

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207932Orig1s000**

**CHEMISTRY REVIEW(S)**



NDA 207932-Orig1-New - Proprietary Name - User Fee - Form 3674/NDA ... Manufacturing Facility Inspection

### Overall Manufacturing Inspection Recommendation

Edit Task / Tr

Task Summary Task Details Issues Updates Inspection Management Form

#### Inspection Management Form

1:43:41 PM

##### Inspection Management Form

NDA 207932-Orig1-New - Proprietary Name - User Fee - Form 3674/NDA - Request for Review - Coversheet(1)

- (b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility
- (b) (4) CSN NON STERILE API BY CHEMICAL SYNTHESIS | Approve Facility
- (b) (4) NEC NOT ELSEWHERE CLASSIFIED | Approve Facility
- (b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility
- (b) (4) NEC NOT ELSEWHERE CLASSIFIED | Approve Facility
- (b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility
- (b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility
- (b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility
- (b) (4) FACILITY PROFILE CANCELLED

Facility DUNS Number: Action Indicated Status: None  
(b) (4)

#### Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

Cancel

Assigned To

**Juandria Williams**

[Edit Assignment](#)

This was done on **Aug 31, 2015**  
(33 days ago)

Status **Complete**

Requested by **Youbang Liu**

This task is waiting on 2 Tasks

Last Update: Aug 31, 2015      Submitted On: Dec 25, 2014

Reference Number: 3664859

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY GRACE LUBAO  
11/04/2015

**Recommendation: Approval**

**NDA 207932  
Review #1  
9/11/2015**

<b>Drug Name/Dosage Form</b>	Belbuca (Buprenorphine Hydrochloride Buccal Film)
<b>Strength</b>	75 µg, 150 µg, 300 µg, 450 µg, 600 µg, 750 µg and 900 µg
<b>Route of Administration</b>	Buccal
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Endo Pharmaceuticals Inc.
<b>US agent, if applicable</b>	N/A

<b>SUBMISSION(S) REVIEWED</b>	<b>SUBMISSION DATE</b>
Original Submission	23-DEC-2014
Response to Quality Information Request	20-MAR-2015
Response to CMC Information Requested	04-MAY-2015
Response to CMC Information Requested	01-JUL-2015
Response to CMC Information Requested	11-AUG-2015
Response to CMC Information Requested	31-AUG-2015

**Quality Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	Sukhamaya Bain, Ph.D.	II/New Drug API
Drug Product	Christopher Hough, Ph.D.	II/Drug Product
Process	Shujun Chen, Ph.D.	DP/II/ Branch VI
Microbiology	Erika Pfeiler, Ph.D.	OPF/DMA
Facility	Juandria Williams, Ph.D.	DIA/ Branch III
Biopharmaceutics	Fang Wu, Ph.D.	DB/Branch III
Project/Business Process Manager	Don Henry	OPRO/IO
Application Technical Lead	Ciby Abraham, Ph.D.	DNP II/Branch IV
Laboratory (OTR)	N/A	
ORA Lead	Paul Perdue	ORA/OO
Environmental Assessment (EA)	N/A	



## Table of Contents

Table of Contents .....	2
Quality Review Data Sheet .....	3
Executive Summary .....	5
Primary Quality Review.....	9
ASSESSMENT OF THE DRUG SUBSTANCE .....	9
2.3.S    DRUG SUBSTANCE .....	9
ASSESSMENT OF THE DRUG PRODUCT .....	18
2.3.P    DRUG PRODUCT.....	18
ASSESSMENT OF THE DRUG PRODUCT .....	18
2.3.P    DRUG PRODUCT .....	18
ASSESSMENT OF THE PROCESS.....	56
2.3.P    DRUG PRODUCT.....	56
R.2      Comparability Protocols.....	88
ASSESSMENT OF THE FACILITIES.....	89
2.3.S    DRUG SUBSTANCE .....	89
2.3.P    DRUG PRODUCT .....	93
ASSESSMENT OF THE BIOPHARMACUETICS .....	100
ASSESSMENT OF MICROBIOLOGY.....	113
2.3.P.6  Reference Standards or Materials.....	<b>Error! Bookmark not defined.</b>
A    APPENDICES .....	<b>Error! Bookmark not defined.</b>
A.2      Adventitious Agents Safety Evaluation ..	<b>Error! Bookmark not defined.</b>
I.    Review of Common Technical Document-Quality (Ctd-Q) Module 1 .....	115
Labeling & Package Insert.....	<b>Error! Bookmark not defined.</b>
II.   List of Deficiencies To Be Communicated.....	118
III.  Attachments .....	<b>Error! Bookmark not defined.</b>
IV.  Administrative.....	8



## Quality Review Data Sheet

**1. LEGAL BASIS FOR SUBMISSION:**

**2. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS <sup>1</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	06-Oct-2014	Reviewed by Y. Lin
	Type II			Adequate	02-Apr-2015	Reviewed by S. Bain
	Type II			Adequate	02-Mar-2015	Reviewed by S. Bain
	Type III			Adequate	N/A	
	Type III			Adequate	N/A	
	Type III			Adequate	N/A	
	Type III			Adequate	N/A	
	Type IV			Adequate	July 28 2015	

<sup>1</sup> Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Application for Buprenex injection from Inivior IUnc.	NDA 18-401	Referenced based on 505(b)(2) submission
Application for Buprenorphine HCL tablet from Roxane Laboratories Inc.	ANDA 78633	Referenced based on 505(b)(2) submission



**QUALITY ASSESSMENT**  
**NDA # 207932**



**3. CONSULTS:**

<b>DISCIPLINE</b>	<b>STATUS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

## Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Based on the recommendation from the following disciplines, drug substance, process, microbiology, biopharmaceutics, facilities, and drug product, CMC recommends the approval of BELBUCA 75 µg, 150 µg, 300 µg, 450 µg, 600 µg, 750 µg and 900 µg buccal films.

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

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Product

##### *Drug Substance*

The drug substance, Buprenorphine HCl is manufactured by (b) (4) and is referenced in DMF# (b) (4) (adequate, last reviewed 10/6/2014) and manufactured by (b) (4) DMF# (b) (4) (adequate, last reviewed 3/2/2015). (b) (4) is manufactured by (b) (4) DMF# (b) (4) (adequate, last reviewed 8/31/2015). Buprenorphine HCl will be the drug substance used for the drug product. Buprenorphine Hydrochloride is a non-hygroscopic crystalline powder. It demonstrates pH dependent aqueous solubility due primarily to the amine functional group; solubility increases with decreasing pH. The retest period of (b) (4) has been assigned for (b) (4) (DMF# (b) (4)) and a retest period of (b) (4) has been assigned for (b) (4) (DMF# (b) (4)).

##### *Drug Product*

Belbucal buccal film utilizes the same BioErodible MucoAdhesive (BEMA®) technology platform that was used by BDSI to develop the FDA-approved mucoadhesive film products, Onsolis® (fentanyl buccal soluble film) and BUNAVAIL™ (buprenorphine and naloxone buccal film). Each individual buprenorphine HCl buccal film is packaged in a child-resistant, (b) (4)/foil (b) (4) package, the same packaging material used for BUNAVAIL®. Buprenorphine HCl buccal film is a non-sterile single-dose, immediate-release oral product.



**QUALITY ASSESSMENT  
NDA # 207932**



Belbuca buccal film contains 75 µg, 150 µg, 300 µg, 450 µg, 600 µg, 750 µg, and 900 µg of buprenorphine per film. The film is light yellow to yellow on one side (mucoadhesive layer) and white to off-white on the other side (backing layer), which is printed with black ink. The strength of a film is dependent on (b) (4) and its size. (b) (4)

Based on the stability data provided, an expiry of 24-months will be granted using the storage statement "Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F)."

**B. Description of How the Drug Product is Intended to be Used**

Belbuca is a film that is applied to the buccal mucosa (oral cavity). The formulation provides analgesia for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.

**C. Basis for Approvability or Not-Approval Recommendation**

The sponsor has provided adequate information to support the manufacturing and control of the drug substance, process, microbiology, biopharmaceutics, facilities, and drug product.

**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>	H	(b) (4)	Acceptable	-



**QUALITY ASSESSMENT**  
**NDA # 207932**



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	-	N/A	-
Alcohol Dose Dumping	<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<ul style="list-style-type: none"><li>• Alcohol dose dumping</li></ul></li></ul>	H	-	Acceptable	There is no dose dumping detected in the in vitro dose dumping study under the condition tested.

\*Risk ranking applies to product attribute/CQA

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

## I. 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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**OVERALL ASSESSMENT AND SIGNATURES: FACILITIES**

**Reviewer's Assessment and Signature:**

There appear to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined acceptable to support approval of NDA 207932.

Post-approval coverage during the next inspection is recommended for the following facilities:

(b) (4)

- 
- 
- 
- 
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- 

Juandria Williams, PhD; OPF/DIA/B3  
September 10, 2015

**Supervisor Comments and Concurrence:**

Vipul Dholakia, PhD; OPF/DIA/B3 (senior reviewer performing secondary review)  
September 10, 2015

Note: additional reviewers can be added, as appropriate

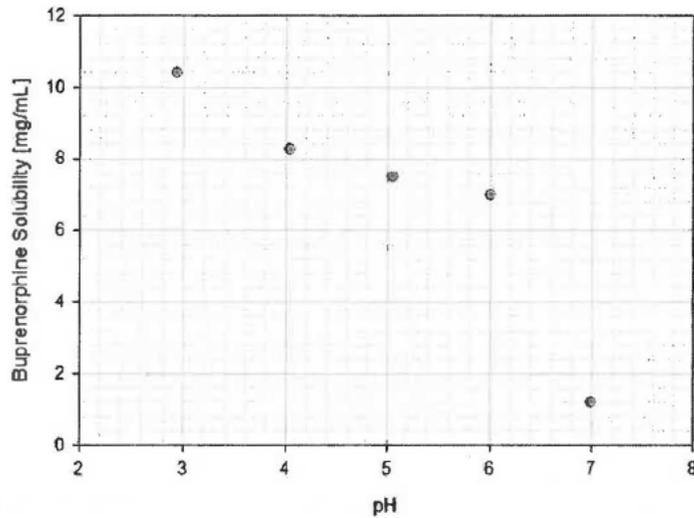
**ASSESSMENT OF THE BIOPHARMACUETICS**

**INTRODUCTION**

Endo Pharmaceuticals Inc. (Endo) is submitting an Original New Drug Application (NDA) via the 505 (b) (2) path for Buprenorphine HCl Buccal Film CIII (BELBUCA™), which is indicated for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in opioid-naïve and opioid-experienced patients.

**BCS CLASSIFICATION**

No information is provided for BCS classification. However, the solubility data are provided as shown in **Biopharm Figure 1**, which shows that buprenorphine hydrochloride demonstrates a pH dependent solubility (b) (4)



Biopharm Figure 1. Buprenorphine HCl Solubility (b) (4)

**DRUG PRODUCT**

Buprenorphine HCl buccal film uses BioDelivery Sciences International’s (BDSI) BioErodible MucoAdhesive (BEMA) delivery technology comprised of flexible, water soluble polymeric film which adheres to the moist buccal mucosa and dissolves, so that there is no residual film to remove from the mucosa.

(b) (4)

Buprenorphine HCl buccal film contains 75 µg, 150 µg, 300 µg, 450 µg, 600 µg, 750 µg, and 900 µg of buprenorphine per film. The strength of a film is dependent on (b) (4) used in its manufacture and size. (b) (4)

(b) (4). Film size was identified as the limiting factor to provide a lower dose range.

(b) (4)

The formulations, (b) (4) were selected for the pivotal clinical studies (EN3409-307, EN3409-308, and EN3409-309) and used to manufacture the pivotal clinical batches, registration batches, and production scale batches. Formulations (b) (4) are the intended commercial formulations. Dissolution results for the registration lots are similar ( $f_2 > 50$ ) to the dissolution results for pivotal clinical lots (page 21 of session 2.3 Introduction to the quality overall summary).

**REVIEW FOCUS**

The biopharmaceutics review will be focused on the evaluation and acceptability of the data provided to support the dissolution method and acceptance criterion.

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

**18A DISSOLUTION METHOD**

The originally proposed dissolution method and acceptance criterion are shown below:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
I	100 rpm	60 mL	37°C	pH 4.5 0.05M NaH <sub>2</sub> PO <sub>4</sub> ·H <sub>2</sub> O phosphate buffer	Drug amount dissolved Q= <sup>(b)</sup> / <sub>(4)</sub> % at 60 minutes

**18A.1 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?**

The dissolution method development report was provided in the following link: <\\cdsesub1\evsprod\nda207932\0000\m3\32-body-data\32p-drug-prod\buprenorphine-hcl\32p2-pharm-dev\drug-prod.pdf>. The following method parameters were evaluated.



(b) (4)

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

**19A. FORMULATION**

The formulations, (b) (4) were used to manufacture the pivotal clinical batches for the pivotal clinical studies EN3409-307, EN3409-308, and EN3409-309, registration batches, and production scale batches. They are the intended commercial formulations. Dissolution results for the registration lots are similar (f2>50) to those for pivotal clinical lots.

**Biopharm Table 1 Buprenorphine Film Dissolution – Similarity Factor (f2)**

Film Strength (µg)	Reference Product	Test		Similarity Factor (f2) <sup>a</sup>
		Lot #	Use	
75	Lot 31711 used in Clinical	32390	Registration Stability	59
		32391	Registration Stability	53
		32392	Registration Stability	59
		32475	Registration Stability	61
	Average of Registration Lots (Lot #: 32390, 32391, 32392, 32475)	33284	1 <sup>st</sup> (b) (4) Scale-up (b) (4)	68
		33272	2 <sup>nd</sup> (b) (4) Scale-up (b) (4) 0 kg)	73
150	Average of Clinical Lots (Lot #: 31710, 31863)	32393	Registration Stability	81
		32395	Registration Stability	56
		32397	Registration Stability	63
		32476	Registration Stability	64
	Average of Registration Lots (Lot #: 32393, 32395, 32397, 32476)	33102	1 <sup>st</sup> (b) (4) Scale-up (b) (4)	63
		33273	2 <sup>nd</sup> (b) (4) Scale-up (b) (4) kg)	94
300	Average of Clinical Lots (Lot #: 31712, 31866)	32398	Registration Stability	73
		32399	Registration Stability	72
		32400	Registration Stability	60
		32477	Registration Stability	54
	Average of Registration Lots	33103	1 <sup>st</sup> (b) (4) Scale-up (b) (4) kg)	53
900	Average of Clinical Lots (Lot #: 31716, 31868)	32404	Registration Stability	69
		32405	Registration Stability	53
		32406	Registration Stability	52
		32479	Registration Stability	56

Average of Registration Lots	33105	1 <sup>st</sup> (b) (4) Scale-up (b) (4) (k $\alpha$ )	57
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<sup>a</sup> A minimum of 3 points, no more than (b) (4)% RSD at early timepoints (15 minutes) and no more than (b) (4)% RSD at later timepoints. Only 1 point after (b) (4)%, average data was utilized. n=6 for clinical, n=12 for registration and scale up batches at release.

(b) (4); RSD= Relative standard deviation

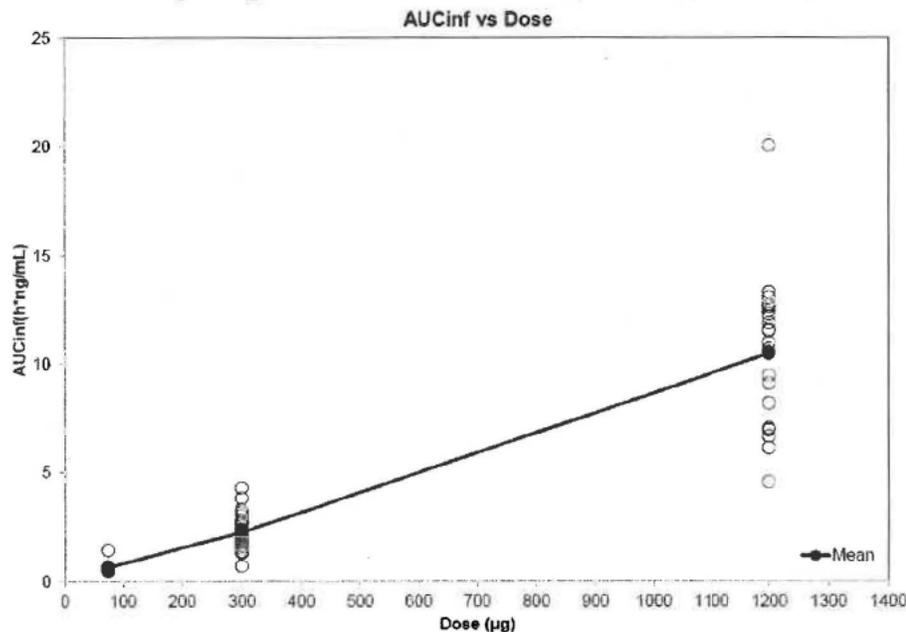
**Reviewer's Assessment:**

According to the analysis presented in **Biopharm Table 1**, dissolution results for the registration lots are similar ( $f_2 > 50$ ) to those for the pivotal clinical lots. The multiple batches manufactured throughout the formulation development are appropriately bridged.

**19 B. DOSE PROPORTIONALITY**

**19B.1 What bioavailability (BA)/bioequivalence (BE) data are available for both pre- and post-approval process? Is associated bioanalytical method submitted?**

The approval of the strengths not tested in the BE/clinical studies is based on an in vivo dose-proportionality study which is reviewed by OCP. According to the dose proportionality study (BUP-117) for BEMA Buprenorphine Buccal Soluble Film 75  $\mu$ g to 1200  $\mu$ g, systemic exposure to buprenorphine (AUC<sub>0-inf</sub>) from BEMA Buprenorphine was proportional to the dose applied to the buccal mucosa (**Biopharm Figure 15**); The mean absolute bioavailability of buprenorphine from 75  $\mu$ g to 1200  $\mu$ g BEMA Buprenorphine ranged from **46% to 51%**, independently of dose and formulation.



Data Source: 5.3.3.1. Study BUP-117 [Figure 5]

**Biopharm Figure 15. AUC<sub>inf</sub> vs Dose in PK dose proportional study (BUP-117) for BEMA Buprenorphine Buccal Soluble Film 75  $\mu$ g to 1200  $\mu$ g**

For details, refer to clinical pharmacology review.

## OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

### Reviewer's Assessment and Signature:

The proposed dissolution method and acceptance criterion are **ADEQUATE**. From the Biopharmaceutics perspective, an approval is recommended for this NDA.

Fang Wu, Ph.D.  
Primary Biopharmaceutics Reviewer  
OPQ/ONDP/DBP  
Date: 08/31/2015

John Duan, Ph.D.  
Secondary Biopharmaceutics Reviewer  
& Branch Chief (Acting)  
OPQ/ONDP/DBP

cc Sandra Suarez, Paul Seo

Supervisor Comments and Concurrence: Concur. John Z. Duan

## ASSESSMENT OF MICROBIOLOGY

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

Belbuca is a dissolvable film for oral administration. Proposed presentations include films containing 75, 150, 300, 450, 600, 750, and 900 µg of the API.

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial



## QUALITY REVIEW



Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use). These criteria include limits for gingival products of NMT (b)(4) CFU/g TAMC and NMT (b)(4) CFU/g TYMC and the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* per gram.

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The drug product will also be tested for Microbial Limits annually as part of the post-approval stability protocol.

### Reviewer's Assessment:

The Microbial Limits specification for Belbuca is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

Erika Pfeiler  
31 August 2015

## OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

### Reviewer's Assessment and Signature:

Recommended for Approval  
Erika Pfeiler  
31 August 2015

### Supervisor Comments and Concurrence:

Recommended for approval  
Stephen Langille  
31 August 2015

Note: additional reviewers can be added, as appropriate

## II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

### R.1 Labeling:

Carton Labels are shown below. All CMC information is satisfactorily included (name, strength, bar code, expiry, manufacturer). The non-proprietary name includes the salt name. Per the current USP salt nomenclature policy and the ICH guidance for naming of Salt APIs, the non-proprietary name should be Buprenorphine rather than Buprenorphine hydrochloride.

Each carton label is color coded for each strength and matches the color coding on each foil pouch, used to individually package the buccal film. The color coding is as described in section 2.3.P.1, Table 1, above.

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

## 14. ENVIRONMENTAL ASSESSMENT: CLAIM FOR CATEGORICAL EXCLUSION

### **Claim for Categorical Exclusion of Buprenorphine Hydrochloride Buccal Films (75 µg, 150 µg, 300 µg, 450 µg, 600 µg, 750 µg, 900 µg) from the Environmental Assessment Requirements of 21 CFR 25.40**

In accordance with 21 CFR 25.31(b), Endo Pharmaceuticals Inc. claims a categorical exclusion from the environmental assessment requirements of 21 CFR 25.40 for approval of this application.

Based upon the estimate of the highest quantity of the active moiety to be produced (for direct use) in the next 5 years, the estimated concentration of the active moiety at the point of entry into the aquatic environment will be below 1 part per billion (ppb). Therefore, this action is subject to a categorical exclusion and will not require the preparation of an environmental assessment. The figures used for this calculation are available upon request.

To our knowledge, no extraordinary circumstances exist pertaining to this action.

Evaluation: Adequate.

### III. List of Deficiencies To Be Communicated

- A. Drug Substance
- B. Drug Product
- C. Process/Facility
- D. Biopharmaceutics
- E. Microbiology
- F. Label/Labeling