

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

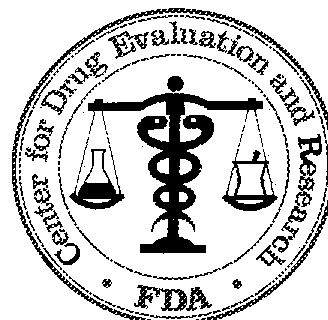
*APPLICATION NUMBER:*

**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 (b) (4) 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.



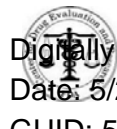
Valerie  
Ampacher



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Julia  
Pinto



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**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**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	Jeffrey Medwid	OPQ/ONDP/DNDPAPI/BII
Drug Product	Valerie Amspacher	OPQ/ONDP/DNDPII/BIV
Process	Tarun Mehta/ Pei-I Chu	OPQ/OPF/DPAIL/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 (b) (4) month retest period. Sufentanil citrate USP is (b) (4).

The drug product is manufactured by AcelRx 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

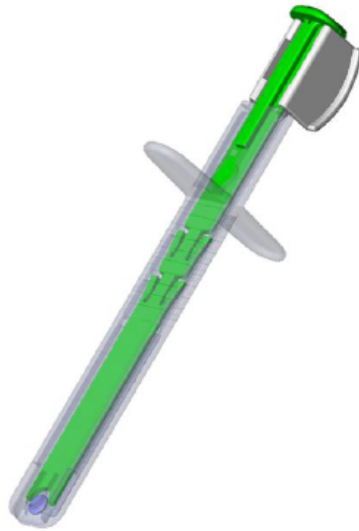
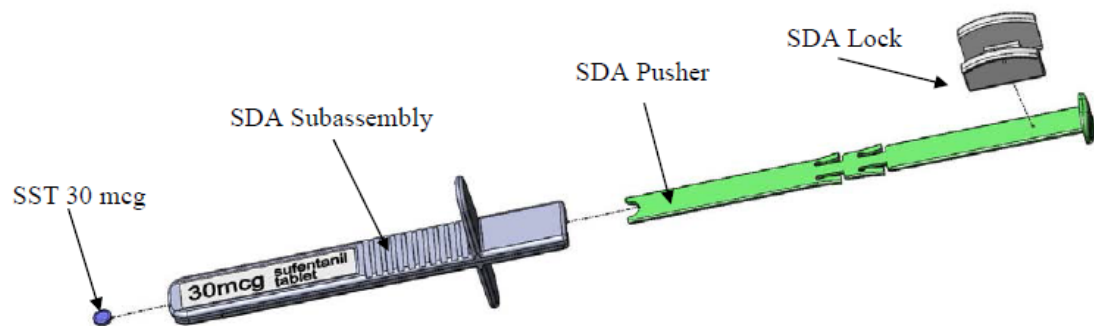


Figure 3.2.P.7.2: 2 SDA Exploded View with Components



**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"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	L	-	N/A	-
Physical stability (API)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	L	-	N/A	-
Content uniformity	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	M	-	L	(b) (4) adequate.
Microbial Limits	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	L	-	-	-
In Vitro Dissolution	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> <li>• Exclude major reformulations</li> <li>• Alcohol dose dumping</li> </ul>	L	-	-	-

\*Risk ranking applies to product attribute/CQA

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



### III. Administrative

#### A. Reviewer's Signature

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

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**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, soluble to 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).<sup>1</sup>

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

(b) (4)

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<sup>1</sup> 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

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Haritha  
Mandula

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