

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

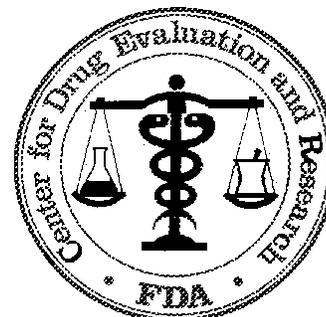
APPLICATION NUMBER:

209128Orig1s000

PRODUCT QUALITY REVIEW(S)

**MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 8 May 2018
TO: NDA 209128
FROM: Valerie Amspacher
 Chemistry reviewer
 ONDP/DNDP II
THROUGH: Julia Pinto
 Acting Branch Chief
 ONDP/DNDP II/Branch IV
SUBJECT: Additional CMC data in 03-May-2018, Resubmission



SUMMARY and CONCLUSION: The OPQ recommendation for this application at the end of the original review cycle was that the application could be approved, from a CMC perspective. The Agency sent a complete response (CR) action to the applicant. The current 03-May-2018, submission is a response to the CR letter.

Although there were no CMC-related comments included in the CR letter, the new submission includes new stability data (in red in the table below).

| Container Closure System | Lot # | Storage Condition | Data Provided (in Months) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|----------------------------------|-------------------------------------------------|
| (b) (4) SDA Subassembly with a green (b) (4) Pusher and white Lock (b) (4) (b) (4); StabilOx (b) (4) Packet (b) (4) (b) (4) Laminate Foil Pouch (b) (4) (b) (4) | 3124436, 3124437, 3124438 | 25°C ± 2°C and 60% RH ± 5% RH | 36 months |
| | | 40°C ± 2°C and 75% RH ± 5% RH | 6 months (previously submitted and reviewed) |
| Same as above | 3124436 | 50°C /Ambient | 1 month (previously submitted and reviewed) |
| Same as above | 3124436 | 5°C/Ambient | 1 month (previously submitted and reviewed) |
| Same as above | 3124436 | -20°C ± 5°C/Ambient | 1 month (previously submitted and reviewed) |

The data remains within specification. There are no discernable trends in any of the tests. Note that the 5°C/Ambient condition was omitted from the Stability table in Section P.8 of the original review dated 31 Aug 2017 due to an error by the reviewer.

The new stability data submitted with the resubmission justifies a shelf-life of 36 months.



Valerie
Ampacher

Digitally signed by Valerie Ampacher
Date: 5/25/2018 01:44:55PM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3



Julia
Pinto

Digitally signed by Julia Pinto
Date: 5/29/2018 06:52:44PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

Recommendation: Approval

**NDA 209128
Review #1**

| | |
|-------------------------|------------------------------|
| Drug Name/Dosage Form | Dsuvia(Sufentanil)tablet |
| Strength | 30 mcg |
| Route of Administration | Sublingual |
| Rx/OTC Dispensed | Rx |
| Applicant | AcelRx Pharmaceuticals, Inc. |
| US agent, if applicable | |

Quality Review Team

| DISCIPLINE | REVIEWER | BRANCH/DIVISION |
|-------------------------------------|-----------------------------------------|------------------------|
| Drug Substance | Jeffrey Medwid | OPQ/ONDP/DNDPAPI/BII |
| Drug Product | Valerie Amspacher | OPQ/ONDP/DNDPII/BIV |
| Process | Tarun Mehta/ Pei-I Chu | OPQ/OPF/DPAII/BVI |
| Microbiology | | |
| Facility | Christina Capacci-Daniel/Daniel DeCiero | OPQ/OPF/DIA/BII |
| Biopharmaceutics | Kelly Kitchens/Haritha Mandula | OPQ/ONDP/DB/BII |
| Regulatory Business Process Manager | Steven Kinsley | OPQ/OPRO/RBPMI/BI |
| Application Technical Lead | Ciby Abraham | OPQ/ONDP/DNDPII/BIV |
| Laboratory (OTR) | | |
| ORA Lead | Caryn McNab/Michael Tollen | |
| Environmental Analysis (EA) | | |

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

| DMF # | Type | Holder | Item Referenced | Status | Date Review Completed | Comments |
|--------------|-------------|---------------|------------------------|---------------|------------------------------|-----------------|
| (b) (4) | Type II | | (b) (4) | Adequate | 7/26/17 | |
| | Type III | | | Adequate | 9/1/17 | |
| | | | | | | |
| | | | | | | |

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the recommendations from drug substance, biopharmaceutics, process, microbiology, facilities, and drug product, CMC recommends the approval of DSUVIA (Sufentanil) 30 mcg sublingual tablets.

II. Summary of Quality Assessments

A. Quality Assessment Overview

The drug substance sufentanil citrate USP is a DEA class II drug manufactured by (b) (4). It is a white to off white powder that is highly soluble in water. The polymorphism and particle size were not fully characterized (b) (4). (b) (4). The drug substance has a (u) (4) month retest period. Sufentanil citrate USP is (b) (4).

The drug product is manufactured by AcclRx Pharmaceuticals, Inc. The dosage form is an immediate release sublingual tablet containing 30 mcg of sufentanil. The sufentanil tablet is a blue-colored flat-faced tablet with rounded edges. It is 3 mm in diameter and 0.85 mm thick with a nominal tablet weight of 7.40 mg. The tablet (b) (4) is designed specifically to facilitate dispensing the tablet from the single dose applicator. One tablet is packaged in a single-use, disposable single dose applicator. The single dose applicator (SDA) is comprised of (b) (4) parts (SDA subassembly, SDA pusher, SDA lock), (b) (4) and one sufentanil tablet. The applicator is co-packaged with an oxygen absorber and placed into a foil laminate pouch. The oxygen absorber is called StabilOX (b) (4). (b) (4) A chipped tablet was found during stability at the initial timepoint. The drug product reviewer, Dr. Valerie Amspacher stated in her review "A chipped tablet was found on stability in batch 3124436 at the Initial timepoint. This is acceptable because the sponsor has in place sampling plans which will reject defective batches 90% of the time (see email from Karthik Iyer on 12 Aug 2017) which is an appropriate industry standard." The expiration date of (b) (4) months at 20°-25°C, excursion permitted to 15°-30°C is granted for the product. A description of the single dose applicator is shown below.

Figure 3.2.P.7.2: 1 Single Dose Applicator

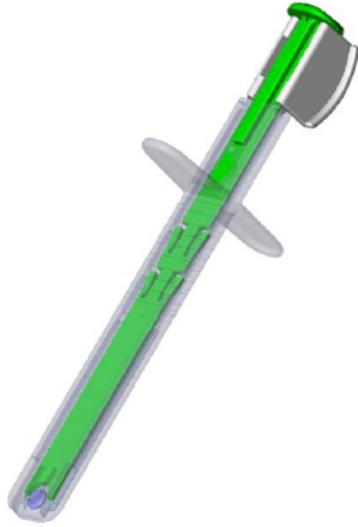
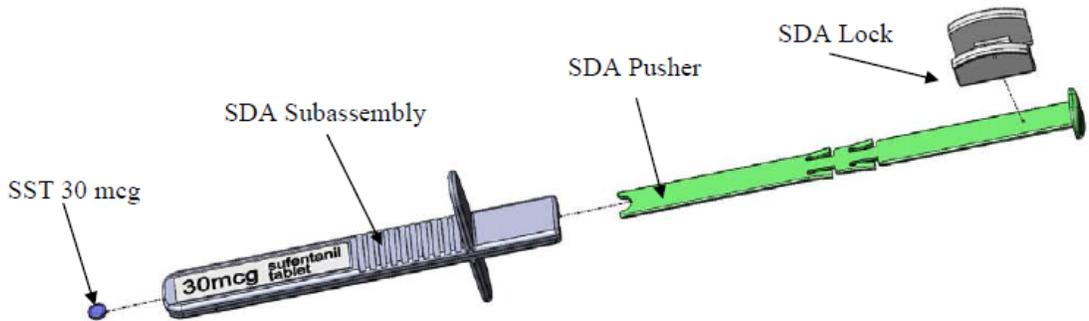


Figure 3.2.P.7.2: 2 SDA Exploded View with Components



B. Special Product Quality Labeling Recommendations (NDA only)- N/A

C. Final Risk Assessment (see below)

Executive Risk Assessment Summary

| From Initial Quality Assessment | | | Review Assessment | | |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|--------------------------|-----------------|--------------------------------------|
| Product attribute/ CQA | Factors that can impact the CQA | Risk Ranking* | Risk Mitigation Approach | Risk Evaluation | Lifecycle Considerations/ Comments** |
| Assay, stability | <ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site | L | - | N/A | - |
| Physical stability (API) | <ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site | L | - | N/A | - |
| Content uniformity | <ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site | M | - | L | (b) (4) adequate. |
| Microbial Limits | <ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment | L | - | - | - |
| In Vitro Dissolution | <ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping | L | - | - | - |
| | | | | | |

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

III. Administrative

A. Reviewer's Signature

Ciby J. Abraham, Ph.D.
Quality Assessment Lead (Acting)
Application Technical Lead
ONDP/DIVII/Branch IV

107 Pages have been Withheld in Full as B4(CCI/TS)
Immediately Following this Page

BIOPHARMACEUTICS

Product Background: The Applicant is seeking approval of Dsuvia™ (sufentanil sublingual tablet), 30 mg, under the 505 (b)(2) path. Sufentanil sublingual tablets are indicated for the management of moderate-to-severe acute pain severe enough to require an opioid agonist, in adult patients in a medically supervised setting.

NDA: 209128

Drug Product Name / Strength: Dsuvia™ (sufentanil sublingual tablet) / 30 mcg

Route of Administration: Sublingual

Applicant Name: AcclRx Pharmaceuticals, Inc.

Review Summary:

The Applicant proposes to use the same dissolution method that was previously reviewed and determined to be acceptable for NDA (b)(4) Sufentanil Tablets, 15 µg. The proposed dissolution method and acceptance criterion are adequate.

From the Biopharmaceutics perspective, NDA 209128 is recommended for **approval**.

List Submissions being reviewed:

| Date of Submission | Purpose of Submission |
|--------------------|----------------------------------------------------------------|
| December 12, 2016 | Original Submission |
| March 15, 2017 | Response to 74 day letter biopharmaceutics information request |
| May 1, 2017 | Response to CMC information request |

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

BCS Designation

Reviewer’s Assessment: The Applicant has not made a BCS claim designation for the drug product.

Solubility: Sufentanil Citrate is soluble in water, sparingly soluble in alcohol, sparingly soluble in acetone and chloroform, and freely soluble in methyl alcohol. Solubility of Sufentanil Citrate in water is 46 mg/mL.

Permeability: This information could not be located

Dissolution: See the following Dissolution Method and Acceptance Criterion assessment

Dissolution Method and Acceptance Criterion

Reviewer's Assessment: ADEQUATE

Dissolution Method

- The following proposed dissolution method was previously reviewed and determined to be acceptable for the 15 µg strength in NDA (b) (4).¹

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|---------------|----------------|--------------|-------|-----------------------|
| 2 | 50 rpm | 50 mL | 37 °C | pH 4.5 acetate buffer |

(b) (4)

5 Pages have been Withheld in Full as B4(CCI/TS)
Immediately Following this Page

¹ DARRTS: NDA (b) (4), RIVIERE, KAREEN, 06/16/2014, REV-QUALBIOPHARM-21(Primary Review)

Biowaiver Request

Reviewer's Assessment: N/A

List of Deficiencies: None

Primary Biopharmaceutics Reviewer Name and Date:

Kelly M. Kitchens, Ph.D., May 5, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Haritha Mandula, Ph.D., June 21, 2017



Kelly
Kitchens

Digitally signed by Kelly Kitchens
Date: 8/28/2017 09:45:46AM
GUID: 508da6fd0002849b46320c175775bdfa



Haritha
Mandula

Digitally signed by Haritha Mandula
Date: 8/29/2017 07:12:44AM
GUID: 508da6fb000282df41459408f32a1ce0



Ciby
Abraham

Digitally signed by Ciby Abraham
Date: 9/20/2017 11:27:12AM
GUID: 512518c000026e22966a3bf7c15f7809

