

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205637Orig1s000

CHEMISTRY REVIEW(S)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 205637/000
Submission Date: 07-AUG-2013
Regulatory: 07-JUN-2014

Action Goal:
District Goal: 08-APR-2014

Applicant: BIODELIVERY SCI INTL
801 CORPORATE CENTER DR STE 210
RALEIGH, NC 27607

Brand Name: BEMA BUPRENORPHINE NX
Estab. Name:
Generic Name: BUPRENORPHINE AND NALOXONE BUCCAL FILM

Priority: 3
Org. Code: 170

Product Number; Dosage Form; Ingredient; Strengths
002; FILM; BUPRENORPHINE HYDROCHLORIDE; 2.1MG
002; FILM; NALOXONE HYDROCHLORIDE; .35MG
003; FILM; NALOXONE HYDROCHLORIDE; .7MG
003; FILM; BUPRENORPHINE HYDROCHLORIDE; 4.2MG
004; FILM; NALOXONE HYDROCHLORIDE; 1.04MG
004; FILM; BUPRENORPHINE HYDROCHLORIDE; 6.3MG
(b) (4)

Application Comment:

FDA Contacts:	X. SHEN	Prod Qual Reviewer	3017961411
	L. RIVERA	Product Quality PM	3017964013
	M. SULLIVAN	Regulatory Project Mgr (HFD-170)	3017961245
	O. STEPHENS	Team Leader (HFD-510)	3017963901

Overall Recommendation:	ACCEPTABLE	on 25-FEB-2014	by R. WITTORF	()	2404023113
	PENDING	on 20-AUG-2013	by EES_PROD		
	PENDING	on 20-AUG-2013	by EES_PROD		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
 FINISHED DOSAGE OTHER TESTER

Establishment Comment: DRUG PRODUCT ANALYSIS, TESTING FOR API AND EXCIPIENTS (on 09-AUG-2013 by L. RIVERA () 3017964013)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	20-AUG-2013				RIVERAL
OC RECOMMENDATION	03-SEP-2013			ACCEPTABLE	WILLIAMSJU

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER

Establishment Comment:

Profile: NOT ELSEWHERE CLASSIFIED OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	20-AUG-2013				RIVERAL
SUBMITTED TO DO THIS SITE WILL PERFORM	25-AUG-2013 (b) (4)	GMP Inspection IN-PROCESS TESTING, MANUFACTURING OF	(b) (4)		WILLIAMSJU
ASSIGNED INSPECTION TO IB	03-SEP-2013	Product Specific and GMP Inspection			VMATUSOV
INSPECTION SCHEDULED	24-JAN-2014		31-JAN-2014		VMATUSOV
INSPECTION PERFORMED NO FDA-483 ISSUED	(b) (4)		(b) (4)		VMATUSOV
DO RECOMMENDATION PAI/GMP INSPECTION DATED (b) (4) IS BEING CLASSIFIED NAI. NO DEFICIENCIES WERE NOTED AND NO FDA-483 WAS ISSUED. THERE ARE NO PENDING ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION.	21-FEB-2014			ACCEPTABLE	VMATUSOV
OC RECOMMENDATION	25-FEB-2014			ACCEPTABLE	WITTORFR

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: IN PROCESS RELEASE AND STABILITY TESTING FOR THE DRUG PRODUCT, TESTING FOR API AND EXCIPIENTS (on 09-AUG-2013 by L. RIVERA () 3017964013)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
<u>OAI Submit To OC</u>					
<u>Request to Extend Re-eval Date To</u>					
<u>Extension Request Comment</u>					
<u>Reason</u>					

SUBMITTED TO OC	20-AUG-2013				RIVERAL
OC RECOMMENDATION	25-AUG-2013			ACCEPTABLE	WILLIAMSJU

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment Comment: DRUG SUBSTANCE MANUFACTURE, RELEASE AND STABILITY TESTING (on 20-AUG-2013 by L. RIVERA ()
3017964013)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
<u>OAI Submit To OC</u>					
<u>Request to Extend Re-eval Date To</u>					
<u>Extension Request Comment</u>					
<u>Reason</u>					

SUBMITTED TO OC	20-AUG-2013				RIVERAL
OC RECOMMENDATION	24-AUG-2013			ACCEPTABLE	WILLIAMSJU

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment Comment: DRUG SUBSTANCE MANUFACTURE, RELEASE AND STABILITY TESTING (on 20-AUG-2013 by L. RIVERA ()
 3017964013)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	20-AUG-2013				RIVERAL
OC RECOMMENDATION	24-AUG-2013			ACCEPTABLE	WILLIAMSJU

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: DRUG SUBSTANCE MANUFACTURE, PACKAGER, RELEASE AND STABILITY TESTING (DMF (b) (4) (on 20-AUG-2013 by L. RIVERA () 3017964013)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
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<u>Reason</u>					

SUBMITTED TO OC	20-AUG-2013				RIVERAL
OC RECOMMENDATION	24-AUG-2013			ACCEPTABLE	WILLIAMSJU

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: IN PROCESS, RELEASE AND STABILITY TESTING FOR DRUG PRODUCT, TESTING FOR API AND EXCIPIENTS (on 09-AUG-2013 by L. RIVERA () 3017964013)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	20-AUG-2013				RIVERAL
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SUBMITTED TO DO	25-AUG-2013	GMP Inspection			WILLIAMSJU
LAST GMP STATUS OF AC FOR CTX/CTL PROFILE > 3 YRS					

ASSIGNED INSPECTION TO IB	04-SEP-2013	GMP Inspection			LTHOMAS
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INSPECTION PERFORMED	(b) (4)		(b) (4)		LTHOMAS
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DO RECOMMENDATION	07-NOV-2013			ACCEPTABLE	LTHOMAS
<p>A GMP INSPECTION OF THE FIRM OCCURRED (b) (4) THAT INCLUDED COVERAGE OF SEVERAL APPLICATIONS. THE QUALITY AND LABORATORY CONTROLS SYSTEMS WERE PRIMARILY COVERED DURING THE INSPECTION AND RECORDS REVIEWED INCLUDED (BUT WERE NOT LIMITED TO): LABORATORY EQUIPMENT QUALIFICATION AND CALIBRATION, MICRO LAB ENVIRONMENTAL MONITORING DATA, METHOD VALIDATION AND TRANSFER, STABILITY PROGRAM DATA, AND LAB DEVIATIONS AND INVESTIGATIONS. AT CLOSE-OUT, A 2-ITEM FDA-483 WAS ISSUED TO FIRM MANAGEMENT FOR THE FOLLOWING DEFICIENCIES:</p> <ul style="list-style-type: none"> - FAILURE TO SCIENTIFICALLY JUSTIFY A DISCREPANCY IN (b) (4) ASSAY TESTING RESULTS DURING A METHOD TRANSFER PROCEDURE - FAILURE TO FOLLOW INTERNAL PROCEDURES REGARDING (b) (4) AND PERFORMANCE OF DAILY CALIBRATION CHECKS FOR A (b) (4) <p>SEVERAL VERBAL OBSERVATIONS WERE ALSO ADDRESSED WITH MANAGEMENT AT CLOSE-OUT AS REPORTED IN THE EIR.</p>					

BASED UPON THE INSPECTION, THE DISTRICT RECOMMENDS APPROVAL OF THE FIRM FOR ITS RESPONSIBILITY AS A CONTROL TESTING LABORATORY IN LISTED APPLICATIONS. BOTH THE CTX AND CTL PROFILE CLASSES WERE FOUND ACCEPTABLE.

OC RECOMMENDATION	07-NOV-2013			ACCEPTABLE	SAFAAIJAZIR
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**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Establishment Comment: [REDACTED] (b) (4) PACKAGING OF THE BUCCAL SOLUBLE FILM (on 09-AUG-2013 by L. RIVERA () 3017964013)
PLEASE CONDUCT PAI AND GMP INSPECTION OF THE FIRM PROVIDING COVERAGE TO THE PACKAGING OPERATION OF THE BUCCAL FILM. THE FIRM IS LISTED AS RESPONSIBLE FOR [REDACTED] (b) (4) [REDACTED] (b) (4) APPROPRIATE STRENGTH UNITS AND THEN PACKAGING. THIS TYPE OF OPERATION MAYBE NEW TO THE FIRM.

PLEASE COMPLETE PAGE 2 OF EES INSPECTION REPORT AND SUBMIT TO PAI MANAGER ALONG WITH A COPY OF ANY FDA 483 ISSUED WITHIN ONE DAY OF COMPLETION OF THE EI. (on 03-SEP-2013 by V. MATUSOVSKY (HFR-CE1515) 2157173738)

Profile: NOT ELSEWHERE CLASSIFIED OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	20-AUG-2013				RIVERAL
SUBMITTED TO DO THE FIRM WILL	25-AUG-2013	10-Day Letter	[REDACTED] (b) (4) APPROPRIATE STRENGTH UNITS, THEN PACKAGE		WILLIAMSJU
ASSIGNED INSPECTION TO IB	03-SEP-2013	Product Specific and GMP Inspection			VMATUSOV
INSPECTION PERFORMED	[REDACTED] (b) (4)		[REDACTED] (b) (4)		VMATUSOV
A ONE-ITEM 483 WAS ISSUED TO THE FIRM. THE DOCUMENTED DEFICIENCY DOES NOT RELATE TO THE PAI PRODUCT.					
DO RECOMMENDATION	17-JAN-2014			ACCEPTABLE	VMATUSOV
THE PAI/GMP INSPECTION OF THIS FIRM CONDUCTED [REDACTED] (b) (4) IS BEING CLASSIFIED VAI. A ONE-ITEM FDA 483 WAS ISSUED TO THE FIRM. THE DOCUMENTED DEFICIENCY DOCUMENTING INADEQUATE REWORK OPERATIONS DOES NOT RELATE TO THE PAI PRODUCT. THERE ARE NO PENDING ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION.					
OC RECOMMENDATION	17-JAN-2014			ACCEPTABLE	SHARPT
THE PAI/GMP INSPECTION OF THIS FIRM CONDUCTED [REDACTED] (b) (4) IS BEING CLASSIFIED VAI. A ONE-ITEM FDA 483 WAS ISSUED TO THE FIRM. THE DOCUMENTED DEFICIENCY DOCUMENTING INADEQUATE REWORK OPERATIONS DOES NOT RELATE TO THE PAI PRODUCT. THERE ARE NO PENDING ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION.					

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/s/

SHANNON J CREWS
06/20/2014

Chemistry Review Cover Sheet

NDA 205637

Bunavail

**(buprenorphine/naloxone buccal
film)**

Arthur B. Shaw, Ph.D.

ONDQA/DNDQIII/DAAAP

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Chemistry Review Data Sheet

1. NDA 205637
2. REVIEW #1
3. REVIEW DATE: May 6, 2014
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Comment</u>
Original	2013-08-07	
Filing review	2013-09-24	
Filing Letter (IR)	2013-10-16	Request batch record, updated 12 month stability, info on (b) (4)
Amendment response to Filing Letter	2013-11-13	Info on (b) (4)
MV Consult Request	2013-11-25	
IR email	2013-11-27	Request details of extraction studies
IR letter	2013-12-02	Request info on (b) (4) for MV
IR email	2013-12-05	Request info on mucoadhesion and separation of films
Amendment Response to 11-17 IR	2013-12-05	Details of extraction testing
Amendment Response to 12-02 IR	2013-12-26	Info about (b) (4) for MV
Amendment	2014-01-23	Link to extraction data in P.2.2
Amendment Response to 12-05 IR	2014-01-30	Mucoadhesion and film separation
IR email	2014-02-10	Request revised test for (b) (4)
Amendment Response to 10-16	2014-02-21	Master Batch Record
Amendment Response to 02-10	2014-02-26	Revised test for (b) (4)
Amendment Response to 10-16	2014-02-27	Updated stability data
Stability consult	2014-03-13	Assay and unknown impurity at (b) (4)
CMC IR Letter	2014-04-08	
Stability Consult review	2014-04-11	Recommend 12 month expiration
Amendment Response to 4-11	2014-05-01	Complete Response

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review #1 NDA 205637

Name: BioDelivery Sciences International
 801 Corporate Center Drive Suite 210
 Raleigh NC 27607
 Representative: Andrew Finn, Pharm. D.
 Telephone: 919-582-9050
 Email: AFinn@bdsi.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Bunavail (proposed)
- b) Non-Proprietary Name (USAN): buprenorphine/naloxone (incorrectly listed as buprenorphine hydrochloride/naloxone hydrochloride on the 356h)
 CAS #
 53152-21-9 buprenorphine hydrochloride
 465-65-6 naloxone hydrochloride
- c) Chem. Type/Submission Priority
 - Chem. Type: 5
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505b(2)

10. PHARMACOL. CATEGORY: partial opioid agonist Note that the label for the “reference drug”, Suboxone, does not include this pharmacological category.

11. DOSAGE FORM: buccal film

12. STRENGTH/POTENCY:

Label strength	Amount of buprenorphine (mg/film)	Amount of naloxone (mg/film)
1		(b) (4)
2	2.1	0.348
4	4.2	0.696
6	6.3	1.044

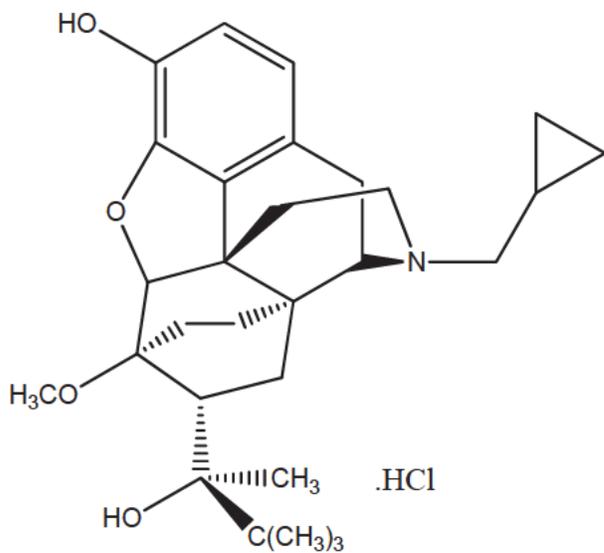
13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: X Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

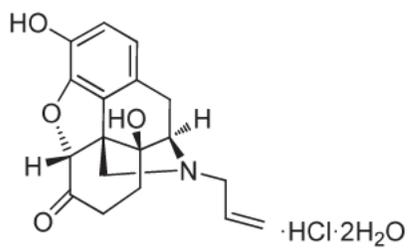
Buprenorphine hydrochloride



IUPAC

(b) (4)

Naloxone hydrochloride dihydrate



C₁₉H₂₁NO₄·HCl·2H₂O

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	Holder	DMF Subject	LOA Date	Review Date
(b) (4)			3/27/2013	Adequate 11-22-2013
			3/28/2013	Adequate 02-18-2014
			3/25/2013	Adequate 04-25-2014
			04/09/2013	Not reviewed since there is sufficient information in the NDA See Section P Container Closure below

B. Other Documents:

Document	DESCRIPTION
IND 110257	Bunavail development

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS:

Discipline	Result	Date	Reviewer
Methods Validation	Pending		
Microbiology	Approval	2014-04-14	John Metcalfe
Statistics	Recommend 12mon the expiration	2014-04-11	Sutan Wu
EES	Acceptable	2014-02-25	

The Chemistry Review for NDA 205637

I. Recommendations

- A. Recommendation and Conclusion on Approvability** The application is approvable from a CMC point of view pending satisfactory responses to issues in IR letter.
- B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substances

The “primary” drug substance that provides the therapeutic effect of the drug product is buprenorphine HCl, while naloxone HCl is included to act as an abuse deterrent.

Buprenorphine hydrochloride is a partial opiate agonist which has been used in many approved drug products and is covered by USP and Ph. Eur. monographs. Complete CMC information is provided in DMF (b)(4), which was reviewed and found acceptable in a review dated February 18, 2014. It is a white solid that is slightly soluble in water. Since the drug substance is (b)(4) to manufacture the drug product the solid state form is not relevant to the drug product characteristics. The DMF holder adequately controls the impurities. The applicant accepts the drug substance based on the supplier’s COA and their own ID test by IR and has the drug substance fully tested by a contract laboratory.

Naloxone hydrochloride is an opiate antagonist which has been used in many approved drug products and is covered by USP and Ph. Eur. monographs. Complete CMC information is provided in DMF (b)(4), which was reviewed and found acceptable in a review dated November 22, 2013. It is a white solid that is soluble in water. Since the drug substance is (b)(4) to manufacture the drug product the solid state form is not relevant to the drug product characteristics. The DMF holder adequately controls the impurities. The applicant accepts the drug substance based on the supplier’s COA and their own ID test by IR and has the drug substance fully tested by a contract laboratory.

Since the drug product is designed to be abuse-deterrent the applicant has performed extraction studies. Therefore the solubility characteristics of the drug substances are important. Buprenorphine HCl is sparingly soluble in water, freely soluble in methanol, soluble in alcohol, practically insoluble in cyclohexane. Naloxone HCl is soluble in water, in dilute acids, and in strong

alkali; slightly soluble in alcohol, practically insoluble in ether and in chloroform.

2. Drug Product

The drug product is a polymeric film containing the drug substances in two layers. One layer, the “mucoadhesive layer (ML)”, contains the therapeutically active drug substance, buprenorphine, which has opiate activity. The other layer, the “backing layer (BL)” contains naloxone, an opiate antagonist, which is intended as an abuse deterrent if the film is dissolved by the user and injected or snorted. The two layers are (b)(4) but in the finished product they cannot be distinguished and the two layers cannot be peeled apart, which means that the buprenorphine layer cannot be dissolved separately by the user. The film is colored yellow throughout the film and has the strength printed on the film. The different strengths have (b)(4) compositions but are different sizes. The ML is intended to be placed against the inside of the cheek, where it adheres to the moist mucosa. As the film dissolves, the buprenorphine is absorbed through the buccal mucosa and the naloxone is swallowed. Historical data shows that the naloxone has no pharmacological effect since it is rapidly metabolized. The applicant's clinical studies have been designed to demonstrate that the buprenorphine is absorbed in clinically relevant quantities and the naloxone is not absorbed. The strength is printed in such a way as to show which side of the film should be placed against the cheek for proper therapeutic use. There is no validated in vitro test for adhesion of the film to the wet mucosa of the inside of the cheek. The adhesion of the film to the cheek and the effectiveness of the directions in the Medication Guide are being evaluated by the clinical review team.

The comparator drug product for this 505(b)(2) application is Suboxone (NDA 20733), a sublingual tablet that contains buprenorphine and naloxone.

The formulation and the manufacturing procedure are based on the applicant’s prior knowledge for a similar procedure used for Onsolis, another opiate-containing buccal film (NDA 22266). The polymer composition and the (b)(4) are expected to impact the drug product’s performance. Mucoadhesion was not considered during development and the composition of the ML was based on the composition of the approved Onsolis. The specifications consist of standard tests for appearance, identity, assay, degradants, content uniformity, dissolution, moisture, weight, and residual solvents. The applicant prepared a Pharmaceutical Development Report (PDR) but did not identify Critical Quality Attributes. The evaluation of modifying parameters in the PDR consisted of testing for dissolution, appearance, and drug content. There is a release test for microbial quality by microbial testing and the product is tested for water activity moisture by moisture testing. This was found acceptable by the Microbiology reviewer. The formulation includes (b)(4) but the applicant has not evaluated the optimal levels. The formulation also includes (b)(4)

The manufacturing procedure involves the following unit steps:



The excipients were found to be compatible with the drug substances and the manufacturing controls are adequate to achieve a reproducible product. There is some data to support any fairly narrow ranges of (b) (4) parameters but there is little flexibility in the overall process. The applicant has proposed (b) (4) and proposes to submit the change as a CBE-30 supplement, since the operating principles of the (b) (4) are the same. The applicant has provided a commitment to provide the relevant data to support the operating parameters in the supplement.

The specifications are adequate to support the release of the drug product with consistent characteristics. The stability data can support only the twelve months provided by the applicant because one of the parameters, an unidentified impurity at (b) (4) increase at both intermediate and accelerated storage conditions (See ICH Q1E).

The applicant has performed extraction studies to compare the ability of drug substances to be extracted from the Bunavail and Suboxone using a number of solvents that addicts might use. The studies show that buprenorphine can be selectively extracted in (b) (4) from both products, leaving the naloxone behind. However the film is not dissolved by the (b) (4) solution while the tablet forms a suspension in the (b) (4) solution. Therefore the product has the potential to be abused by injecting the (b) (4) solution containing buprenorphine without naloxone. While this is not an approvability issue, it is an important consideration for the clinical review team.

All inspections are satisfactory.

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

The drug product is intended to be used by patients addicted to opiates to satisfy their craving for opiates by providing a dose of buprenorphine. It is intended to be placed on the inside of the cheek, where the drug product adheres until it dissolves. The buprenorphine is intended to be absorbed through the buccal mucosal directly into the bloodstream while the opiate antagonist is swallowed with no pharmacological effect.

C. Basis for Approvability or Not-Approval Recommendation

The application may be approved based on the demonstration that the drug product can be manufacturing consistently and is adequately controlled by conformance with the specifications.

III. Administrative

See DARRTS signatures and cc's

128 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ARTHUR B SHAW
05/06/2014

PRASAD PERI
05/06/2014
I concur

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 205-637

2. DATES AND GOALS:

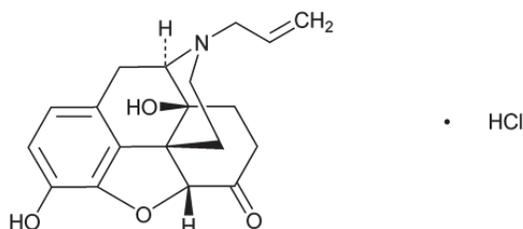
Letter Date: 31-Jul-2013	Submission Received Date : 7-Aug-2013
PDUFA Goal Date:	7-Jun-2014 (falls on a Sat.)
Filing Date	6-Oct-2013
74-Day Letter	20-Oct-2013
Primary Review Due	3-May-2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Bunavail™
Established or Non-Proprietary Name (USAN):	Buprenorphine and naloxone film
Dosage Form:	Buccal Film
Route of Administration	Topical
Strength/Potency	(b) (4) 2.1/0.348, 4.2/0.696, 6.3/1.044 mg bup/nal
Rx/OTC Dispensed:	Rx

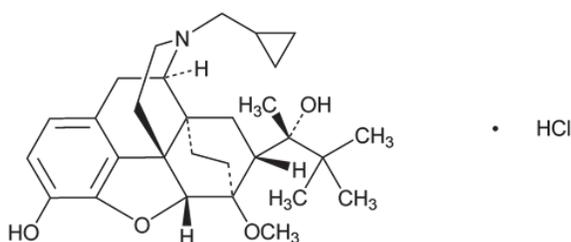
4. INDICATION: Maintenance Treatment of Opioid Dependence

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



• HCl

Naloxone Hydrochloride
 $C_{19}H_{21}NO_4 \cdot HCl$. (b) (4)



• HCl

Buprenorphine Hydrochloride
 $C_{29}H_{41}NO_4 \cdot HCl$. 504.10.

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6. NAME OF APPLICANT: BioDelivery Sciences International

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification:	Type 5
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization:	DAAAP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology	X		Impurity specifications will be discussed through the review process
Methods Validation	X		Recommended pending opinion of the CMC reviewer
Environmental Assessment		X	
CDRH		X	
Other	X		Microbiology (John Metcalfe)

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Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes <input checked="" type="checkbox"/> No
CMC Filing Issues:
1.

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes <input checked="" type="checkbox"/> No
CMC Comments for 74-Day Letter:
<ol style="list-style-type: none">1. As per 314.54(a)(1)(i), 505(b)(2) applications must provide a master batch record or a proposed master batch record. We note that you have provided executed batch records. Submit a master batch record, proposed master batch record, or confirm that the executed batch records in Module 3.2.R is identical to the master batch record for the intended commercial manufacturing process.2. Submit your 12 month stability update for each registration batch as soon as possible to facilitate our review of the data. The data should be formatted for ease of review by our statisticians.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes <input checked="" type="checkbox"/> No	Dr. Karen Riviere will be the biopharmaceutics reviewer for this application
Biopharmaceutics Filing Issues:	
1. NA	

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes <input checked="" type="checkbox"/> No
Biopharmaceutics Comments for 74-Day Letter:
<ol style="list-style-type: none">1. There is insufficient data to support the adequacy of the selected dissolution method. Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:<ol style="list-style-type: none">a. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters supporting the proposed dissolution method as the optimal test for your product (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.). The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.

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- | |
|--|
| <p>b. Data to support the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., $\pm 10\text{-}20\%$ change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent.</p> <p>2. Provide the complete dissolution profile data (raw data and mean values) from the pivotal clinical batches supporting your selection of the proposed dissolution acceptance criteria for your proposed product.</p> <p>3. Provide dissolution profile comparisons between the highest and lower strengths in three different media (pH 1.2, 4.5, 6.8) to meet the f_2 similarity requirements.</p> |
|--|

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?	
Yes	X No
Microbiology Filing Issues:	
See Microbiology Filing Review for details and for any potential Microbiology review issues. Dr. John Metcalfe will be microbiology reviewer for this application	

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Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	None

Is a team review recommended?	Yes	X	No
Suggested expertise for team: This application will be used in piloting the team based review practice where the drug product, manufacturing process, and facility reviewers work in concert. I recommend a senior reviewer adept at reviewing non-standard dosage forms.			

Summary of Critical Issues and Complexities:

BEMA Buprenorphine NX (buprenorphine and naloxone buccal film) is an oral transmucosal form of buprenorphine hydrochloride and naloxone hydrochloride dihydrate (6:1 ratio of free bases). BEMA Buprenorphine NX uses the BioErodible MucoAdhesive (BEMA®) bilayer delivery technology which is comprised of water soluble polymeric films. BEMA Buprenorphine NX films are yellow on both sides, with an ink mark on the mucoadhesive side. BEMA Buprenorphine NX is designed to enable buccal absorption of buprenorphine, with minimal systemic absorption of naloxone when used as directed, and co-extraction of naloxone with buprenorphine in situations of attempted abuse. The drug product is manufactured using (b)(4) [redacted] to achieve one of three dose strengths. The technology is adapted from the approved Onsolis ® (fentanyl buccal film). The reviewer may wish to consult with the transdermal working group regarding issues that involve (b)(4) [redacted] compatibility and packaging of the buccal film.

All clinical supplies (other than those used for clinical studies BNX-101 and BNX-106) and registration stability batches were manufactured at (b)(4) [redacted] scale. The same equipment will be used for the commercial production. However, the reviewer should evaluate the effect of changes to the (b)(4) [redacted] conditions for the buccal film.

- The labeled strength of the drug product was a discussion topic at the pNDA meeting 2-May-2013. Refer to meeting minutes provided below for guidance on the issues at hand.**
- The proposed drug product specifications for buprenorphine and naloxone assay range from (b)(4) [redacted]%. The reviewer should evaluate the justification for these ranges and confirm that they would achieve a clinically effective dose as labeled.**
- Note that the Controlled Substance Staff will review the extractables study of the drug product for abuse liability studies. The reviewer will need to be clear with the review division that the CMC E/L evaluation concerns the container closure system.**
- The applicant is claiming that the citrus blend flavoring is “certified as FDA/FEMA GRAS”. The reviewer will need to evaluate this claim or confirm this flavorant is**

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qualified according to the non-clinical reviewer.

5. The reviewer should confirm that the applicant has committed to test at least one drug substance batch per year for the full list of release specifications as agreed upon in the NDA before manufacturing your drug product. Also, every drug substance batch is still expected to be tested with a subset of the full release specifications. This issue was discussed at the 2-May-2013 pNDA meeting, but the initial triage could not confirm this commitment.
6. The reviewer should evaluate the content uniformity of (b)(4) and may need to consult the biometrics group for their input.
7. The reviewer should evaluate the effect of changes to the (b)(4) conditions for the buccal film.
8. The sponsor was asked to provide product development information to demonstrate that the drug product has sufficient pliability, strength and integrity through the end of its shelf life. In other words, demonstrate that the film does not become brittle and break upon handling. The reviewer should evaluate whether this data is necessary as a release or stability test.
9. The sponsor was strongly advised to submit 12 months of stability data at filing. The stability package includes 12 months of long-term and intermediate data for two development batches that do not correspond to the proposed to-be-marketed dose strengths. However, the three registration batches at each strength were manufactured almost exactly one year ago. Therefore, we anticipate a stability update relatively early in the review cycle.
10. The applicant is proposing to drop microbial limits testing. The microbiology reviewer should be contacted regarding this plan.

Labeling issues raised in the Meeting Minutes from the 2-May-2013 pNDA meeting:

Question 8 The actual dosages are: (b)(4) 2.10/0.348 mg; 4.20/0.696 mg; and 6.30/1.044 mg. Is it acceptable to round the labeled dosages to: 1/0.2 mg; 2/0.3 mg; 4/0.7 mg; and 6/1.0 mg for prescribing simplicity?

FDA Response:

The labeled doses should be sufficiently informative as to prevent potential dosing errors and to comply with current regulations for labeling. We recommend using three significant figures except when there would be a “0” as the last digit, where two significant figures could be adequate. Provide your draft labeling with justification for how the labeled doses appear in your NDA submission. Note that this issue is being discussed further within ONDQA and should the policy evolve regarding rounding, we will communicate it to you.

BDSI May 1, 2013, the sponsor provided revised package label examples for consideration.

Discussion:

The Sponsor stated that they believe that medication errors and difficulty prescribing may occur if they are required to use (b)(4) significant digits, particularly since this is a combination product,

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[REDACTED] (b) (4)

The Division [DMEPA] responded that the proposed proprietary name (*Bunavail*) was acceptable.

[REDACTED] (b) (4)

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Initial Quality Assessment/FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		X	At the 3-May-2013 pNDA meeting, the sponsor was strongly encouraged to submit 12 months of stability data for the registration batches. At this time, only 6 months are on file, but those batches were manufactured 19-Sep-2012, so an early stability update can be expected. Furthermore, discussions between the clinical division and ONDQA led to the agreement that filing the NDA in light of the lack of stability data would be the decision of DAAAP.

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential filing issue</i> or a <i>potential review issue</i> .				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		

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	Parameter	Yes	No	Comment
6.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
7.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

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	Parameter	Yes	No	Comment
8.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
9.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
10.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

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D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
11.	Does the section contain a description of the DS manufacturing process?	X		However, the complete manufacturing process descriptions will be found in the referenced DMF (b)(4) (Naloxone HCl) and DMF (b)(4) (Buprenorphine HCl). Note that section 3.2.S.4.1 contains a technical bulletin from the DMF owners and may contain complimentary information to the DMFs.
12.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	Refer to DMF (b)(4) (latest review 19-Feb-2013 with one pending amendment to be reviewed) and DMF (b)(4) (last reviewed 3-Oct-2012 with one pending amendment to be reviewed)
13.	Does the section contain information regarding the characterization of the DS?		X	
14.	Does the section contain controls for the DS?	X		
15.	Has stability data and analysis been provided for the drug substance?		X	
16.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
17.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

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E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
18.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
19.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
20.	Is there a batch production record and a proposed master batch record?		X	The applicant will be asked to provide a master batch record to the submission (see comments for 74-day letter).
21.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
22.	Have any biowaivers been requested?	X		
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		Refer to DMF (b)(4) product (b)(4)
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		See notes above regarding paucity of stability data and anticipated stability amendment.
26.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	None noted in the IQA
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	None noted in the IQA

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
28.	Is there a methods validation package?	X		

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G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product		X	NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	LOA DATE	COMMENTS
	II			27-Mar-13	Active, LoA is in DARRTS, last reviewed 3-Oct-2012
	III			9-Apr-13	Active; LoA appears to be in DARRTS as supporting document 244; last reviewed 21-Sep-2009
	II			No date on letter	Active; LoA appears to be in DARRTS as supporting document 29; last reviewed 19-Feb-2013
	IV			25-Mar-13	Active; New DMF; LoA may be contained in new submission

I. LABELING				
	Parameter	Yes	No	Comment
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		

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ONDQA-BIOPHARMACEUTICS				
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
33.	Does the application contain dissolution data?	x		
34.	Is the dissolution test part of the DP specifications?	x		See the Initial Assessment section for the proposed dissolution method and acceptance criterion.
35.	Does the application contain the dissolution method development report?		x	See the Initial Assessment section for the IR comment that will be conveyed to the Applicant.
36.	Is there a validation package for the analytical method and dissolution methodology?	x		
37.	Does the application include a biowaiver request?	x		
38.	Is there information provided to support the biowaiver request?	x		
39.	Does the application include a IVIVC model?		x	Not Applicable.
40.	Is information such as BCS classification mentioned, and supportive data provided?		x	Not Applicable.
41.	Is information on mixing the product with foods or liquids included?		x	Not Applicable.
42.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		There is a BE study (BNX-110), a dose proportionality/linearity study across a 6-fold range of doses from (b) (4) mg (BNX-106), and a relative bioavailability study between the 4.2/0.696 mg BUNAVAIL dose and a 6.3/1.044 mg BUNAVAIL dose in healthy subjects (BNX-107). OCP will review these studies.

INITIAL BIOPHARMACEUTICS ASSESSMENT

This 505(b)(2) New Drug Application relies on the Agency's previous findings of nonclinical and clinical safety and effectiveness for the reference drug Suboxone sublingual tablet, the subject of NDA 20733 held by Reckitt Benckiser Healthcare.

In addition to the bioequivalence study (BNX-110) to demonstrate buprenorphine bioequivalence between BEMA Buprenorphine NX and Suboxone sublingual tablet, BDSI has conducted a dose proportionality/linearity study (BNX-106) across a 6-fold range of doses (b) (4) mg) and a relative bioavailability study between the 4.2/0.696 mg Bunavail dose and a 6.3/1.044 mg Bunavail dose in healthy subjects (BNX-107). Safety information in support of BEMA Buprenorphine NX is based on a single 12-week safety study and Suboxone sublingual tablet labeling.

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The Biopharmaceutics information in this submission includes a drug product development section with the proposed dissolution method and acceptance criteria, and a request of a biowaiver from conducting bioavailability/bioequivalent clinical trials using Bunavail film dosage strengths below the 4.2/0.696 mg buprenorphine/naloxone.

The proposed dissolution method is:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
I	100 rpm	500 mL	37°C	sodium phosphate buffer pH 4.5

The proposed acceptance criteria are:

Buprenorphine Acceptance Criterion
$Q = \frac{(b)}{(4)}\% \text{ at } 50 \text{ min}$

Naloxone Acceptance Criterion
$Q = \frac{(b)}{(4)}\% \text{ at } 40 \text{ min}$

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of 1) the proposed dissolution methodology, 2) the proposed acceptance criteria, and 4) data/information supporting a biowaiver from conducting bioavailability/bioequivalent clinical trials using Bunavail film dosage strengths below the 4.2/0.696 mg buprenorphine/naloxone.

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This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

[See appended electronic signature page](#)

Olen M. Stephens
CMC-Lead
Division III
Office of New Drug Quality Assessment

Art Shaw
CMC Reviewer
Division III
Office of New Drug Quality Assessment

John Metcalfe
Microbiology Reviewer

[See appended electronic signature page](#)

Kareen Riviere
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

[See appended electronic signature page](#)

Tapash Ghosh
Biopharmaceutics Team Leader or Designee
Office of New Drug Quality Assessment

[See appended electronic signature page](#)

Prasad Peri
Branch Chief
Division III
Office of New Drug Quality Assessment

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APPENDIX

Table 1 Specification for Buprenorphine Hydrochloride

Test	Acceptance Criteria	USP Monograph
Appearance	White or off-white crystalline powder, free from visible evidence of contamination	Not specified
Identity: A) IR (USP<197K>) B) Titration C) Chloride (USP<191>)	A) Consistent with reference standard B) A blue color appears C) Meets the requirements of the tests for chloride	A) Consistent with reference standard B) A blue color appears C) Meets the requirements of the tests for chloride
Identity by HPLC (CTM0496)	Matches retention time of reference standard	Not specified
	(b) (4)	Not specified
Residue on ignition (USP<281>)	NMT (b) (4)%	NMT (b) (4)%
pH (USP<791>)	4.0 to 6.0	4.0 to 6.0
Related substances (EP): ¹ PhEur Impurity (b) (4) PhEur Impurity PhEur Impurity PhEur Impurity PhEur Impurity PhEur Impurity Individual impurities Total impurities	NMT (b) (4) NMT NMT NMT NMT NMT NMT NMT	Not specified
Chromatographic purity (USP): Individual impurity Total impurities	NMT (b) (4) NMT	NMT (b) (4) NMT
Specific optical rotation (USP<781S>)	-92° to -98°	-92° to -98°
Water (USP<921> method I)	NMT (b) (4)%	NMT (b) (4)%
Assay (USP)	98.5% to 101.0%	98.5% to 101.0%
Particle Size (CTM0522)	D10 NMT (b) (4) μm D50 NMT μm D90 NMT μm	Not specified
Heavy Metals (USP<231>)	Color of test preparation solution is not darker than standard preparation solution; color of monitor preparation solution is equal to or darker than standard preparation solution	Not specified

¹ (b) (4)

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Table 1 Specification for Naloxone Hydrochloride Dihydrate

Test	Acceptance Criteria	USP Monograph
Appearance	White or almost white powder, free from visible foreign particulates	Not specified
Identity by IR, USP<197K>	Consistent with reference standard	Consistent with reference standard
Identity by HPLC (CTM0496)	Matches retention time of reference standard	Not specified
(b) (4)	(b) (4)%	NLT (b) (4)% and NMT (b) (4)%
Loss on Drying (hydrous form), USP<731>	11.0% max	NMT 11.0%
Specific Rotation, USP<781S>	-170° to -181°	Between -170° to -181°
Assay (dried basis), titration, USP	98.0% to 100.5%	98.0% to 100.5%
Related substances (TLC, USP): (b) (4) and other impurities	(b) (4)% max	NMT 1.0%
Related Substances (EP<2.2.29>): EP Impurity (b) (4) EP Impurity (b) (4) EP Impurity (b) (4) EP Impurity (b) (4) EP Impurity (b) (4) Unknown related substances Total related substances	(b) (4)% max (b) (4)% max (b) (4)% max (b) (4)% max (b) (4)% max (b) (4)% max (b) (4)% max	Not specified
Related Substances (EP<2.2.29>): EP Impurity (b) (4)	(b) (4)% max	Not specified
Related Substances (MS-HPLC, M-3765): (b) (4)	(b) (4)% max	Not specified
Water (EP<2.5.12>)	(b) (4)%	Not specified
Heavy Metals (USP<231>)	Color of test preparation solution is not darker than standard preparation solution; color of monitor preparation solution is equal to or darker than standard preparation solution	Not specified

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Table 2 Components and Composition of BEMA[®] Buprenorphine NX, Buccal Film

Component	Amount (% w/w) for all strengths		Function	Quality Standard
	Mucoadhesive	Backing		
Buprenorphine Hydrochloride	17.479	-	Active	USP
Purified Water	(b) (4)			USP
Propylene Glycol				USP
Sodium Benzoate				USP-NF
Methylparaben				USP-NF
Propylparaben				USP-NF
Ferric Oxide, Yellow				USP-NF
Citric Acid, (b) (4)				USP
Vitamin E Acetate				USP
Monobasic Sodium Phosphate, (b) (4)				USP
Polycarbophil				USP
Hydroxypropyl Cellulose				USP-NF
Hydroxyethyl Cellulose				USP-NF
Carboxymethylcellulose Sodium				USP
Sodium Hydroxide				USP-NF
Dibasic Sodium Phosphate, (b) (4)				USP
Saccharin Sodium	USP			
Citrus Blend Flavor	2			
Naloxone Hydrochloride	-	0.809	Active	USP
(b) (4) Blue Ink	(b) (4)			3
Total				100.00

² Certified as FDA/FEMA GRAS.

³ Classified by FDA as a color additive mixture, exempt from certification (21CFR 80.35(b) and 21CFR 73.1); all ingredients are GRAS or are specifically approved for use in FDA regulations.

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Table 1 Proposed Drug Product Specifications for BEMA[®] Buprenorphine NX

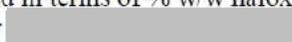
Test	Limit	Method
Appearance	Each unit is transparent, light yellow to yellow in color and rectangular with legible and clear ink marking: (b) (4) BN2 (2.1/0.348 mg film) BN4 (4.2/0.696 mg film), or BN6 (6.3/1.044 mg film)	Visual Inspection
Identification (Buprenorphine)	The retention time difference between the peak of interest in the sample and the buprenorphine standard is within (b) (4)%	HPLC, CTM0496 or PDR-ATM-BJV-0009
Identification (Naloxone)	The retention time difference between the peak of interest in the sample and the naloxone standard is within (b) (4)%	HPLC, CTM0496 or PDR-ATM-BJV-0009
Assay (Buprenorphine base)	(b) (4)% L.C.	HPLC, CTM0496 or PDR-ATM-BJV-0009
Assay (Naloxone base)	(b) (4)% L.C.	HPLC, CTM0496 or PDR-ATM-BJV-0009
Content Uniformity (Buprenorphine base)	Meets USP<905> requirements	HPLC, USP<905>, CTM0496 or PDR-ATM-BJV-0009
Content Uniformity (Naloxone base)	Meets USP<905> requirements	HPLC, USP<905>, CTM0496 or PDR-ATM-BJV-0009
Weight (b) (4) 2.1/0.348 mg film 4.2/0.696 mg film 6.3/1.044 mg film	(b) (4) (b) (4)mg (b) (4)mg (b) (4)mg	Gravimetric, CTM0496 or PDR-ATM-BJV-0009
Dissolution (Buprenorphine)	Q (b) (4)% at 50 min	USP<711>, CTM0497 or PDR-ATM-BJV-0015

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Test	Limit	Method
Dissolution (Naloxone)	Q (b)(4)% at 40 min	USP<711>, CTM0497 or PDR-ATM-BJV-0015
Related Substances: Norbuprenorphine  Total unspec. & naloxone related ⁴	NMT (b)(4)% w/w NMT (b)(4)% w/w or NMT (b)(4)% w/w ^{1,3} NMT (b)(4)% w/w ¹ NMT (b)(4)% w/w ² NMT (b)(4)% w/w ²	HPLC, TM0563 or PDR-ATM-BJV-0017
Moisture	(b)(4)% w/w	Karl Fischer CTM0494
Residual Solvents	Complies with USP<467>	USP<467>

¹ Expressed in terms of % w/w buprenorphine.

² Expressed in terms of % w/w naloxone.

³ Limit for  (b)(4) limit for 2.1/0.348, 4.2/0.696, and 6.3/1.044 mg films is (b)(4)%.

⁴ Total unspecified and naloxone related is defined as sum of naloxone related substances and all individual unspecified unknowns.

Table 2 Specification Limits for Specific Residual Solvents

Residual Solvent	Limit	Method
	(b)(4)	TM0593
		TM0589
		TM0590

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/s/

OLEN M STEPHENS

09/24/2013

From a CMC perspective, the NDA is recommended to be filed. Draft comments for the 74-day letter are included.

KAREEN RIVIERE

09/24/2013

TAPASH K GHOSH

09/24/2013

PRASAD PERI

09/24/2013

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

- 1. OMPQ Reviewer: Juandria Williams
- 2. NDA/BLA Number: 205637
Submission Date: 08/06/2013
21st C. Review Goal Date:
PDUFA Goal Date: 06/07/2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	BUNAVAIL™ (proposed)
Established or Non-Proprietary Name (USAN) and strength:	Buprenorphine and naloxone buccal film (b)(4) mg, 2.1/0.348 mg, 4.2/0.696 mg, and 6.3/1.044 mg
Dosage Form:	Film

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	BioDelivery Sciences International
Responsible Organization (OND Division):	DAAAP

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marketing Applications

II. Application Detail

1. INDICATION: For the maintenance treatment of opioid dependence
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: (b)(4) mg, 2.1/0.348 mg, 4.2/0.696 mg, and 6.3/1.044 mg
4. Rx/OTC DISPENSED: xRx OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		x		
2.	Breakthrough Therapy Designation		x		
3.	Orphan Drug Designation		x		
4.	Unapproved New Drug		x		
5.	Medically Necessary Determination		x		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		x		
7.	Rolling Submission		x		
8.	Drug/device combination product with consult		x		
9.	Complex manufacturing	x			Refer to Section IV
10.	Other (e.g., expedited for an unlisted reason)		x		

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marketing Applications

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	x		DS: Section 3.2.S.2.1 in eCTD DP: Section 3.2.P.2.1 in eCTD
12.	Do all sites indicate they are ready to be inspected (on 356h)?	x		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	x		DS: Section 3.2.S.2.1 in eCTD DP: Section 3.2.P.2.1 in eCTD
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	x		DS: Section 3.2.S.2.1 in eCTD DP: Section 3.2.P.2.1 in eCTD
15.	Additional notes (non-filing issue)	x		
	1. Are all sites registered or have FEI #?			
	2. Do comments in EES indicate a request to participate on inspection(s)?		x	As of this IMA draft, no requests have been made.
	3. Is this first application by the applicant?	x		

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marketing Applications

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		x	

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?		x	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion?	x		
	Have all EERs been updated with final PAI recommendation?	x		
19.	<p>From a CGMP/facilities perspective, is the application fileable?</p> <p>If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.</p>	x		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements? No			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		x	See process description below

There are, in effect, two drug substances: buprenorphine hydrochloride and naloxone hydrochloride dehydrate. The buprenorphine acts as the therapeutic active while the naloxone minimizes systemic exposure while maintaining the abuse-deterrent characteristics associated with coextraction.

Buprenorphine Hydrochloride Manufacturing Summary



(b) (4)

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marketing Applications

(b) (4)

Naloxone Hydrochloride Manufacturing Summary

(b) (4)

8. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?	x		See description below

BEMA Buprenorphine NX is an oral transmucosal form of buprenorphine hydrochloride and naloxone hydrochloride dehydrate (6:1 ratio of free bases) intended for application to the buccal mucosa. This drug product (a film) uses the BioErodible MucoAdhesive (BEMA) delivery technology. The film consists of two layers, a backing side that contains naloxone hydrochloride dihydrate and a mucoadhesive side that contains the drug substance, buprenorphine hydrochloride.

(b) (4)

(b) (4)

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V. Overall Conclusions and Recommendations

Is the application fileable? Yes
Based on Section IV, is a KTM warranted for any PAI? Yes. If yes, please identify the sites in the above chart. <ul style="list-style-type: none">• Adhesives Research Inc.• Sharp Corporation
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? No
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL (DARRTS)

V. Dholakia (Acting BC for DGMPA/NDMAB) – 9/11/2013

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/s/

JUANDRIA WILLIAMS
09/12/2013

VIPULCHANDRA N DHOLAKIA
09/12/2013