CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208042Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 208042
Review # 2

Drug Name/Dosage Form	Buprenorphine and Naloxone Sublingual Film
Strength	16mg/4ml
Route of Administration	Oral, Sublingual Film
Rx/OTC Dispensed	Rx
Applicant	Teva Pharmaceuticals USA
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission	March 8 2018	Drug Product/Facilities

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	N/A	OPQ/ONDP/DNDPAPI/BII
Drug Product	Julia Pinto	OPQ/ONDP/DNDPII/BIV
Process	N/A	OPQ/OPF/DPAII/BVI
Microbiology	N/A	OPQ/OPF/DMA/BI
Facility	Christina Capaccci-Daniel	OPQ/OPF/DIA/BII CDRH/OC
Biopharmaceutics	N/A	OPQ/ONDP/DB/BII
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Julia Pinto	OPQ/ONDP/DNDPII/BIV
Laboratory (OTR) FDA St. Louis Labs	N/A	
Environmental Analysis (EA)	N/A	OPQ/ONDP/DNDPII/BIV

Executive Summary

Recommendation: OPQ team recommends approval of this NDA. All facilities are adequate in support of the manufacture, testing and release of drug substance and drug product batches of Cassipa® (Buprenorphine and Naloxone) Sublingual Film.

Summary of Quality Assessment:

This resubmission provides for a response to the complete response of September 2016.
The CR for this NDA was recommended because FDA Inspectors were not able to complete the inspection of Lohmann Therapy Systems, the manufacturing facilities for the drug product. The Facility was not ready for inspection. With this resubmission, the Lohmann facilities were ready for inspection, and Office of Facilities within OPQ recommend this facility as adequate. The inspection review is attached.

Further this resubmission provides for the addition of the new facility , Atavis Laboratories, UT, Inc in Salt Lake City, UTAH (FEI 1000117147) to replace the now closed sites of (b) (4) and in (b) (4). Actavis facility will be responsible for the commercial release and stability testing of the drug product.
Lohmann Therapy Systems will be responsible for the release testing of both drug substances. (b) (4) will tst for particle size and residual solvents of both drug substances. All analytical methods were transferred from (b) (4) to Lohmann and (b) (4). Transfer reports with validation results are provided. No changes in the methods or specifications are proposed. The manufacturing process remains the same but for the use of a different (b) (4). The (b) (4) is replaced with a (b) (4) . (b) (4) The process and the formula are otherwise unchanged from that reviewed in the previous cycle.

The drug substance, Buprenorphine HCl remains adequate with a retest period of (b) (4) months when stored at (b) (4)°C. The second drug substance, Naloxone HCl dihydrate, is also adequate with a retest period of (b) (4) months when stored at (b) (4)°C.

The Drug product is a sublingual film comprising 16mg of buprenorphine and 4mg of naloxone. It is an immediate release formulation which releases both active ingredients within (b) (4) minutes. The films are 22.3 mm x 25.4 mm with a thickness of 150um and a weight of 93mg. Each film is packaged (b) (4) in a child resistant (b) (4) pouch. The pouch comprises (b) (4). Sufficient stability data is provided to support an expiry of 24 months when stored under the following conditions.
"Store at (b) (4); excursions permitted between 15° and 30°C (59° and 86°F). (b) (4) ".

Finally, Teva has changed the primary contact for this NDA. The new contact is Cherri Petrie at:

Contact: Cherri Petrie
Senior Director, Regulatory Affairs, US Generics
Actavis Laboratories UT, Inc., an indirect, wholly-owned subsidiary of
Teva Pharmaceuticals USA, Inc.
577 Chipeta Way
Salt Lake City, Utah 84108
Phone: (801) 588-6633
Fax: (908) 659-2250
Email: RegulatoryAffairsUS@tevapharm.com

_____
Reviewer and Application Technical Lead

Julia C. Pinto, Ph.D.
Branch Chief, OPQ/ONDP/Division II/Branch IV

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Post-Approval Commitments

Reviewer's Assessment: N/A under facilities

Lifecycle Management Considerations

Routine surveillance coverage and continued process monitoring over the lifecycle of this product.

List of Deficiencies: None

Primary Facilities Reviewer Name and Date: Rebecca Dombrowski 6/28/2018

Secondary Reviewer Name and Date:

Concur with the Acceptable recommendation.

Christina Capacci-Daniel, PhD – 06Jul2018
Acting QAL, OPQ/OPF/DIA/IABII

Christina Capacci-Daniel

Digitally signed by Christina Capacci-Daniel
Date: 7/06/2018 12:29:43PM
GUID: 51dc71a50000c6c3f0b616578caafab6

Rebecca Dombrowski

Digitally signed by Rebecca Dombrowski
Date: 7/06/2018 12:44:34PM
GUID: 54234745007246a8294be0d050c46d74

Julia Pinto

Digitally signed by Julia Pinto
Date: 8/23/2018 04:54:15PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

Recommendation:
NDA: Complete Response

NDA 208042
Review # 1

Drug Name/Dosage Form	**Buprenorphine and Naloxone Sublingual Film**
Strength	**16 mg/4 mg**
Route of Administration	Oral, Sublingual Film
Rx/OTC Dispensed	Rx
Applicant	**Teva Pharmaceuticals USA**
US agent, if applicable	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	**Erika Englund**	**OPQ/ONDP/DNDPAPI/BII**
Drug Product	**Xiaobin Shen**	**OPQ/ONDP/DNDPII/BIV**
Process	**Pei-I Chu**	**OPQ/OPF/DPAII/BVI**
Microbiology	**Eric Adeeku**	**OPQ/OPF/DMA/BI**
Facility	**Rebecca Dombrowski**	**OPQ/OPF/DIA/BII**
Biopharmaceutics	**Vidula Kolhatkar/Kelly Kitchens**	**OPQ/ONDP/DB/BII**
Regulatory Business Process Manager	Steve Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	**Ciby Abraham**	**OPQ/ONDP/DNDPII/BIV**
Laboratory (OTR)		
ORA Lead	**Paul Perdue**	
Environmental Assessment (EA)		

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
16419	Type II	Teva	Buprenorphine	Adequate	1/6/2016	Xiaobin Shen, Ph.D. found DMF adequate
(b) (4)	Type II		(b) (4)	Adequate	12/21/2015	Weiqin Jiang found DMF adequate
	Type II			Adequate information provided in the NDA	NA	Manufacturing process supply
	IV			Adequate	16-Aug-2016	
	III			Adequate information provided in the NDA	NA	
	IV			Adequate information provided in the NDA	NA	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	Not needed	Acceptable	10-Aug-2016	Xiaobin Shen, Ph.D.
Pharmacology/Toxicology	Ongoing	Anticipated as acceptable	10-Aug-2016	Elizabeth Bolan, Ph.D.

CDRH				
Clinical				
Other				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the recommendations from Process and Facilities, CMC recommends a Complete Response. Drug substance, microbiology, biopharmaceutics, drug product recommend approval for the Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg. The drug product manufacturer, LTS Lohmann Therapy Systems site located in NJ (FEI 1000121692) was not ready for inspection and a withhold recommendation was provided by the home district (NWJ-DO). Without the manufacturing site ready for inspection, the process group had deficiencies about the manufacturing process of the Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg.

Deficiencies:

1. You have stated in your application that (1) the (b) (4) are considered high risk factors to product content uniformity, (2) critical process parameters such as (b) (4) will affect product assay results, and (3) acceptable (b) (4) will be evaluated and established during process scale-up and process validation. Provide the commercial (b) (4) equipment information, the critical process parameters for (b) (4) the commercial manufacturing process.

To address this deficiency, provide commercial (b) (4) equipment information, critical process parameters for (b) (4) for the commercial process.

2. Confirm that you will continue to perform the (b) (4) test for the commercial batches. In addition, you have proposed to conduct the content uniformity test in the drug product specification. Provide justification that your sampling plan and acceptance criteria for the content uniformity test provides statistical assurance that batches of drug product will meet appropriate specifications and statistical quality control criteria.

To address this deficiency, provide justification that your sampling plan and acceptance criteria for content uniformity provides statistical assurance that the drug product batches will meet specifications.

3. You have selected (b) (4) film as a (b) (4) during the manufacturing of buprenorphine and naloxone sublingual film. Provide information on

the composition, physical attributes acceptance specification and a safety statement for (b) (4).

To address this deficiency, provide information on the composition, physical attributes acceptance specification and a safety statement for (b) (4).

Information Requests:

1. Based on the USP salt policy, the product name throughout the package insert, all labeling pouches and cartons should use the active base only. Since the APIs used are in their salt forms, an equivalent statement should be included to state that the indicated active moiety strengths are equivalent to 17.25 mg of buprenorphine hydrochloride and 4.89 mg of naloxone hydrochloride dihydrate respectively.
See "Naming of Drug Products Containing Salt Drug Substances"
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm379753.pdf

(b) (4)

(b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

I. Summary of Quality Assessments

A. Description of the Product

Drug Substance

The drug substance, Buprenorphine HCl, USP is manufactured by Teva Czech Industries s.r.o. (TCI) and is referenced in DMF# 16419. Buprenorphine HCl is a white or almost white crystalline powder. Only one crystal form is found. The retest period for Buprenorphine HCl is (b) (4) months, when stored at (b) (4).

The drug substance, Naloxone HCl Dihydrate, USP is manufactured by (b) (4) and is referenced in DMF# (b) (4). Naloxone HCl Dihydrate is a white crystalline powder. Only one crystal form is found. The retest period is (b) (4) months, when stored at (b) (4) °C.

Drug Product

Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg is used for sublingual [redacted] use. The test product is designed to be an immediate release dosage form and releases the two drug compounds within [redacted] minutes. The unit dimension of the film is 22.3 mm x 25.4 mm, thickness: ~ 150 µm, and weight: 93 mg. The films are packaged individually in child resistant and [redacted] pouches, consisting from [redacted] Based on the stability data provided, an expiry of 24-months will be granted using the storage statement "Store at [redacted]; excursions permitted between 15° and 30°C (59° and 86°F). [redacted]".

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

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

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(b) (4)

ASSESSMENT OF THE BIOPHARMACUETICS

38. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

The following FDA-recommended dissolution method for Buprenorphine HCl/Naloxone HCl Dihydrate Sublingual Tablets was chosen as the dissolution method for the proposed product, Buprenorphine HCl and Naloxone HCl Sublingual Film:

Table 2: Teva Dissolution Parameters

Dissolution Medium	Water
Volume	500 mL
Temperature	37 ± 0.5 °C
Apparatus	USP Apparatus 1 (Basket)
Rotation Speed	100 rpm
Distance from bottom	2.5 cm
Sampling Time (single point)	15 minutes
(profile)	1, 3, 5, 7, 10, 15, and 20 minutes

The applicant proposed the following acceptance criteria:

Table 3.2.P.5.6- 4. Justification for Dissolution Specifications

Name	Proposed Limits	Justification
Dissolution Single Point (15 minutes) - Buprenorphine - Naloxone	Q = (b) (4)%	Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms and available data

Applicant's Response:

The Applicant submitted a complete dissolution method development report where they evaluated different dissolution apparatus, medium, rotation speed, and medium volume. Dissolution method development was conducted using Teva Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg, Batch 9903174, which has the exact same formulation as the submission batches.

Solubility data: The solubility of the drug substances in Buprenorphine and Naloxone Sublingual Film, 16/4 mg, was measured in buffer pH 1.2, pH 4.0, pH 4.5, pH 6.8, pH 8.0 and water at 37°C. Excess amount of drug substances were added into each buffer separately. The samples were stirred at room temperature for about 2 hours and then moved to a 37°C water bath to shake for overnight. The solubility results of Buprenorphine HCl and Naloxone HCl are summarized in the following table:

Table 1: Solubility Results of Buprenorphine HCl and Naloxone HCl

Medium	Solubility (mg/mL)	
	Buprenorphine HCl	Naloxone HCl
pH 1.2	4.36	160.15
pH 4.0	17.40	182.21
pH 4.5	10.25	190.63
pH 6.8	0.03	3.10
pH 8.0	0.003	1.29
water	16.98	195.81
Reference: POMD_0714_8704		

(b) (4)

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(b) (4)

[redacted]

Discriminating capacity of the dissolution method: The applicant has stated that based on the Risk Assessment and development work conducted as part of QbD principles implementation, dissolution Critical Quality Attributes (CQA) were determined as very robust and there were no API, Formulation and Process related variables that could potentially impact dissolution. The possibility that there will be large batch to batch variability in dissolution that can potentially impact safety and efficacy is very low. However in order to still attempt to generate batches with variable dissolution profiles, several batches were manufactured in which the formulation composition was modified. The following table represents the composition of several batches manufactured using formulation modifications, where batches 017, 025, 029, and 080 are drug products manufactured using formulation modifications, and the final formulation batches are the commercial formulations:

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The formulation variation assessment represents an extreme case of formulation since the final formulation of the product is fixed and there are no material related attributes (excipient variability) that can impact dissolution. However, even with these extreme variations in composition all dissolution results at 15 minutes pass the proposed specification. Only single point dissolution was performed for Formulation Rx 3117-025 as the API in the profile samples precipitated over time. The single point results showed (b) (4)% Buprenorphine and (b) (4)% Naloxone released at 15 minutes from Rx 3117-025.

Table 28: Dissolution Results of Formulation Change (PR10664/p1-96)

Formulation	Buprenorphine %Released			Naloxone %Released		
Time (mins)	Rx3117-017	Rx3117-029	Rx3117-080	Rx3117-017	Rx3117-029	Rx3117-080
1	(b) (4)					
3						
5						
7						
10						
15						
20						

Based on the above results, it can be concluded that the proposed product and process are very robust with respect to dissolution and the product is very rapidly dissolved, and therefore the potential for large expected variability in dissolution that can impact safety and efficacy is very low. The main goal of the dissolution method is therefore to serve as a quality control tool to monitor batch to batch consistency and repeatability.

Reviewer's comments: Mean data for formulations Rx3117-017, Rx3117-029 and Rx3117-080 for Buprenorphine and Naloxone were provided. Single point dissolution results for formulation Rx 3117-025 were provided ((b) (4)% Buprenorphine and (b) (4)% Naloxone released at 15 minutes). Based on the data, Buprenorphine and Naloxone

demonstrated rapid dissolution despite formulation variations (more than (b) (4)% dissolved in 15 minutes). This rapid dissolution is similar to the dissolution of the proposed product.

Dissolution method validation: The proposed dissolution method was validated. The following table summarizes the validation results:

Item #	Validation Element	Experimental Design	Acceptance Criteria	Results		Pass/Fail
				Buprenorphine	Naloxone	
1	System Suitability	(b) (4)				Pass
2	Specificity					Pass
3	Linearity					Pass
4	Accuracy					Pass
5	Precision (Repeatability and Intermediate Precision)					Pass
6	Filtration Bias Study					Pass
7	Range					Pass
8	Solution Stability					Pass
9	Robustness					Pass

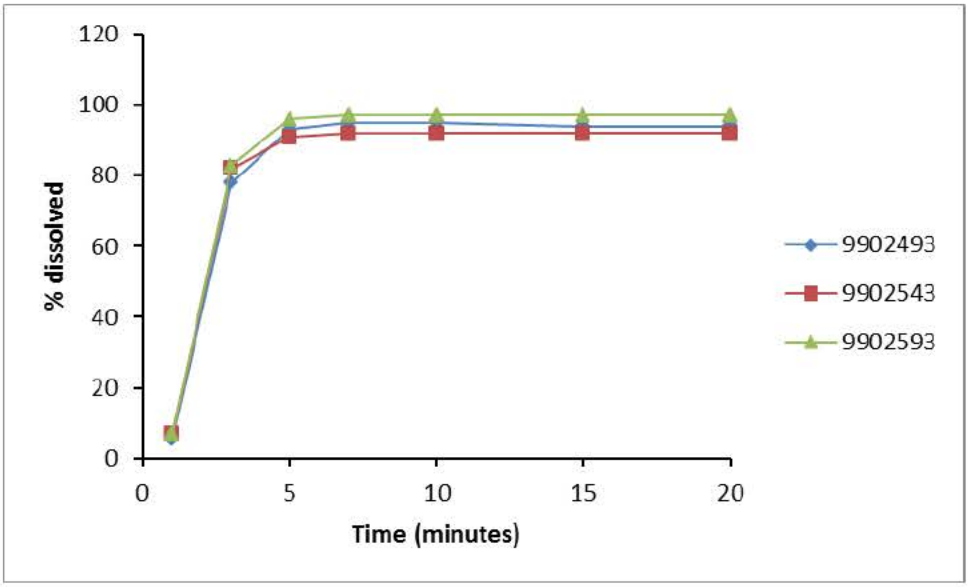
Reviewer's comments: The proposed dissolution method is acceptable and adequately validated.

The applicant submitted complete data (individual, mean, % RSD) for 12 units each of three submission batches.

The following represents the dissolution data for buprenorphine from three submission batches, 9902493, 9902543, and 9902593:

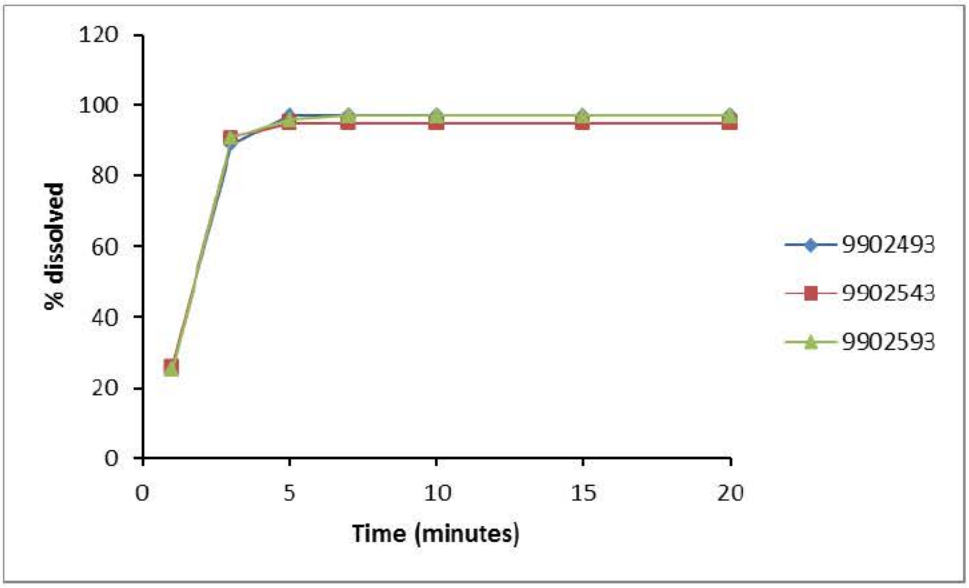
Lot no.	% dissolved	1 min	3 min	5 min	7 min	10 min	15 min	20 min
9902493	Mean	6	78	93	95	95	94	94
	Max	(b) (4)						
	Min							
	% RSD	24.4	7.6	1.6	1.0	1.0	1.0	1.0
9902543	Mean	7	82	91	92	92	92	92
	Max	(b) (4)						
	Min							
	% RSD	41.7	5.1	1.3	0.7	0.7	0.6	0.7

9902593	Mean	7	83	96	97	97	97	97
	Max	(b) (4)						
	Min							
	% RSD	32.5	6.9	1.5	0.9	1.0	1.1	1.1



The following table summarizes the submitted data for naloxone from three submission batches, 9902493, 9902543, and 9902593:

Lot no.	% dissolved	1 min	3 min	5 min	7 min	10 min	15 min	20 min
9902493	Mean	26	89	97	97	97	97	97
	Max	(b) (4)						
	Min							
	% RSD	7.0	3.4	0.9	0.7	0.6	0.7	0.7
9902543	Mean	26	91	95	95	95	95	95
	Max	(b) (4)						
	Min							
	% RSD	13.7	2.4	0.5	0.8	1.0	0.9	0.9
9902593	Mean	25	91	96	97	97	97	97
	Max	(b) (4)						
	Min							
	% RSD	11.0	3.4	1.0	0.8	0.8	0.8	0.8



Reviewer's Assessment: Adequate.

- **The proposed dissolution method is acceptable.**
- **The dissolution method was adequately validated for system suitability, accuracy, specificity, precision, stability and robustness. The standard solution is stable for at least 15 days when stored under ambient conditions. The sample solution is stable for at least 4 days when stored under ambient conditions. The method demonstrated linearity for the range 0.2 µg/mL to 48 µg/mL of Buprenorphine, and the range 0.05 µg/mL to 12 µg/mL of Naloxone. The linearity study covered a range from 0.625% to 150% of the sample concentration for the 16 mg/4 mg strength. The HPLC method is adequate.**
- **Based on the data provided the proposed dissolution specifications are acceptable.**

39. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Applicant's Response: N/A

Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg submission batch (Batch # 9902493) was used for clinical studies. The batch formula of Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg for the submission batches (#9902493, 9902543 and 9902593) and the proposed commercial batches is identical as depicted in the table below:

Table 2.3.2.5-1: Batch Formula for Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg for Exhibit ANDA Batches (#9902493, 9902543 and 9902593) and Proposed Commercial Batch

Component	16 mg/4 mg		
	Pivotal ANDA Batch (b) (4) Films Weight in kg	Commercial Batch (b) (4) Films Weight in kg	% w/w
Buprenorphine Hydrochloride, USP			(b) (4)
Naloxone Hydrochloride Dihydrate, USP			
Polyethylene Oxide, NF (b) (4)			
Maltitol, NF (b) (4)			
Lemon-Lime Flavor (b) (4)			
Anhydrous Citric Acid, USP (b) (4)			
Povidone, USP (b) (4) (b) (4)			
Acesulfame Potassium Salt, NF (b) (4)			
Sodium Phosphate, Dibasic, Anhydrous, USP			
FD&C Yellow #6 (b) (4)			
Butylated Hydroxyanisole, NF (b) (4)			
(b) (4)			
Blue Ink (b) (4)			
Total Weight:			

(b) (4)

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature: Adequate

The Applicant proposed the following dissolution method:

Apparatus:	**USP apparatus I (Basket)**
Rotation speed:	**100 rpm**
Dissolution medium:	**water, 500 mL**
Temperature:	**37 ± 0.5 °C**
Sampling time (single point):	**15 minutes**
(profile):	**1, 3, 5, 7, 10, 15 and 20 minutes**

The Applicant has proposed the following specifications:

For buprenorphine
Q = (b) (4) %; sample time 15 minutes Meets USP <711> S1, S2, or S3 criteria as appropriate

For Naloxone
Q = (b) (4) %; sample time 15 minutes Meets USP <711> S1, S2, or S3 criteria as appropriate

Based on the data provided the proposed dissolution method and specifications are *acceptable*.

From the Biopharmaceutics perspective, NDA 208042 for Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg is recommended for approval.

Reviewer's Signature
Vidula Kolhatkar, Ph.D.
Branch II
Division of Biopharmaceutics/ONDP
July 14, 2016

Secondary Review Comments and Concurrence:

I concur with the Biopharmaceutics assessment and recommendation for approval.

Kelly M. Kitchens, Ph.D.
Acting Biopharmaceutics Quality Assessment
Division of Biopharmaceutics, Branch 2
July 15, 2016

ASSESSMENT OF MICROBIOLOGY

1. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: See question 34.

Reviewer's Assessment: Adequate.

2.3.P.7 Container/Closure System

2. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: N.A.

Reviewer's Assessment: N.A.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

3. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: No excipients proposed in Teva's formulation for Buprenorphine and Naloxone Sublingual Film for 16 mg/4 mg is sourced from animals.

Reviewer's Assessment: Adequate.

4. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: N.A.

Reviewer's Assessment: N.A.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
Adequate.

Pei-I Chu, 04/09/2016

Secondary Review Comments and Concurrence:
Concur with reviewer evaluation and conclusions, Ubrani V. Venkataram, 4/14/2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

5. Is the applicant's claim for categorical exclusion acceptable?

6. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

The applicant requested a categorical exclusion in accordance with 21 CFR 25.31(a) based on two rationales:

1. The drug product will not be administered at higher dosage levels, for longer duration, or for different indications than previously in effect for the listed drug product.

2. Data available to the agency do not establish that, at the expected level of exposure, the substance may be toxic to organisms in the environment.

Reviewer's Assessment: Acceptable.

The claim for categorical exclusion is acceptable and adequate for environmental assessment.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:
Xiaobin Shen, Ph.D. Completed on 22-Aug-2016
CMC Reviewer
Branch IV, Division II
Office of New Drug Product

Secondary Review Comments and Concurrence:

I Concur with Dr. Shen's review of the environmental assessment.

Julia C. Pinto, Ph.D.
Acting Branch Chief, ONDP/Division II/Branch IV

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

(Attach proposed text)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use

(b) (4)

(b) (4) **safely and effectively. See full prescribing information for**

(b) (4)

(b) (4)

sublingual film (b) (4) **CIII**

Initial U.S. Approval: 2002

---------- **INDICATIONS AND USAGE** ----------

(b) (4)

(b) (4) indicated for the maintenance treatment of opioid dependence.

(b) (4)

(b) (4) (1)

---------- **DOSAGE AND ADMINISTRATION** ----------

- (b) (4)

  (b) (4) as a single daily dose. (2.1)
- (b) (4)
- Place one (b) (4)

  (b) (4) film under the tongue, close to the base on the left or right side and allow to completely dissolve. (2.2)
- (b) (4) must be administered whole. Do not cut, chew, or swallow. (2.2)

---------- **DOSAGE FORMS AND STRENGTHS** ----------

Sublingual film: 16 mg buprenorphine with 4 mg naloxone. (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Buprenorphine hydrochloride and naloxone hydrochloride	Acceptable. (b) (4)
Dosage form, route of administration	Sublingual film, sublingual administration	Acceptable.
Controlled drug substance symbol (if applicable)	CIII	Acceptable.
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Sublingual film: 16 mg buprenorphine with 4 mg naloxone.	Acceptable.

Conclusion: Acceptable with comments.
Based on the USP salt policy, the product name throughout the package insert, all labeling pouches and cartons should use the active base only. Hence the applicant should revise the product name to Buprenorphine and Naloxone Sublingual Film. The product strength of 16 mg/4 mg is based on the active moieties already. Since the APIs used are in their salt forms, an equivalent statement should be included to state that the indicated active moiety strengths are equivalent to 17.25 mg of buprenorphine hydrochloride and 4.89 mg of naloxone hydrochloride dehydrate respectively.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Sublingual film	Acceptable.
Strengths: in metric system	Buprenorphine 16 mg/ Naloxone 4 mg	Acceptable.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	A flexible, rectangular film with uniformly distributed orange color, imprinted with "16" in blue ink as a strength identifier ("16" may appear to be green in color)	Acceptable.

Conclusion: Acceptable.

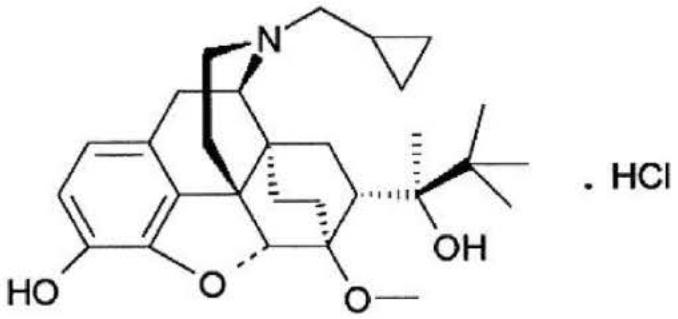
#11: Description (21CFR 201.57(c)(12))

(Attach proposed text)

11 DESCRIPTION

[redacted], 16 mg/4 mg is a flexible, rectangular film with uniformly distributed orange color, imprinted with "16" in blue ink as a strength identifier ("16" may appear to be green in color). The film can be removed from the pouch as an intact piece. It contains buprenorphine HCl, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist, and naloxone HCl dihydrate, an opioid receptor antagonist, at a ratio of 4:1 (ratio of free bases). It is intended for sublingual administration and is available as 16 mg buprenorphine with 4 mg naloxone. Each sublingual film also contains acesulfame potassium salt, anhydrous citric acid, butylated hydroxyanisole, butylated hydroxytoluene, FD&C Blue No. 1, FD&C Yellow #6, lemon-lime flavor, maltitol, polyethylene oxide, povidone, propylene glycol, shellac, and sodium phosphate, dibasic, anhydrous.

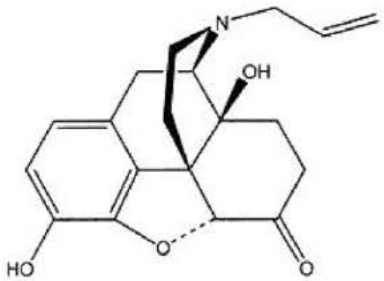
Chemically, buprenorphine HCl is (2*S*)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride. It has the following chemical structure:



$C_{29}H_{41}NO_4 \cdot HCl$ M.W. 504.10

Buprenorphine HCl is a white or [redacted] white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol, and practically insoluble in cyclohexane.

Chemically, naloxone HCl dihydrate is 17-allyl-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate. It has the following chemical structure:



$C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O$ M.W. 399.87

Naloxone hydrochloride dihydrate is a white or [redacted] white powder and is soluble in water, [redacted] soluble in alcohol, and practically insoluble in toluene and ether.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Buprenorphine hydrochloride and naloxone hydrochloride	Acceptable. [redacted]
Dosage form and route of administration	Sublingual film	Acceptable.

Active moiety expression of strength with equivalence statement for salt (if applicable)	16 mg buprenorphine with 4 mg naloxone	Deficient.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Each sublingual film also contains acesulfame potassium salt, anhydrous citric acid, butylated hydroxyanisole, butylated hydroxytoluene, FD&C Blue No. 1, FD&C Yellow #6, lemon-lime flavor, maltitol, polyethylene oxide, povidone, propylene glycol, shellac, and sodium phosphate, dibasic, anhydrous.	Acceptable.
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ therapeutic class	Buprenorphine HCl, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist; Naloxone HCl dihydrate, an opioid receptor antagonist.	Acceptable.
Chemical name, structural formula, molecular weight	Yes, see the section reproduced above.	Acceptable.
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa, solubility, or pH)	Yes, see the section reproduced above.	Acceptable.

Conclusion: Deficient.

Based on the USP salt policy, the product name throughout the package insert, all labeling pouches and cartons should use the active base only. Hence the applicant should revise the product name to Buprenorphine and Naloxone Sublingual Film. The product strength of 16 mg/4 mg is based on the active moieties already. Since the APIs used are in their salt forms, an equivalent statement should be included to state that the indicated active moiety strengths are equivalent to 17.25 mg of buprenorphine hydrochloride and 4.89 mg of naloxone hydrochloride dihydrate respectively.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

(Attach proposed text)

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4) sublingual film, 16 mg/4 mg is a flexible, rectangular film with uniformly distributed orange color, imprinted with "16" in blue ink as a strength identifier ("16" may appear to be green in color), in child-resistant polyester/foil laminated pouches, 30 (b) (4) films per carton. The film can be removed from the pouch as an intact piece.

- NDC 0093-2155-33 (buprenorphine/naloxone 16 mg/4 mg/film; content expressed in terms of free base) – 30 films per carton.

Store at 20° to 25°C (68° to 77°F) (b) (4)

Patients should be advised to store buprenorphine-containing medications safely and out of sight and reach of children.

Rx only

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	16 mg/4 mg	Acceptable.
Available units (e.g., bottles of 100 tablets)	30 films per carton.	Acceptable.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	A flexible, rectangular film with uniformly distributed orange color, imprinted with "16" in blue ink as a strength identifier ("16" may appear to be green in color). NDC 0093-2155-33.	Acceptable.
Special handling (e.g., protect from light, do not freeze)	NA.	NA.
Storage conditions	Store at 20° to 25°C (68° to 77°F) (b) (4)	Acceptable.

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Lohmann Therapy Systems, Corporation (LTS) West Caldwell, NJ 07006 Manufactured For: TEVA PHARMACEUTICALS USA, INC. North Wales, PA 19454	Acceptable.

Conclusion: Acceptable.

2. Container and Carton Labeling

1) Immediate Container Label

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4) ont size and prominence are appropriate.	Acceptable.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The strengths are based on the active moieties.	Acceptable.
Route of administration 21.CFR 201.100(b)(3))	Specified together with the dosage form.	Acceptable.
Net contents* (21 CFR 201.51(a))	Specified.	Acceptable.
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Provided in carton label.	Acceptable.
Lot number per 21 CFR 201.18	Included.	Acceptable.
Expiration date per 21 CFR 201.17	Included.	Acceptable.
"Rx only" statement per 21 CFR 201.100(b)(1)	Included.	Acceptable.
Storage (not required)	Included.	Acceptable.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Included.	Acceptable.
Bar Code per 21 CFR 201.25(c)(2)***	Included.	Acceptable.
Name of manufacturer/distributor (21 CFR 201.1)	Included.	Acceptable.
Others	Referenced to package insert for usage directions.	Acceptable.

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Acceptable.
The need for revision of product name to active moiety based is addressed in a prior section.

2) **Carton Labeling**
(Attach the proposed carton labeling here)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	(b) (4) Font size and prominence are appropriate.	Acceptable.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	The strengths are based on the active moieties.	Acceptable.
Net contents (21 CFR 201.51(a))	Specified.	Acceptable.
Lot number per 21 CFR 201.18	Specified.	Acceptable.
Expiration date per 21 CFR 201.17	Specified.	Acceptable.
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Specified.	Acceptable.
Sterility Information (if applicable)	NA.	NA.
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Specified.	Acceptable.
Storage Conditions	Specified.	Acceptable.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Specified.	Acceptable.
Bar Code per 21 CFR 201.25(c)(2)**	Specified.	Acceptable.
Name of manufacturer/distributor	Specified.	Acceptable.
"See package insert for dosage information" (21 CFR 201.55)	Specified.	Acceptable.
"Keep out of reach of children" (optional for Rx, required for OTC)	NA.	NA.
Route of Administration (not	Implied in dosage form.	Acceptable.

required for oral, 21 CFR 201.100(d)(1) and (d)(2))		

Conclusion: Acceptable.
The need for revision of product name to active moiety based is addressed in a prior section.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
Xiaobin Shen, Ph.D. Completed on 15-Aug-2016
CMC Reviewer
Branch IV, Division II
Office of New Drug Product

Secondary Review Comments and Concurrence:
I Concur with Dr. Shen's assessment of the drug product labeling

Julia C. Pinto, Ph.D.
Acting Branch Chief, ONDP/Division II/Branch IV

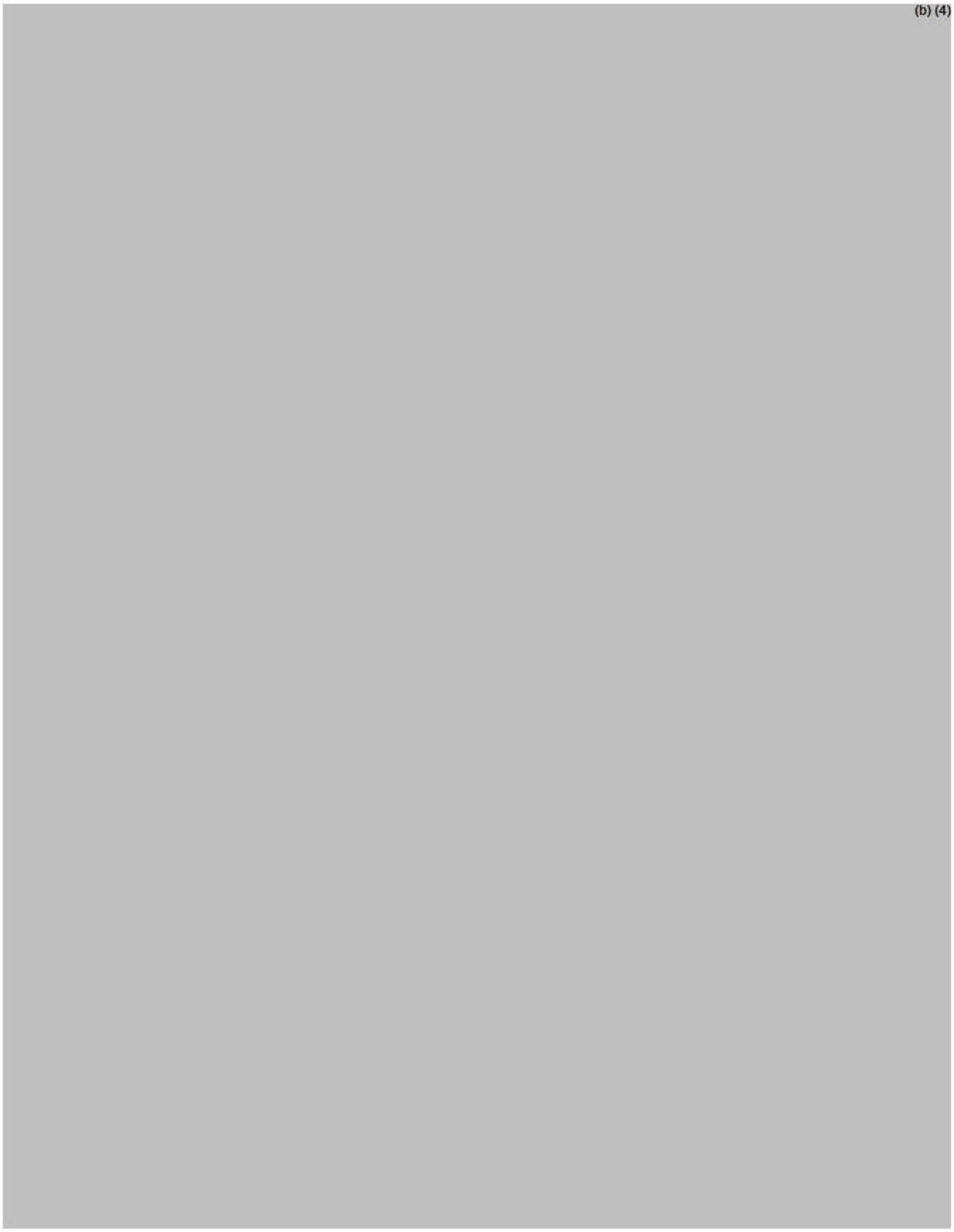
I. List of Deficiencies To Be Communicated

Drug Substance

Process

(b) (4)

(b) (4)



CR Comments:

You have stated in your application that (1) the (b) (4) are considered high risk factors to product content uniformity, (2) critical process parameters such as (b) (4) will affect product assay results, and (3) acceptable

[redacted] will be evaluated and established during process scale-up and process validation. Provide the commercial [redacted] equipment information, the critical process parameters for [redacted] the commercial manufacturing process.

Confirm that you will continue to perform the [redacted] test for the commercial batches. In addition, you have proposed to conduct the content uniformity test in the drug product specification. Provide justification that your sampling plan and acceptance criteria for the content uniformity test provides statistical assurance that batches of drug product will meet appropriate specifications and statistical quality control criteria.

You have selected [redacted] film as a [redacted] during the manufacturing of buprenorphine and naloxone sublingual film. Please provide information on the composition, physical attributes acceptance specification and a safety statement for [redacted].

Facility

Biopharmaceutics

Microbiology

Environmental

Label/Labeling

Based on the USP salt policy, the product name throughout the package insert, all labeling pouches and cartons should use the active base only. Hence the applicant should revise the product name to Buprenorphine and Naloxone Sublingual Film. The product strength of 16 mg/4 mg is based on the active moieties already. Since the APIs used are in their salt forms, an equivalent statement should be included to state that the indicated active moiety strengths are equivalent to 17.25 mg of buprenorphine hydrochloride and 4.89 mg of naloxone hydrochloride dihydrate respectively.

II. Attachments

A. Lifecycle Knowledge Management

Executive Risk Assessment Summary

From Initial Quality Assessment			Review Assessment		
Product	**Factors that can**	**Risk**	**Risk Mitigation**	**Risk**	**Lifecycle**

attribute/ CQA	impact the CQA	Ranking*	Approach	Evaluation	Considerations/ Comments**
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	-	-
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	-	-
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	-	-
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	-	-
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	-	-