 1 to 2 hours on Day 27. The increases in $AUC_{(0-24h)}$ and C_{max} were dose-dependent. An increase in the exposure was noted with increasing doses; however, the increase was not quite dose-proportional.
2. No treatment-related deaths were noted in either gender.
3. No treatment-related localized irritation in the cheek pouch was noted.

4. Primary clinical signs observed are consistent with the pharmacological properties of sufentanil. Treatment-related clinical signs include rigid muscle tone, hypoactivity, impaired equilibrium, impaired muscle coordination, decreased respiration, and shallow breathing.
5. The NOAEL was identified as 180 mcg/day (in agreement with the Applicant), however, as the animals were blocked with naltrexone, these data should be interpreted with caution regarding conclusion for the systemic safety of sufentanil. This NOAEL corresponds to AUC value of 82.7 ng·h/mL on Day 27 for combined genders after repeated daily dosing for 28 days. C_{max} value at this dose on Day 27 was 16.5 ng/mL for combined genders.

Methods

Doses: 0, 15, 90, and 180 mcg/day
 Frequency of dosing: Once daily
 Route of administration: Sublingual
 Dose volume: Not applicable
 Formulation/Vehicle: Tablets/placebo sublingual tablet
 Species/Strain: Golden Syrian Hamster/Crl:LVG[SYR]RB
 Number/Sex/Group:

Toxicology Groups ((b) (4) 591014M and (b) (4) 591014F)

Group Number	Treatment	Number of Tablets/Dose	Dosage Level (µg/day)	Number of Animals ^a	
				Males	Females
1	Placebo to Sufentanil Sublingual NanoTabs™	6	0	15	15
2	Sufentanil Sublingual NanoTabs™ (15 µg)	1	15	15	15
3	Sufentanil Sublingual NanoTabs™ (30 µg)	3	90	15	15
4	Sufentanil Sublingual NanoTabs™ (30 µg)	6	180	15	15

Toxicokinetic Groups ((b) (4) 591014A and (b) (4) 591014B)

Group Number	Treatment	Number of Tablets/Dose	Dosage Level (µg/day)	Number of Animals	
				Males	Females
1A	Placebo to Sufentanil Sublingual NanoTabs™	6	0	3	3
2A	Sufentanil Sublingual NanoTabs™ (15 µg)	1	15	9	9
3A	Sufentanil Sublingual NanoTabs™ (30 µg)	3	90	9	9
4A	Sufentanil Sublingual NanoTabs™ (30 µg)	6	180	9	9

^a = 10 animals/sex/group were euthanized following 28 days of dose administration; the remaining 5 animals/sex/group were euthanized following a 14-day nondosing (recovery) period.

Age: Approximately 7 weeks old (at initiation of treatment)

Weight: Toxicology Group: at randomization
Males (range): 94 g to 117 g
Females (range): 87 g to 112 g

Toxicokinetic Group: at randomization
Males (range): 95 g to 118 g
Females (range): 88 g to 110 g

Satellite groups: None

Unique study design: To avoid systemic opioid effects, animals were pretreated with naltrexone prior to treatment.

Deviation from study protocol: Deviations are described under the appropriate observation(s).

Observations and Results

Toxicokinetics

Blood samples were collected via the retro-orbital plexus under isoflurane anesthesia for toxicokinetic evaluation. Blood samples were collected from Group 1A animals predose, and approximately 1 hour on Study Days 0 and 27. Blood samples were collected from Groups 2A-4A animals at predose, at approximately 15, 30, and 45 minutes after dosing and at approximately 1, 2, 4, 8, and 24 hours after dosing on Study Days 0 and 27. Plasma concentrations of sufentanil were determined by using LC/MS/MS method. The lower limit of quantification was 50.0 pg/mL.

Table 6 Toxicokinetic parameters for sufentanil in male and female Golden hamsters

Sufentanil Dosage ($\mu\text{g}/\text{day}$):	Gender	Study Day 0			Study Day 27		
		15	90	180	15	90	180
Parameters (Units)							
Males							
AUC _{last} (ng·h/mL)		16.6	192	153	17.4	40.0	75.3
AUC _{inf} (ng·h/mL)		17.3	201	158	NA	NA	NA
C _{max} (ng/mL)		4.02	17.2	25.1	4.01	11.8	12.1
T _{max} (h)		0.75	4	0.5	2	1	2
T _{1/2} (h)		5.8	5.2	5.0	4.0	4.3	NR
Accumulation Ratio		NA	NA	NA	1.0	0.21	0.49
Females							
AUC _{last} (ng·h/mL)		24.6	152	247	10.9	60.3	90.1
AUC _{inf} (ng·h/mL)		24.7	154	254	NA	NA	NA
C _{max} (ng/mL)		5.27	20.9	30.0	2.39	10.9	20.9
T _{max} (h)		1	4	1	2	2	1
T _{1/2} (h)		3.0	3.5	4.7	3.9	NR	4.4
Accumulation Ratio		NA	NA	NA	0.44	0.40	0.37
Genders Combined							
AUC _{last} (ng·h/mL)		20.6	172	200	14.2	50.1	82.7
AUC _{inf} (ng·h/mL)		21.0	177	206	NA	NA	NA
C _{max} (ng/mL)		4.64	19.1	27.6	3.20	11.3	16.5
T _{max} (h)		0.88	4.0	0.75	2.0	1.5	1.5
T _{1/2} (h)		4.4	4.3	4.8	4.0	NR	4.6
Accumulation Ratio		NA	NA	NA	0.69	0.29	0.41

Units for dose-normalized AUC_{last} are (ng·h/mL)/(mg/kg); units for dose-normalized C_{max} are (ng/mL)/(mg/kg)

NR = Not reportable

Toxicokinetic analysis is presented in the above table. Hamsters buccally administered sufentanil sublingual Nanotabs via cheek pouch were systemically exposed to sufentanil. Exposure to sufentanil was dose-dependent; AUC and C_{max} increased with increasing doses, except for males on Study Day 0. Increase in exposure appeared to be less than dose-proportional over the 15 to 180 mcg/day range. Sufentanil was rapidly absorbed; T_{max} ranged from 0.5 to 4 hours on Study Day 0 and 1 to 2 hours on Study Day 27. There was no notable difference in systemic exposure between male and females.

Mortality

All animals were observed twice daily (morning and afternoon) for morbidity and mortality throughout the duration of the study.

None, all animals survived to the scheduled necropsies.

Clinical Signs

Clinical observations, including examination of the buccal mucosa of the cheek pouch, was performed on the toxicology animals twice daily, prior to dosing, and 30 minutes to 1 hour following dosing. As part of the clinical observation, respiration rate was counted in 5 animals/sex/group twice weekly. Respiration rate was counted 30 minutes to 1 hour after dosing over a 10-second period. During the recovery period, the toxicology animals were observed once daily.

Detailed physical examinations of the buccal mucosa of the cheek pouch (both right and left pouches) were performed on all animals 1 week prior to randomization (\pm 2 days), on the day of randomization, weekly (\pm 2 days), weekly (\pm 2 days) during the dosing period (dosing), and the recovery periods, and on the day of the scheduled necropsies. Edema and erythema were evaluated in accordance with the method of Draize.

No treatment-related observations of localized irritation in the buccal mucosa of the cheek pouch were observed following the sublingual administration of sufentanil Nanotabs at doses up to 180 mcg/day.

Table 7 Observed clinical signs in Golden hamsters administered sufentanil Nanotabs buccally for 28 days

Clinical Observations: Total Occurrence/№ of Animals				
	Dose (mcg/day)			
	0	15	90	180
Males				
Clinical Observation				
Behavior – CNS				
Prior to Dosing				
Rigid muscle tone	0/0	0/0	0/0	1/1
Impaired muscle coordination	0/0	0/0	0/0	2/2
30-min to 1-hour post-dosing				
Rigid muscle tone	0/0	200/15	300/15	290/15
Hypoactivity	0/0	32/14	43/15	55/15
Impaired equilibrium	0/0	5/5	33/15	26/15
Body flattened	0/0	36/14	95/15	56/15
Impaired muscle coordination	0/0	64/14	103/15	130/15
Cardio-pulmonary				
30-min to 1-hour post-dosing				
Decreased respiration	0/0	48/15	110/15	98/15
Shallow respiration	0/0	8/8	27/12	24/13
Females				
Clinical Observation				
Prior to Dosing				
Rigid muscle tone	0/0	0/0	0/0	1/1
Impaired muscle coordination	0/0	0/0	0/0	3/2
Circling	0/0	0/0	0/0	1/1
30-min to 1-hour post-				

Clinical Observations: Total Occurrence/№ of Animals				
	Dose (mcg/day)			
	0	15	90	180
dosing				
Rigid muscle tone	0/0	275/15	336/15	326/15
Hypoactivity	0/0	12/8	23/12	34/13
Impaired equilibrium	0/0	7/5	28/13	14/10
Body flattened	0/0	83/15	101/15	156/15
Impaired muscle coordination	0/0	70/15	138/15	156/15
Circling	0/0	2/2	6/4	9/6
Cardio-pulmonary				
30-min to 1-hour post-dosing				
Decreased respiration	0/0	80/15	118/15	111/15
Shallow respiration	0/0	2/2	6/4	9/6

As depicted in the table above, primary central nervous system treatment-related clinical signs observed at 30 minutes to 1 hour post-dosing included rigid muscle tone, hypoactivity, impaired equilibrium, body flattened, impaired muscle coordination, decreased respiration, and shallow respiration. These treatment-related clinical signs were observed in all treatment groups primarily during the first week of dosing. "Thereafter, observations of rigid muscle tone, body flattened and impaired muscle coordination continued to be noted somewhat consistently for the remainder of the dosing period in males and females, but at a lower incidence...."

Consistent with the expected pharmacological effects of sufentanil on respiration, treatment-related effects on respiration rate/breathing were observed. Relative to the control group, respiration rate was lower in all treatment-related animals throughout the dosing period, reaching statistical significant sometimes and often in male and female animals, respectively. Compared to the control group, respiration rate was lower by approximately 81% and 41% in females and males, respectively.

Body Weights

Body weights were recorded prior (1 week) to randomization (\pm 2 days), on day of randomization, Study Day 0 (prior to dosing), twice weekly during the dosing and recovery periods, and on the day prior to the scheduled necropsy (toxicology group only). Final body weight (fasted) was recorded on the day of the scheduled necropsy. Body weight data was presented as mean body weights and mean body weight gain for the corresponding intervals.

Figure 2 Mean body weight data in male Golden hamster buccally administered sufentanil for 28 days

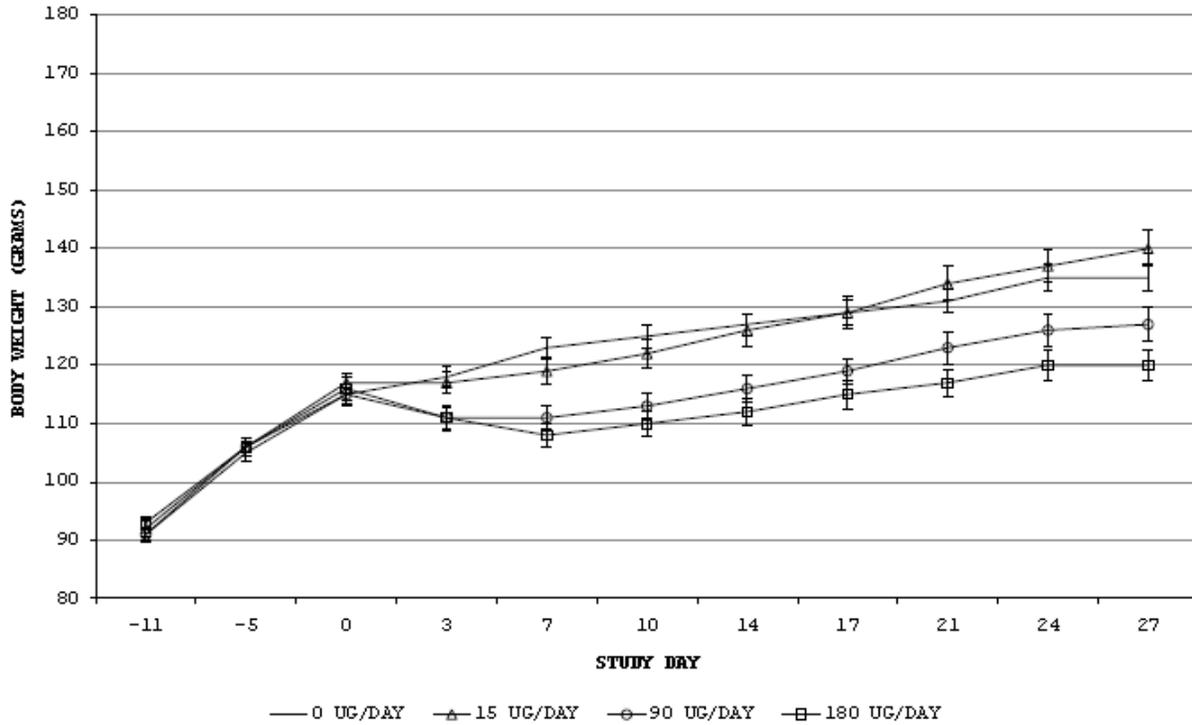
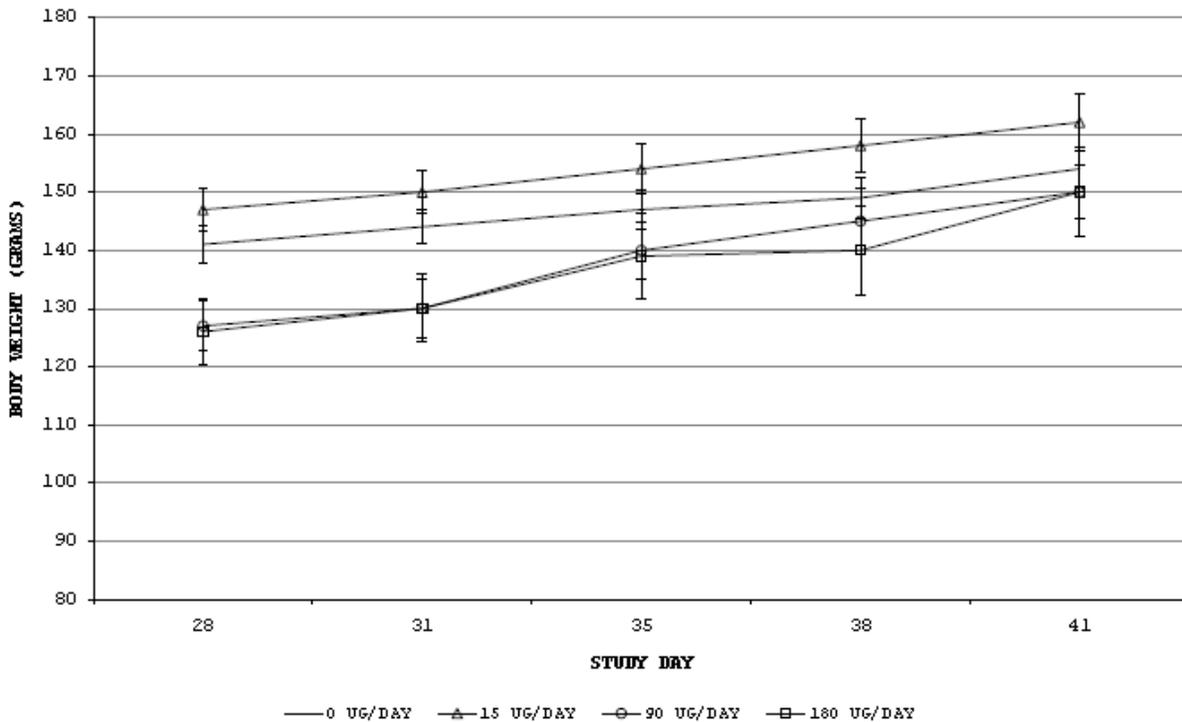


Figure 3 Mean body weight data during the recovery periods in male Golden hamster buccally administered sufentanil for 28 days



Males. Applicant's body weight data are presented in the figures above. A dose - dependent treatment-related decreases in body weight were noted in males. At the end of the treatment dosing period on Day 27, mean body weights were 5.9% and 11.1% lower in the 90 and 180 mcg/day groups, respectively, compared to the control groups. The mean body weights for the 90 and 180 mcg/kg/day groups were comparable to the vehicle control at the end of the recovery period.

Sufentanil-related effects on body weight gain were noted in the 90 and 180 mcg/day group during the first 1-2 weeks of the dosing period. A statistical significant decrease in mean body weight gain was observed during Study Days 0-3 (MD: 233.3%); HD: 266.7%) and 3-7 (MD: 100.0%; HD: 160%) compared to the control group. However, at the end of the treatment period, the mean body weight gain was comparable to control values.

Figure 4 Mean body weight data in female Golden hamster buccally administered sufentanil for 28 days

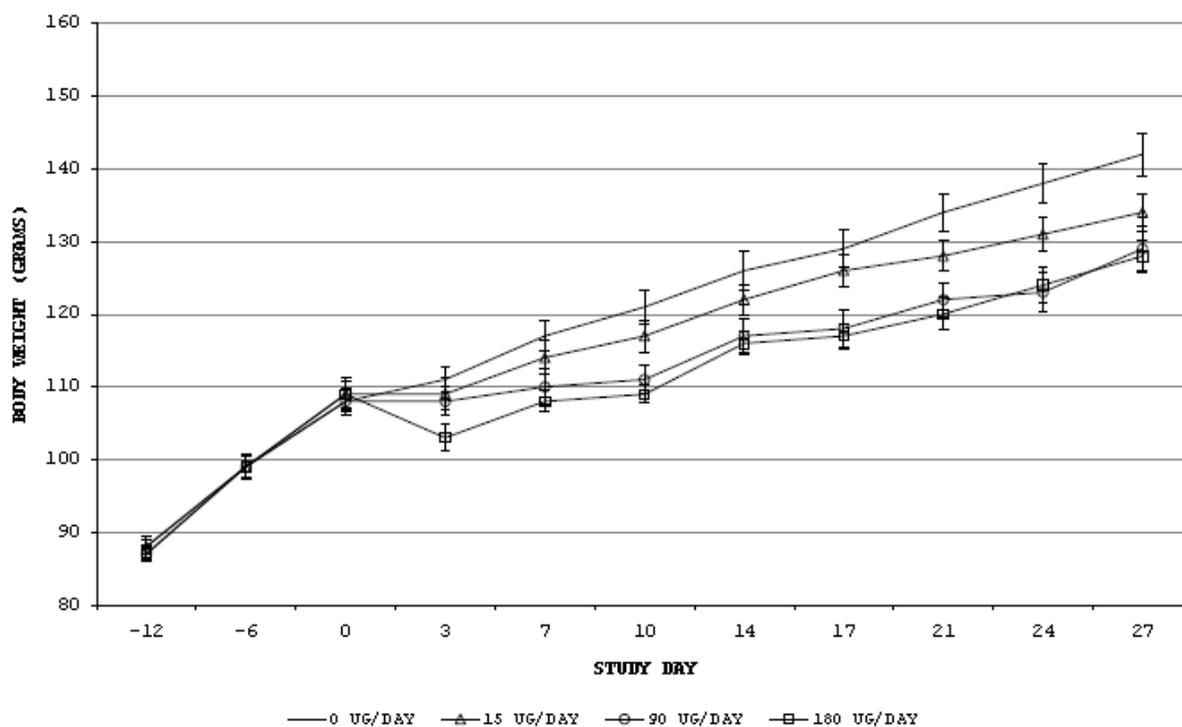
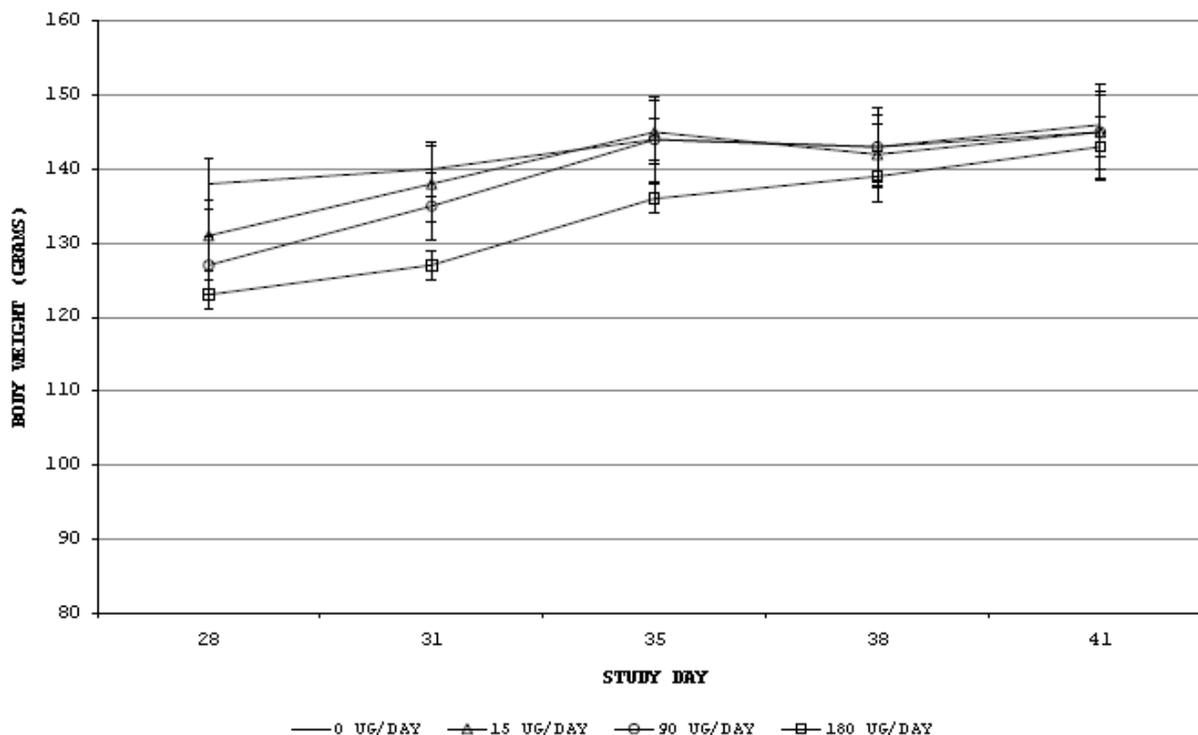


Figure 5 Mean body weight data during the recovery periods in female Golden hamster buccally administered sufentanil for 28 days



Females. Applicant's body weight data are presented in the figures above. A dose-dependent treatment-related decrease in body weight was noted. At the end of the treatment dosing period on Day 27, mean body weights were 5.6%, 9.2%, and 9.9% lower in the 15, 90, and 180 mcg/day groups, respectively, compared to the control groups. The mean body weights for the 15, 90, and 180 mcg/kg/day groups were comparable to the vehicle control at the end of the recovery period.

Sufentanil-related effects on body weight gain were noted in the 90 and 180 mcg/day group during the first 1-2 weeks of the dosing period. A statistical significant decrease in body weight gain was observed during Study Days 0-3 (HD: 400%), 3-7 (MD: 71.4%) and 7-10 (MD: 75%, HD: 75%) compared to the control group. At the end of the treatment period, the mean body weight gain was comparable to control values.

Food Consumption

Food consumption was measured for the toxicology groups only. Food consumption was recorded at Week 1 (± 2 days) prior to randomization, and twice weekly (± 2 days) throughout the dosing and recovery periods. Food intake was calculated as food g/animals/day for the corresponding body weight intervals.

Table 8 Mean interval food intake (g/animal/day)

Dose (mcg/kg/day) →	Mean Food Consumption (g/kg/day) ± SD (% change of control)			
	0	15	90	180
Males				
Interval				
Day -11 -5	16.0 ± 4.7	17.0 ± 2.1 (+6.25%)	17.0 ± 2.9 (+6.25%)	17.0 ± 2.9 (+6.25%)
Day 0 to 3	12.0 ± 4.3	10.0 ± 2.0 (-16.7%)	10.0 ± 3.5 (-16.7%)	6.0 ± 2.8** (-50.0%)
Day 3 to 7	16.0 ± 4.3	12.0 ± 2.8* (-25.0%)	11.0 ± 3.2** (-31.3%)	11.0 ± 4.0** (-31.3%)
Day 7 to 10	13.0 ± 5.7	12.0 ± 2.4 (-7.7%)	11.0 ± 4.4 (-7.7%)	10.0 ± 2.8 (-23.1%)
Day 10 to 14	17.0 ± 4.5	12.0 ± 2.3 (-29.4%)	15.0 ± 4.5 (-11.8%)	15.0 ± 4.9 (-11.8%)
Day 14 to 17	15.0 ± 4.9	14.0 ± 3.9 (-6.7%)	19.0 ± 2.1 (+26.7%)	10.0 ± 5.0 (-33.3%)
Day 17 to 21	17.0 ± 6.1	15.0 ± 2.5 (-11.8%)	14.0 ± 2.9 (-17.7%)	14.0 ± 4.5 (-17.7%)
Day 21 to 24	17.0 ± 5.4	11.0 ± 3.7* (-35.3%)	12.0 ± 3.7* (-29.4%)	19.0 ± 5.1 (+11.8%)
Day 24 to 27	11.0 ± 2.7	12.0 ± 2.0 (+9.1%)	11.0 ± 1.6 (0%)	11.0 ± 2.4 (0%)
Females				
Day -12 -6	15.0 ± 4.9	13.0 ± 4.8	14.0 ± 3.2	15.0 ± 5.0
Day 0 to 3	11.0 ± 2.9	14.0 ± 4.2 (+27.3%)	13.0 ± 5.1 (-18.2%)	11.0 ± 5.4 (-0%)
Day 3 to 7	13.0 ± 2.2	10.0 ± 1.8* (-23.1%)	9.0 ± 2.2** (-30.8%)	10.0 ± 1.5* (-23.1%)
Day 7 to 10	17.0 ± 4.2	16.0 ± 3.1 (-5.9%)	16.0 ± 4.5 (-5.9%)	15.0 ± 5.9 (-11.8%)
Day 10 to 14	14.0 ± 4.6	12.0 ± 4.2 (-14.3%)	12.0 ± 4.1 (-14.3%)	15.0 ± 5.5 (+7.1%)
Day 14 to 17	12.0 ± 3.6	15.0 ± 5.3 (+25.0%)	14.0 ± 5.1 (+16.7%)	12.0 ± 2.1 (0%)
Day 17 to 21	12.0 ± 4.2	13.0 ± 3.6 (+8.3%)	12.0 ± 2.1 (0%)	12.0 ± 4.3 (0%)
Day 21 to 24	16.0 ± 7.9	11.0 ± 4.9 (-31.3%)	11.0 ± 2.9 (-31.3%)	18.0 ± 2.6 (-12.5%)
Day 24 to 27	15.0 ± 4.1	13.0 ± 2.3 (-13.3%)	12.0 ± 1.7 (-20.0%)	13.0 ± 4.6 (-13.3%)
*: Statistically significant when compared to control at p ≤ 0.05 (Dunnett's test)				
**: Statistically significant when compared to control at p ≤ 0.01 (Dunnett's test)				

Food consumption data is presented in the table above. Treatment-related effects on food consumption were observed. Relative to control, decrease in food consumption was mainly noted during the first 2 weeks of the dosing period in the 15, 90, and 180 mcg/day male and female groups. Relative to the vehicle control group from Study Day 3 to 7, the mean food intake (g/animal/day) was statistically significantly lower in both male and females. Lower food consumption was correlated with the decrease body weight. At the end of the recovery period, food consumption was comparable to the control group.

Ophthalmoscopy

Using an indirect ophthalmoscope and slit lamp biomicroscope, an ophthalmological examination was performed on all animals once prior to randomization and near the end of the dosing period.

Examination of the eyes at the end of the 28-day dosing period did not show any apparent test-article related effects.

ECG

Not performed.

Hematology

Blood was collected from the retro-orbital sinus under isoflurane anesthesia from all animals (fasted overnight) assigned to the scheduled necropsies at the end of the treatment period and in the recovery group at the end of the recovery period. The following hematology parameters were examined:

Hematology Parameters	
White Blood Cell Parameters	Red Blood Cell Parameters
White blood cell count	Erythrocyte count (RBC)
Differential leukocyte count (Percent and Absolute)	Red Cell Morphology
- Neutrophil (NEUT)	
- Monocyte (MONO)	
- Lymphocyte (LYM)	
- Eosinophil (EOS)	
- Basophil (BASO)	
- Large unstained cell (LUC)	
	Red Cell Distribution Width (RDW)
	Hemoglobin Distribution Width (HDW)
	Hemoglobin (HGB)
	Hematocrit (HCT)
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	Mean corpuscular hemoglobin concentration (MCHC)
	Mean platelet volume (MPV)
	Absolute Reticulocyte Count (RET)
	Percentage of Reticulocyte
	Platelet Estimate
	Platelet Count (PLT)

Coagulation: The following coagulation parameters were examined:

Coagulation Parameters
Activated partial thromboplastin Time (APTT)
Prothrombin Time (PT)

Table 9 Significant changes in hematology parameters in Golden hamster following sublingual administration of sufentanil

Parameter	Hematology: Percent Change from Control			
	Dose (mcg/day)			
	0	15	90	180
Main Study Group				
Males				
RBC (mil/mcL)	8.02 ± 0.312	+7.2*	+11.9*	+11.1*
HGB (g/dL)	17.4 ± 0.063	+9.8**	+14.4**	+12.6**
HCT (%)	50.4 ± 1.64	+10.5**	+16.3**	+13.1**
HDW (g/dL)	1.81 ± 0.061	0.0	+3.3	+5.5**
RDW (%)	12.2 ± 0.37	+2.5	+5.7*	+6.6*
Females				
RBC (mil/mcL)	8.46 ± 0.288	+5.3*	+9.20**	+10.0**
HGB (g/dL)	17.4 ± 0.69	+10.9**	+12.6**	+13.2**
HCT (%)	50.5 ± 1.68	+10.7**	+13.5**	+13.1**
RDW (%)	13.1 ± 0.39	+6.1**	+8.4**	+8.4**
APTT (sec)	15.9 ± 1.52	+4.4	+11.3	+13.2*
Recovery Group				
Males				
RBC (mil/mcL)	9.46 ± 0.433	+1.2	-4.3	-7.3
HGB (g/dL)	18.2 ± 0.52	+2.2	-3.3	-6.6
HCT (%)	52.4 ± 1.40	2.5	-2.1	-5.5
HDW (g/dL)	1.86 ± 0.027	-1.1	-0.5	4.8
RDW (%)	12.4 ± 0.25	0.0	2.4	4.8*
Females				
RBC (mil/mcL)	8.61 ± 0.329	-2.6	-2.6	-0.7
HGB (g/dL)	17.7 ± 0.49	-0.6	-1.7	0.0
HCT (%)	50.6 ± 1.59	0.6	-0.8	1.8
RDW (%)	12.6 ± 0.27	0.8	1.6	4.8
APTT (sec)	17.1 ± 0.90	-2.3	4.1	-0.6
*: Significant different from the control group at 0.05 (Dunnett's test).				
**: Significant different from the control group at 0.01 (Dunnett's test).				

Results indicated some significant changes in hematology parameters in the LD, MD, and HD groups at the end of the 28-day dosing period. Significant changes

noted are summarized in the table above. Treatment-related alterations in red cell hematologic parameters were observed in males and females sublingually administered sufentanil. Relative to the control, red blood cell counts (RBC), red cell distribution (RDW), and hemoglobin distribution width (HDW) were higher. Hematological changes observed in red blood cell parameters, with the exception of RWD in HD male group, were reversible; these hematological changes were comparable to the control at the end of the recovery period. *The reviewer does not consider these changes to be toxicologically relevant.*

Clinical Chemistry

Blood was collected from the abdominal aorta under isoflurane anesthesia from all surviving animals (fasted overnight, water allowed) in the main study group at the end of the treatment period and in the recovery group at the end of the recovery period. The following clinical chemistry parameters were examined:

Plasma Chemistry Parameters	
Alanine aminotransferase (ALT)	Bicarbonate (HCO ₃)
Albumin (ALB)	Potassium (K)
Alkaline phosphatase (ALP)	Sodium (NA)
Aspartate amino transferase (AST)	Total bilirubin (Total Bili)
Calcium (CA)	Urea nitrogen (URE)
Chloride (CL)	Total Protein (T.Pro)
Total Cholesterol (Cholesterol)	Triglycerides (TRG)
Creatinine (Creat)	Albumin /globulin ratio (A/G)
Creatinine Kinase (CK)	Sorbitol dehydrogenase (SDH)
Gamma glutamyltransferase (GGT)	Direct bilirubin (Direct Bili)
Globulin (Glob)	Indirect bilirubin (Indirect Bili)
Glucose (GLU)	Hemolysis

Table 10 Selected serum chemistry parameters - primary necropsy (mean % difference from control)

Dosage Level (µg/day)	Males				Females			
	0	15	90	180	0	15	90	180
Cholesterol (mg/dL)	108	128 (18.5)	148 (37.0)	150 (38.9)	104	96 (-7.7)	110 (5.8)	118 (13.5)
ALP (U/L)	145	149 (2.8)	160 (10.3)	173 (19.3)	170	173 (1.8)	192 (12.9)	169 (-0.6)

Table 11 Selected serum chemistry parameters - recovery necropsy (mean % difference from control)

Dosage Level ($\mu\text{g/day}$)	Males				Females			
	0	15	90	180	0	15	90	180
Cholesterol (mg/dL)	110	130 (18.2)	132 (20.0)	124 (12.7)	95	89 (-6.3)	97 (2.1)	101 (6.3)
ALP (U/L)	139	147 (5.8)	135 (-2.9)	156 (12.2)	191	180 (-5.8)	186 (-2.6)	187 (-2.1)

Treatment-related changes in cholesterol and alkaline phosphatase levels were noted. Significant changes in clinical chemistry parameters are summarized in the Applicant's table above. Relative to control, cholesterol was significantly higher in the LD, MD, and HD male groups; alkaline phosphatase was significantly higher in the HD male group. In females, alkaline phosphatase was significantly higher in the MD group compared to control. At the end of the recovery period, cholesterol levels were not significantly different, but remained slightly higher compared to the control group.

Urinalysis

Not performed.

Gross Pathology

Surviving animals were euthanized by exsanguination under carbon dioxide inhalation on completion of treatment (Day 28) or recovery period (Day 42). Macroscopic evaluation was performed on all animals at the scheduled sacrificed (Weeks 26 and 30). Macroscopic evaluation was performed on all orifices, external surface of the body, cranial cavity, thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

There were no apparent treatment-related macroscopic changes.

Organ Weights

Relative organ-to-body weights and organ-to brain weights were calculated for all animals at the scheduled necropsy. Organs weighed are tabulated below:

Adrenal glands (paired)
Brain
Epididymides
Heart
Kidneys (paired)
Liver
Spleen
Paired organs were weighed together.

There were no apparent treatment-related effects on organ weights. However, statistically significant relative organ weight changes were observed in the brain, kidney, heart, and liver. Relative to final body weight, brain weights was higher in the HD males (14%) and females (11%) and MD females (11%); higher heart weights in the HD males (18%) and females (26%) and in the MD males (12.0%); higher kidney weights in the HD males (10%) and females (7%). There were no correlating gross or histological lesions. These organ weight changes were considered to be an indirect test article-related effect of lower final body weight. These findings are not considered biologically significant.

Histopathology

Adequate Battery: Yes

Peer Review: The peer review pathology report was submitted and signed by Ann Radowsky, DVM, PhD, DACVP, DABT (b) (4).

Histological Findings

The following tissues were collected from all animals. Histological examination was conducted on the high-dose, control group animals. Also, all gross lesions from all the animals were examined microscopically. All tissues were fixed in 10% neutral buffered formalin with the exception of the eyes (with optic nerves) that were fixed in Davidson's solution and the epididymis/testes that were fixed in a modified Davidson's solution. Tissue selected for microscopic analysis were processed and stained with Hematoxylin Eosin stain and examined by light microscopy.

There were no apparent treatment-related histologic changes. Also, there were no signs of treatment-related irritation in the cheek pouches.

Special Evaluation

None

Dosing Solution Analysis

The Applicant did not perform homogeneity and concentration assessments.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

No Ames assays using sufentanil were conducted for NDA 209128.

7.2 *In Vitro* Assays in Mammalian Cells

No *in vitro* genotoxicity studies in mammalian cells with sufentanil were conducted for NDA 209128.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

No *in vivo* genotoxicity studies with sufentanil were conducted for NDA 209128.

7.4 Other Genetic Toxicity Studies

Ames assays studies using impurities (b) (4) along with *in silico* assessment of other impurities (b) (4) were conducted. These study reports were previously reviewed by Dr. BeLinda Hayes. The review by Dr. Hayes is included in this section.

Study title: (b) (4) **Impurity B** (b) (4) **: Salmonella-E. Coli/Mammalian microsomal Reverse Mutation Assay**

Study no.: (b) (4) 10-114
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: February 8, 2010
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: EP-B, Lot № B7928P146-3, 96.6% purity

Key Study Findings

Under the conditions of the study, (b) (4) was negative in the bacterial reverse mutation assay.

Methods

Strains: *Salmonella typhimurium* TA100, TA1535, TA98, and TA1537
Escherichia coli WP2uvrA

Concentrations in definitive study: Without S9 mix:
All tester strains: 100, 250, 500, 1000, 2500, and 5000 mcg/plate

With S9 mix:
All tester strains: 100, 250, 500, 1000, 2500, and 5000 mcg/plate

Basis of concentration selection: Doses were obtained after a preliminary dose range finding toxicity-mutation assay with 25, 50, 100, 250, 500, 1000, 2500, and 5000 mcg/plate in all strains in the presence and absence of the metabolic activation system. Precipitation and cytotoxicity (i.e., reduction in the background lawn) were not observed in any of the strains with or without the metabolic activation system.

Negative control: Dimethyl sulfoxide (DMSO)

Positive control: Without S9 mix:
Sodium azide (AF-2, 1.0 mcg/plate) for TA100 and TA1535
4-nitroquinoline-N-oxide (AF-2, 2.0 mcg/plate) for WP2uvrA
2-nitrofluorene (NaN₃, 2.5 mcg/plate) for TA98
ICR-191 acridine (9-AA, 0.5 mcg/plate) for TA1537

With S9 mix:
2-aminoanthracene (2-AA, 2.5 mcg/plate) for TA98, TA100, TA1535, and TA1537
2-AA (10 mcg/plate) for WP2uvrA

Formulation/Vehicle: Solution/DMSO

Incubation & sampling time: The reverse mutation test was performed according to the pre-incubation and plate-incorporation method. The test and control substances were carried out in triplicate with and without S9-mix. In the pre-incubation stage, the test substance solution, negative control, or positive control were mixed with the bacterial cells and incubated with gentle shaking for 20 min at 37°C (pre-incubation). After pre-incubation,

2 mL of the molten top agar was added to the mixture, and poured onto a minimal glucose agar plate. The agar plate was incubated at 37°C for 2 days. The mean number of revertants per plate was calculated for the control and test plates.

Study Validity

The study appears to be valid for the following reasons: 1) the appropriate strains were tested, 2) the appropriate controls were used, and 3) the positive control substances produced reliable results and were within or close to the historical control range. The assay methods, positive and negative controls, and the concentrations of drug used for the definitive study were adequate.

Results

Under the conditions of the study, [REDACTED] ^{(b) (4)} was negative in the bacterial reverse mutation assay.

In the dose-range finding assay, [REDACTED] ^{(b) (4)} was evaluated at concentrations of 25, 50, 100, 250, 500, 1000, 2500, and 5000 mcg/plate with and without metabolic activation. Precipitation and cytotoxicity (i.e., reduction in the background lawn) were not observed in any strain in either the presence or absence metabolic activation. Based on these data, concentrations of 100, 250, 500, 1000, 2500, and 5000 mcg/plate were evaluated in the confirmatory assay.

Table 12 Confirmatory Mutagenic Assay: Summary results
in the Ames assay

(b) (4)

REVERTANT COLONIES PER PLATE—Mean (SD)



(b) (4)

Results from the confirmatory assay are presented in the Applicant's table above. There was no evidence of base-pair or frameshift mutagenic potential of (b) (4) (b) (4) that would be expected from metabolic activation. The positive controls induced mutation frequencies as expected; the mean revertants per plate were within historical control data for the laboratory, thus confirming the ability to detect mutations under the conditions of the assay. Compared to the vehicle control groups, (b) (4) (b) (4) did not increase the number of revertants for the *Salmonella typhimurium* strains (TA98, TA100, TA1535, or TA1537) or the *Escherichia coli* test strain (WP2uvrA) in the presence or absence of the metabolic activator. A slight reduction in the background lawn was observed at 5000 mcg/plate in TA98, TA1537, and TA1535 in the presence and absence of metabolic activation.

Study title: (b) (4) : **Salmonella-E Coli/Mammalian
Microsome Reverse Mutation Assay**

Study no.: (b) (4) 11-143
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: March 15, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: (b) (4), Lot No
B8802P146, 97.64% purity

Key Study Findings

Under the conditions of the study, (b) (4) was negative in the bacterial reverse mutation assay.

Methods

Strains: *Salmonella typhimurium* TA100, TA1535, TA98, and TA1537
Escherichia coli WP2uvrA

Concentrations in definitive study: Without S9 mix:
 All tester strains: 100, 250, 500, 1000, 2500, and 5000 mcg/plate

With S9 mix:
 All tester strains: 100, 250, 500, 1000, 2500, and 5000 mcg/plate

Basis of concentration selection: Doses were obtained after a preliminary dose-range finding toxicity mutation assay with 25, 50, 100, 250, 500, 1000, 2500, and 5000 mcg/plate in all strains in the presence and absence of the metabolic activation system. Precipitation was not observed in any of the strains with or without the metabolic activation system. Cytotoxicity (i.e., reduction in the background lawn/mean number of revertant colonies) was observed at 5000 mcg/plate in TA1537 and TA1535 in the absence of metabolic activation.

Negative control: Dimethyl sulfoxide (DMSO)

Positive control: Without S9 mix:
 Sodium azide (AF-2, 1.0 mcg/plate) for TA100 and TA1535
 4-nitroquinoline-N-oxide (AF-2, 2.0 mcg/plate) for WP2uvrA
 2-nitrofluorene (NaN₃, 2.5 mcg/plate) for TA98
 ICR-191 acridine (9-AA, 0.5 mcg/plate) for TA1537

With S9 mix:
 2-aminoanthracene (2-AA, 2.5 mcg/plate) for TA98, TA100, TA1535 and TA1537
 2-AA (10 mcg/plate) for WP2uvrA

Formulation/Vehicle: Solution/DMSO

Incubation & sampling time: The reverse mutation test was performed according to the pre-incubation and plate-incorporation method. The test and control substances were carried out in triplicate with and without S9-mix. In the pre-incubation stage, the test substance

solution, negative control, or positive control were mixed and incubated with gentle shaking for 20 min at 37°C (pre-incubation). After pre-incubation, 2 mL of the molten top agar was added to the mixture, and poured onto a minimal glucose agar plate. The agar plate was incubated at 37°C for 2 days. The mean number of revertants per plate was calculated for the control and test plates.

Study Validity

The study appears to be valid for the following reasons: 1) the appropriate strains were tested, 2) the appropriate controls were used, and 3) the positive control substances produced reliable results and were within or close to the historical control range. The assay methods, positive and negative controls, and the concentrations of drug used for the definitive study were adequate.

Results

Under the conditions of the study, (b) (4) was negative in the bacterial reverse mutation assay.

Table 13 Confirmatory Mutagenic Assay: Summary results
(b) (4) in the Ames Assay

(b) (4)

REVERTANT COLONIES PER PLATE—Mean (SD)^a

(b) (4)

Results from the confirmatory assay are presented in the Applicant's table above.

There was no evidence of base-pair or frameshift mutagenic potential of (b) (4)

(b) (4) that would be expected from metabolic activation. The positive controls induced mutation frequencies as expected; the mean revertants per plate were within historical control data for the laboratory, thus confirming the ability to detect mutations under the conditions of the assay. Compared to the vehicle control groups, (b) (4) (b) (4) did not increase the number of revertants for the *Salmonella typhimurium* strains (TA98, TA100, TA1535, or TA1537) or the *Escherichia coli* test strain (WP2uvrA). Precipitation and cytotoxicity were not observed in any strain in the presence or absence of the metabolic activation.

7.5 DEREK and Leadscope Assessment of (b) (4) Impurity A and (b) (4)

The potential toxicities of sufentanil degradation products, (b) (4) Impurity A (b) (4), were assessed using the *in silico* toxicity program DEREK for Windows and Leadscope. These *in silico* analyses were previously reviewed by Dr. BeLinda Hayes, and the review by Dr. Hayes is included in this section. The structures of the compounds that were evaluated are shown in the figures below.



Carcinogenicity, chromosome damage, genotoxicity and mutagenicity endpoints were searched in the DEREK analysis. The DEREK evaluation did not indicate genotoxicity, mutagenicity, chromosome damage, or carcinogenic potential (b) (4) Impurity A and (b) (4); these two impurities will be considered qualified for genotoxic potential.

Carcinogenicity and genotoxicity were also searched in the Leadscope Model Applier Suites to predict the toxicity of (b) (4) Impurity A and (b) (4). The Leadscope evaluation predicted that these two impurities were negative for

genotoxicity and rodent carcinogenicity. The Agency only considers these QSAR models valid for predictions of mutagenicity at this time.

A consult was submitted to CDER Office of Translational Sciences requesting them to independently evaluate the potential mutagenicity of (b) (4). The mutagenic potential of these sufentanil impurities was evaluated using a quantitative structure-activity relationship (QSAR) model. CDER Office of Transitional Sciences validated the Applicant's DEREK and Leadscope predictions. As shown in the predictions below, QSAR model analysis predicted that (b) (4) would be negative for genetic toxicity in the Salmonella mutagenicity test and did not contain a structural alert. (b) (4) was also predicted to be negative for rodent carcinogenicity.

Figure 8 (b) (4) **QSAR predictions**

Software	Salmonella Mutagenicity	E. coli Mutagenicity
Derek Nexus	NSA	NSA
Model Applier	-	-
CASE Ultra/MC4PC	-	-
Overall Software Prediction	-	-
Overall Expert Prediction	-	-

Figure 9 (b) (4) **QSAR predictions**

Software	Salmonella Mutagenicity	E. coli Mutagenicity
Derek Nexus	NSA	NSA
Model Applier	-	-
CASE Ultra/MC4PC	-	-
Overall Software Prediction	-	-
Overall Expert Prediction	-	-

8 Carcinogenicity

No new carcinogenicity studies were conducted for NDA 209128.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

No new fertility and early embryonic developmental toxicity study was conducted for NDA 209128.

9.2 Embryonic Fetal Development

No new embryo-fetal developmental toxicity studies were conducted for NDA 209128.

9.3 Prenatal and Postnatal Development

No new prenatal and postnatal developmental toxicity was conducted for NDA 209128.

10 Special Toxicology Studies

A repeat-dose cheek pouch irritation study in hamsters using sufentanil was conducted, and the study report was previously reviewed by Dr. R. Daniel Mellon. The review by Dr. Mellon is included in this section.

Study title: A Repeat-Dose Cheek Pouch Irritation Study of ARX-F01 Sublingual Sufentanil NanoTabs in the Hamster (Final)

Study no.: 692032
 Study report location: SDN-1, Volume 4
 Conducting laboratory and location: (b) (4)
 Date of study initiation: Not stated, study dated 14-Mar-2008
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: 10 mcg tablets (9.6 mcg)
 80 mcg tablets (75 mcg)

The study employed male and female Golden Syrian hamsters (*Mesocricetus auratus*). The tablets were placed deep into the left cheek pouch and the animals were observed for 10 minutes to determine if they expelled the tablet or not. The right cheek pouch was the untreated control. The study design is depicted in the table below, reproduced from the submission:

Table 14 Study Design: 4-Day Hamster Cheek Pouch

Group/Identification	Sufentanil Dose (µg)	Naltrexone HCl Dose (mg/kg)	Number of Doses per Day	Days of Exposure	Number of Animals ^c
1/ ARX-F01 Placebo: 1 tablet	0	10	5	4	9 males/ 9 females
2/ ARX-F01 Placebo: 2 tablets ^a	0	10	5	4	9 males/ 9 females
3/ ARX-F01 10µg Sublingual Sufentanil NanoTabs TM : 2 tablets ^b	20	10	5	4	9 males/ 9 females
4/ ARX-F01 80 µg Sublingual Sufentanil NanoTabs TM : - 1 tablet	80	10	5	4	9 males/ 9 females

a Both tablets were placed into the same cheek pouch

b 20 µg dose was delivered using two 10 µg tablets into the same cheek pouch

c 3 males and 3 females per group designated as recovery animals (Recovery period of 1 week).

Tablet formulations tested included the 10 mcg strength and the 80 mcg strength. The composition of the tablets is provided in the tables below:

Table 15 Composition of Placebo Formulations (5-Day Hamster Cheek Pouch)

Composition:

Component	Amount per Tablet (Mg)	Amount in Tablet (%)
Sufentanil Citrate, USP		(b) (4)
Mannitol, EP/USP/JP		
Di-calcium Phosphate (b) (4)		
USP/FCC/EP		
Hydroxypropyl Methylcellulose (b) (4)		
EP		
Stearic Acid, NF/EP/BP/JP		
Magnesium Stearate, NF (b) (4)		
Total		

Table 16 Composition of 80 mcg Tablets (5-Day Hamster Cheek Pouch)

Composition:

Component	Amount per Tablet (Mg)	Amount in Tablet (%)
Sufentanil Citrate, USP		(b) (4)
Mannitol, EP/USP/JP		
Di-calcium Phosphate (b) (4)		
USP/FCC/EP		
Hydroxypropyl Methylcellulose (b) (4)		
EP		
Stearic Acid, NF/EP/BP/JP		
Magnesium Stearate, NF (b) (4)		
Total		

As noted in the table above, to avoid systemic opioid effects, animals were pretreated with naltrexone prior to treatment. Animals were examined for mortality, signs of ill health, and test-article-related effects. Local tissue evaluations were conducted prior to each dose and body weights were recorded daily. Animals were sacrificed on Day 5 for acute assessments or Day 11 for delayed observations. Gross necropsy was completed on animals. Local tissue was examined microscopically. All standard toxicology study tissues were stored, but not analyzed histopathologically.

Key Study Findings

Clinical Signs

There was transient and sporadic swelling and reddening of the cheek pouch across groups and even in one control animal. However, these findings were not deemed clinically significant or clearly dose dependent. Overall, there was no adverse local tissue reaction with the sublingual formulations.

11 Integrated Summary and Safety Evaluation

The Applicant AcclRx Pharmaceuticals, Inc. has submitted a New Drug Application (NDA) for Sufentanil Sublingual Tablet 30 mcg (Dsuvia), a drug-device combination product, for the management of moderate-to-severe acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate, in adult patients in a medically supervised setting. The applicator is used as a placement aid for the healthcare professional to deliver a single sufentanil 30 mcg sublingual tablet, on an as needed basis, per patient request, with a minimum of 1 hour between doses, and thereby the maximum daily dose (MDD) for the Dsuvia product is 720 mcg (30 mcg X 24 tablets). The current NDA was submitted via 505(b)(2) pathway with Sufenta (NDA 19050, which was first approved in 1984) as a reference product, and the nonclinical development program outlined in this NDA submission relies, in part, on the FDA's previous findings and safety and efficacy of Sufenta. To bridge the alternative route of administration (sublingual) from the reference product for the intravenous and epidural routes of administration, the Applicant conducted the nonclinical studies, including a GLP 28-day cheek pouch toxicity study in hamsters and a GLP repeat-dose cheek pouch irritation study in hamsters. Additionally, Ames assays using impurities (b) (4), along with *in silico* assessments to qualify the safety of other product degradants, were conducted. The highlights of these studies along with available pharmacology and toxicology data of sufentanil from the Sufenta drug label and literature are described in this section.

Sufentanil is an opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The Applicant included available binding data of sufentanil to mu-, kappa- and delta-opioid receptors from the literature. See Table 17.

Table 17 Sufentanil binding constant (specificity relative to mu receptor) at opioid receptors [taken directly from 2.4 Nonclinical Overview, p 8]

Source	Mu (nM)	Kappa (nM)	Delta (nM)	Citation
Rat cerebrum	1.25	-	45 (36)	Clark 1988
Rat brain	1.5	-	-	Ilien 1988
Rat brain	0.6	-	-	Rosenbaum 1985
Rat brain ex vivo	2.8	-	-	Cox 1998
Rhesus monkey cortex	1.18	>10,000 (>850)	81.1 (69)	Clark 1988
Guinea pig cerebellum	-	998	-	Clark 1988
Rhesus monkey cortex	0.19	37.8 (200)	25.0 (130)	Emmerson 1994

- = Not tested

The principal therapeutic action of sufentanil is analgesia and sedation, which is thought to be mediated through opioid-specific receptors throughout the central nervous system

(CNS). Like all opioid agonists, there is no ceiling effect to analgesia. When used in balanced general anesthesia, sufentanil has been reported to be as much as 10 times as potent as fentanyl. Pharmacodynamics features of sufentanil include respiratory depression by direct action on brain stem respiratory centers, miosis even in total darkness, peripheral vasodilation, which may result in orthostatic hypotension or syncope, and a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Opioids inhibit the secretion of adrenocorticotrophic hormone, cortisol, and luteinizing hormone in humans. They also stimulate prolactin, growth hormone secretion, and pancreatic secretion of insulin and glucagon. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility.

Opioids also have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models although the clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Sufentanil is highly lipophilic, thus allowing rapid distribution and penetration in the CNS. Plasma protein binding of sufentanil, related to the alpha acid glycoprotein concentration, was approximately 93% in healthy males, 91% in mothers, and 79% in neonates. Sufentanil is metabolized in the liver and small intestine. Approximately 80% of the administered dose is excreted within 24 hours, and only 2% of the dose is eliminated as unchanged drug. In adults, IV sufentanil is metabolized rapidly with an elimination half-life of ~2.7 hours, however, in neonates (0-1 month old) the elimination half-life is ~7.2 hours.

Sufentanil was not genotoxic in the *in vitro* bacterial reverse mutation assay (Ames assay) or in the *in vivo* rat bone marrow micronucleus assay. Long-term studies in animals to evaluate the carcinogenic potential of sufentanil have not been conducted.

Fertility and early embryonic developmental toxicity studies were conducted in male and female rats that were intravenously administered sufentanil doses of 0.005, 0.02, or 0.08 mg/kg for 56 days and 14 days prior to mating through gestation, respectively. Increased mortality was noted in all sufentanil-dosed groups. Lower pregnancy rates were noted following treatment of males at doses of 0.02 and 0.08 mg/kg, suggesting the potential for an adverse effect on fertility in males. Increased resorption of fetuses and reduced litter size was noted in high dose females, suggesting the potential for embryo-fetal toxicity, likely due to maternal toxicity.

In an embryo-fetal developmental toxicity study in rats, pregnant rats were intravenously administered sufentanil doses of 0.005, 0.02, or 0.08 mg/kg/day. No malformations or other embryotoxic effects were noted despite maternal toxicity (increased mortality in

the mid- and high-dose groups). No evidence of malformations or adverse effects on the fetus was also reported in a published study (Fujinaga, 1988) in which pregnant rats were administered 10, 50, or 100 mcg/kg/day sufentanil continuously from Gestation Day 5 through Gestation Day 20 via subcutaneously implanted osmotic minipumps.

In an embryo-fetal developmental toxicity study in rabbits, pregnant rabbits were intravenously administered sufentanil doses of 0.005, 0.02, or 0.08 mg/kg/day. Decreased live fetuses per litter and decreased litter size in the high-dose group were noted in the presence of maternal toxicity (decreased body weight gain and mortality in the high-dose group).

In a pre- and post-natal developmental toxicity study, pregnant rats were intravenously administered sufentanil doses of 0.005, 0.02, or 0.08 mg/kg/day from Gestation Day 16 through Lactation Day 21. Sufentanil reduced birth weights in the mid- and high-dose groups, decreased live fetuses in the high-dose group, and decreased pup survival in all groups in the presence of maternal toxicity (decreased weight gain and increased mortality in all groups).

Table 18 Exposure margins of animal data with maximum human daily dose of 720 mcg/60 kg/day, based on a body surface area comparison (b) (4)

	Route	Dose (mg/kg/day)	Exposure Margin	Rounded Exposure Margin
Fertility and Early Embryonic Development				
Male and Female Rat	Intravenous	0.005	0.07	0.07
		0.02	0.27	0.3
		0.08	1.08	1.1
Embryo-Fetal Development				
Rat	Intravenous	0.005	0.07	0.07
		0.02	0.27	0.3
		0.08	1.08	1.1
Rat	Subcutaneous	0.01	0.14	0.1
		0.05	0.68	0.7
		0.1	1.35	1.4
Rabbit	Intravenous	0.005	0.14	0.1
		0.02	0.54	0.5
		0.08	2.16	2.2
Pre- and Postnatal Development				
Rat	Intravenous	0.005	0.07	0.07
		0.02	0.27	0.3
		0.08	1.08	1.1

In a non-GLP PK study to compare the intravenous administration of sufentanil to the sublingual administration of sufentanil, two different experimental sublingual

formulations of 5 mcg Nanotabs (numbered 1 and 2) or IV injection of 5 mcg Sufentanil solution was administered to three male beagle dogs with a 3- or 4-day washout period between doses. The PK data indicate that the relative bioavailability via the sublingual route was approximately 60%. In a second non-GLP study, IV and sublingual formulations were compared to oral administration of a sufentanil solution (5 mcg). The results suggest that relative oral bioavailability of sufentanil was 11%.

In the GLP 28-day buccal pouch irritation/toxicity study, Golden Syrian hamsters were sublingually (via cheek pouch) administered once daily doses of 0, 15, 90, or 180 mcg/day of Sufentanil NanoTabs. The hamsters in the control group were administered placebo sublingual tablet, with the same number of tablets that were administered in the high dose group (6 tablets). To avoid systemic opioid effects, animals were pretreated with 10 mg/kg Naltrexone HCl (subcutaneous injection) prior to treatment.

In the 28-day cheek pouch study, sufentanil was readily absorbed following sublingual administration via the cheek pouch. T_{max} ranged from 0.5 to 4 hours on Day 0 and from 1 to 2 hours on Day 27. An increase in the exposure was noted with increasing doses; but not dose-proportional. There were no treatment-related deaths. No treatment-related localized irritation in the buccal mucosa of the cheek pouch and unremarkable histopathology finding in the cheek pouch were noted. Primary clinical signs observed are consistent with the pharmacological properties of sufentanil, including rigid muscle tone, hypoactivity, impaired equilibrium, impaired muscle coordination, decreased respiration, and shallow breathing. The NOAEL in the study was identified as 180 mcg/day, however, as the animals were blocked with naltrexone, these data should be interpreted with caution regarding conclusion for the systemic safety of sufentanil. This NOAEL corresponds to AUC_{last} value of 82.7 ng·h/mL on Day 27 for combined males and females after repeated daily dosing for 28 days. C_{max} value at this dose on Day 27 was 16.5 ng/mL for combined males and females.

A 4-day local tolerance study with sufentanil was conducted in Golden Syrian hamsters [GLP]. One placebo tablet in Group 1, two placebo tablets in Group 2, two 10 mcg tablets in Group 3, and one 80 mcg tablet [in Group 4 were placed deep into the left cheek pouch, and the animals were observed for 10 minutes to determine if they expelled the tablet or not. To avoid systemic opioid effects, animals were pretreated with 10 mg/kg Naltrexone HCl prior to treatment. The right cheek pouch was the untreated control. Histopathological examination was only performed on local tissues. There was no adverse local tissue reaction with the sublingual formulations.

In the GLP *in vitro* bacterial reverse mutation assays with (b) (4) Impurity B) or (b) (4) up to 5000 mcg/plate was evaluated in five test strains (TA100, TA1535, TA98, TA1537, and WP2uvrA) with or without S9, and the results showed that (b) (4) and (b) (4) were negative mutagenic potential under the study condition.

The potential toxicities of sufentanil degradation products, (b) (4) were assessed using the *in silico* toxicity program DEREK for Windows and Leadscope. The DEREK evaluation did not indicate genotoxicity, mutagenicity, chromosome damage, or carcinogenic potential (b) (4). Similarly, the Leadscope evaluation predicted that these two impurities were negative for genotoxicity and rodent carcinogenicity. The Agency only considers these QSAR models valid for predictions of mutagenicity at this time. The result for mutagenicity was also confirmed by QSAR model analysis by CDER Office of Translational Sciences. These assessments for these two sufentanil degradation products are considered qualified for the genotoxic potential, and these degradants are considered non-genotoxic.

There are no safety concerns with impurities of the drug substance, degradants of the drug product, and excipients. FD&C Blue No. 2 (b) (4) has not been used in the FDA-approved sublingual drug products. However, based on the fact that color additive FD&C Blue No. 2 is provisionally listed under 21 CFR §74.1102 for use in ingested drugs, and FD&C Blue No. 2 (b) (4) is used in the FDA-approved oral drug products, along with available clinical data of the sublingual use of FD&C Blue No. 2 (b) (4), the Reviewer considers that there is adequate safety information for the sublingual use of FD&C Blue No. 2.

From a nonclinical pharmacology toxicology perspective, nonclinical information provided for NDA 209128 is adequate to support an approval recommendation with no nonclinical post-marketing requirements.

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/s/

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09/07/2017

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09/07/2017
I concur.