

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205637Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205637 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Bunavail Established/Proper Name: buprenorphine and naloxone Dosage Form: buccal film		Applicant: BioDelivery Sciences International Agent for Applicant (if applicable):
RPM: Matthew Sullivan		Division: Anesthesia, Analgesia, and Addiction Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 6/12/2014</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>6/7/2014</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 3- New Dosage Form
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) AP 6/6/2014
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> Review(s) <i>(indicate date(s))</i> 	1/23/2014 1/14/2014
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> None DMEPA: <input type="checkbox"/> None 6/5/2014 (2), 5/23/2014, 3/10/2014 DMPP/PLT (DRISK): <input type="checkbox"/> None 5/23/2014 OPDP: <input type="checkbox"/> None 5/23/2014 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 4/29/2014
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>1/8/2014</u> If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	Various dates
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 5/2/2013 <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A 2/7/2012, 1/18/2011
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/6/2014
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/15/2014
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 1 (6/5/2014)
Clinical	
❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review 5/1/2014, 10/2/2013 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	5/1/2014
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> N/A 5/13/2014

❖ Risk Management	
<ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<p>6/5/2014</p> <p>6/5/2014</p> <p><input type="checkbox"/> None 6/5/2014</p>
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/5/2014, 4/28/2014, 9/26/2014
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested 4/29/2014
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) Supervisory Review(s) (<i>indicate date for each review</i>) Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<p><input checked="" type="checkbox"/> No separate review</p> <p><input checked="" type="checkbox"/> No separate review</p> <p><input type="checkbox"/> None 5/1/2014, 9/17/2014</p>
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 5/6/2014 (2), 9/24/2014
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 4/14/2014, 9/18/2014
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None 4/11/2014
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	5/6/2014
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 2/25/2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW W SULLIVAN
06/13/2014

EXCLUSIVITY SUMMARY

NDA # 205637

SUPPL # 0000

HFD # 170

Trade Name Bunavail

Generic Name buprenorphine and naloxone

Applicant Name BioDelivery Sciences International

Approval Date, If Known June 6, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 022410	Suboxone SL film
NDA# 020733	Suboxone SL tablets
NDA# 204242	Zubsolv SL tablets

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study BNX-201

An open label study to assess the safety and tolerability of BEMA Buprenorphine NX in opioid dependent subjects

Objectives:

- To assess the safety and tolerability of BEMA Buprenorphine NX administered once daily for 12 weeks to opioid-dependent subjects stabilized on Suboxone tablets or films

Design:

- Open-label study in subjects that had been maintained on 8-32 mg Suboxone tablets or film for at least 30 days
- Subjects were to be evaluated and excluded for abnormalities of the buccal mucosa that could affect drug absorption

Study LCR-04-01

A Double-Blind, Placebo-Controlled, Four-Treatment, Four-Period Crossover Study To Determine The Lowest Dose Of Naloxone That Will Produce A Withdrawal Response When Administered With Buprenorphine In Opioid Dependent Subjects

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study BNX-201

An open label study to assess the safety and tolerability of BEMA Buprenorphine NX in opioid dependent subjects

Study LCR-04-01

A Double-Blind, Placebo-Controlled, Four-Treatment, Four-Period Crossover Study To Determine The Lowest Dose Of Naloxone That Will Produce A Withdrawal Response When Administered With Buprenorphine In Opioid Dependent Subjects

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor

in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 110267 YES ! NO
! Explain:
(for Study BNX-201)

Investigation #2 !
!
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ! NO
Explain: ! Explain:
Study LCR-04-01 was not carried out under an IND, but the NDA Sponsor (BDSI) states that it provided study funding, reviewed the study protocol, performed study monitoring, and contracted for additional services with 
 (b) (4)

Investigation #2 !
!
YES ! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Matt Sullivan
Title: Supervisory Regulatory Health Project Manager
Date:

Name of Office/Division Director signing form: Rigoberto Roca, MD
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12;

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/s/

MATTHEW W SULLIVAN
06/06/2014

RIGOBERTO A ROCA
06/06/2014

From: [Sullivan, Matthew](#)
To: "Adrian Hepner"
Cc: [Renee Boerner](#); [Andrew Finn](#)
Subject: RE: NDA 205637
Date: Friday, May 23, 2014 3:00:44 PM
Attachments: [Bunavail.PI.doc](#)
[BUNAVAIL_NDA_205636_MG.docx](#)
[image001.png](#)

Hi –

Attached are the current drafts for the PI and MG.

They have not been reviewed by management, and therefore there may be additional changes that are necessary.

Please “accept” and changes you agree with. Any revisions that you’d like to make please do in tracked changes as well. Additionally, if you wish to provide brief supportive comments on some item, feel free to do so via Word comments. If, however, your comments are more than a few sentences, please put those in a separate document.

I think we have a comment to this effect in the document, but please try to ensure that the numbering, margins, bolding, etc, are all correct when you send this back to us.

I realize that Monday is a holiday, but we would greatly appreciate getting the documents back by Wednesday of next week.

Thanks, and please let me know if you have any questions.

Matt

From: Adrian Hepner [mailto:AHepner@bdsi.com]
Sent: Friday, May 23, 2014 11:12 AM
To: Sullivan, Matthew
Cc: Renee Boerner; Andrew Finn
Subject: NDA 205637
Importance: High

Dear Matt,

Following-up our recent call, we would like to confirm that the Agency will be providing revised REMS and labeling material for the above referenced NDA by close of business today. As discussed, BDSI is planning to allocate all necessary resources to respond in a timely manner, right after Memorial Day.

Thank you in advance for your feedback.

Kind regards,

Adrian

Adrian Hepner, MD, PhD

Vice President, Clinical Research & Regulatory Affairs



BioDelivery Sciences International, Inc.

801 Corporate Center Drive, Suite 210

Raleigh, NC 27607

+1 (919) 582-0298 | Phone

+1 (919) 582-9051 | Fax

AHepner@bdsi.com

www.bdsi.com

(NASDAQ:BDSI)

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/s/

MATTHEW W SULLIVAN
05/23/2014

From: Sullivan, Matthew
To: [Renee Boerner \(RBoerner@bdsi.com\)](mailto:RBoerner@bdsi.com)
Cc: [Andrew Finn \(AFinn@bdsi.com\)](mailto:AFinn@bdsi.com); [Adrian Hepner \(AHepner@bdsi.com\)](mailto:AHepner@bdsi.com)
Subject: NDA 205637/ PMR for QT prolongation
Date: Friday, May 16, 2014 5:08:00 PM

Hi Renee –

We have identified the need for a postmarketing study for NDA 205637:

> A clinical trial to assess the risk of QT prolongation with Bunavail buccal film. This study should not be designed utilizing (b) (4) in any arm.

We request that you submit a brief protocol summary and schedule milestone dates with justification for our review.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Supervisory Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

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/s/

MATTHEW W SULLIVAN
05/16/2014



NDA 205637

DISCIPLINE REVIEW LETTER

Biodelivery Sciences International
Suite 210
801 Corporate Center Dr
Raleigh, NC 27607

Attention: Renee Boerner, PhD
Senior Director, Regulatory Affairs

Dear Dr. Boerner:

Please refer to your New Drug Application (NDA) dated August 6, 2013, received August 7, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for BEMA buprenorphine NX (buprenorphine and naloxone) buccal (b)(4) film.

We also refer to your amendments dated December 18, 2013, and January 30, February 24 and 26, and March 17, 2014.

Our review of the Biopharmaceutics section of your submission is complete, and we have identified the following deficiency:

You have not provided adequate data to support a biowaiver for the (b)(4) mg buprenorphine/naloxone strength (b)(4)

We are providing these comments to you before completing our review of your entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan, MS
Supervisory Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MATTHEW W SULLIVAN
05/09/2014

From: Sullivan, Matthew
To: "Renee Boerner"
Cc: Adrian Hepner; Andrew Finn
Subject: NDA 205637 - carton and container labeling comments
Date: Friday, April 11, 2014 11:30:00 AM

Hi Renee –

Please address these carton and container labeling comments.

Thanks

Matt

Foil package Labels

1. Remove the (b) (4) number strength presentation ((b) (4)) since it is not considered an accurate representation of the actual strength. We recommend using a single statement of strength that reflects both active ingredient strengths accurately at least to the second decimal place (the hundredth) similar to the following:

(b) (4)

Additionally, increase the font size of the statement of strength for increased prominence.

2. Increase the font size of the established name to ensure that the established name is half the size of the proprietary name as required per 21 CFR 201.10(g)(2).
3. Revise the statement “ (b) (4) ” to read “Use entire film. Do not cut, tear, chew, or swallow film”. Relocate this statement from the back panel to the principal display panel for increased prominence of this important information. To accommodate this, consider moving the statements “Keep out of reach...medical care.” and the URL address (www.Bunavail.com) to the back panel.

Carton Labeling

4. See recommendation 1 and 2 above.
5. Add the statement “Use entire film. Do not cut, tear, chew, or swallow film” to the principal display and back panels.

APPEARS THIS WAY ON ORIGINAL

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/s/

MATTHEW W SULLIVAN
04/11/2014



NDA 205637

INFORMATION REQUEST

BioDelivery Sciences International
Attention: Renee Boerner, PhD
Senior Director, Regulatory Affairs
801 Corporate Center Drive, Suite 210
Raleigh, North Carolina 27607

Dear Dr. Boerner:

Please refer to your August 6, 2013, New Drug Application (NDA) submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Bunavail (buprenorphine and naloxone) buccal film, (b) (4) 2.1/ 0.35, 4.2/ 0.7, 4.3/ 1.04 mg buprenorphine/naloxone.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following information request. We request a response by **Tuesday, April 18, 2014**, in order to continue our evaluation of your NDA.

- A. Regarding Method M3765 for testing (b) (4) in the naloxone drug substance:
1. Explain why the acceptance criterion in the (b) (4) for the % difference between L4 bracketing standards and L4 linearity standards is (b) (4) when the result of the determination of precision in the Methods Validation Report yields a Relative Standard Deviation (RSD) of (b) (4), indicating that (b) (4).
 2. Provide the source and specifications for the (b) (4) reference standard.
 3. You are advised that an information Request Letter was sent to the holder of DMF (b) (4) on February 18, 2014.
- B. Regarding the drug product
1. Regarding the Pharmaceutical Development
 - a. Provide data to support the choice of the (b) (4) and their levels in the drug product.
 - b. Provide the pHs of the different formulations used in the formulation development.
 - c. Explain why the statement is made in the Pharmaceutical Development Report (PDR, Page 85) that (b) (4).
 - d. Explain how the (b) (4) was obtained as well as the samples under “(b) (4)” (PDR, Page (b) (4)).

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

(b) (4)



4. Regarding the Excipients

- a. Provide the specifications for receipt of all of the excipients which should include, at a minimum, an identity test and a copy of a Certificate of Analysis (COA) from the supplier.
 - b. Provide sample COAs for all of the excipients.
 - c. The specifications for the ink should include a test for color.
5. Regarding Control of the Drug Product
- a. Regarding the Specifications. We recommend amending the acceptance criteria as follows, based on the Batch Analysis
 - 1) Buprenorphine and naloxone assay: (b) (4) %.
 - 2) Weight Variation in the content Uniformity: (b) (4) % of the target weight.
 - 3) (b) (4)
 - b. Regarding the Analytical Procedures
 - 1) Include a standard color comparator in the test for Appearance.
 - 2) Provide the data to support the assignment of a value of (b) (4) for the Relative Response Factors in Method TM0563.
 - 3) Provide chromatograms showing the identification of the peaks corresponding to identified impurities.
 - c. Regarding the Methods Validation
 - 1) Provide data to show that the HPLC method for Assay and Content Uniformity is linear up to the value of (b) (4) buprenorphine/mL, which is the expected concentration for the 6.3 mg strength films.
 - 2) Provide the components and composition for Placebos A and B used in the validation for Method CTM0496.
 - 3) Provide an evaluation for the robustness of the HPLC Methods CTM0496 and TM0563.
 - 4) Provide a chromatogram showing the results of the injection of related substances at (b) (4) % in the validation of method TM0563.
 - d. Regarding the Batch Analysis
 - 1) Provide the results for the individual measurements of the films used to assess the weight variability in the batch analysis of the Content Uniformity.
 - 2) Explain the difference between “NR” (not reportable) and “ND” (not detected) in the batch analysis reports.
6. Regarding the Reference Standards: Provide the sources, qualification procedures, and specifications for the working standards for buprenorphine hydrochloride, buprenorphine base, and naloxone hydrochloride.
7. Regarding the Stability: You are advised that, since the accelerated and intermediate stability data for the unidentified impurity at (b) (4) show a significant increase, the stability data cannot be extrapolated beyond the twelve months data provided in the application.

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
04/08/2014



NDA 205637

**METHODS VALIDATION
MATERIALS RECEIVED**

Biodelivery Systems Incorporated
Attention: Andrew Finn, Pharm. D.; Adrian Hepner MD, Ph.D.
801 Corporate Center Drive
Suite 220
Raleigh, NC 27607

Dear Andrew Finn:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bunavail (buprenorphine/naloxone) Buccal Film and to our February 7, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on March 7, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
03/10/2014

From: Sullivan, Matthew
To: ["Renee Boerner"](#)
Cc: [Adrian Hepner](#); [Andrew Finn](#)
Subject: RE: NDA 205637 0022
Date: Friday, February 28, 2014 11:44:00 AM

Hi Renee –

Please address this item for us:

Provide the exact location in the revised manufacturing procedure that incorporates the changes in the (b) (4) to yield potency between (b) (4) which was specified in the amendment submitted on February 27, 2014, Section 3.2.P.8.1.

From: Renee Boerner [mailto:RBoerner@bdsi.com]
Sent: Thursday, February 27, 2014 2:55 PM
To: Sullivan, Matthew
Cc: Adrian Hepner; Andrew Finn
Subject: NDA 205637 0022

Dear Matt,

Today on behalf of BDSI, (b) (4) submitted sequence 0022 to NDA 205637 for review via the Electronic Submission Gateway. Sequence 0022 includes the 12 month stability data. Attached please find the cover letter for your reference.

Kind Regards,
Renee

Renee Boerner, PhD
Senior Director, Regulatory Affairs
BioDelivery Sciences International, Inc.
801 Corporate Center Drive, Suite 210
Raleigh, North Carolina 27607 USA
Phone (919) 582-0295

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/s/

MATTHEW W SULLIVAN
02/28/2014

Rivera, Luz E (CDER)

From: Rivera, Luz E (CDER)
Sent: Monday, February 10, 2014 5:28 AM
To: rboerner@bdsi.com
Subject: NDA 205637

Good morning Dr. Boerner,

We are reviewing your NDA 205637 and request additional information to continue our evaluation.

- Submit a revised test procedure to include the requirement to compare the sample response to the (b) (4) limits standard.

Please submit the information requested by email to me (Luz.E.Rivera@fda.hhs.gov) and officially submit to the application.

Please acknowledge the receipt of this request

Thank you,
Luz E Rivera, Psy.D.
LCDR, US Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ ONDQA
Division of New Drug Quality Assessment III
luz.e.rivera@fda.hhs.gov
301 796 4013

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/s/

LUZ E RIVERA
02/10/2014



NDA 205637

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Biodelivery Systems Incorporated
Attention: Andrew Finn
801 Corporate Center Drive
Suite 220
Raleigh, NC 27607
FAX: (919) 582-9051

Dear Andrew Finn:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bunavail (buprenorphine/naloxone) Buccal Film.

We will be performing methods validation studies on Bunavail (buprenorphine/naloxone) Buccal Film, as described in NDA 205637.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

M-3765 Determination of [REDACTED] (b) (4) in drug substance and drug product by LC-MS

Samples and Reference Standards

20 samples of Bunavail (buprenorphine/naloxone) Buccal Film
5 samples of placebo film
200 mg Naloxone HCl drug substance
2 * 125 mg USP Naloxone reference standard
200 mg [REDACTED] (b) (4) reference standard

Equipment

[REDACTED] (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
02/07/2014

**PeRC PREA Subcommittee Meeting Minutes
January 8, 2014**

PeRC Members Attending:

Lynne Yao
Rosemary Addy
Hari Cheryl Sachs
Wiley Chambers
Tom Smith
Karen Davis-Bruno
Peter Starke
Gregory Reaman
Daiva Shetty
Julia Pinto
Lily Mulugeta
Maura O'Leary
Rachel Witten
Dianne Murphy
Jane Inglese

Agenda

PREA

BLA	(b) (4) 125476	Entyvio (vedolizumab) Partial Waiver/Deferral/Plan	Crohn's disease and ulcerative colitis
NDA	(b) (4)	(b) (4)	(b) (4)
NDA	9190/S-024	Lipiodol (ethiodized oil) Full Waiver	Selective intra-arterial use for computed tomography (CT) of the liver to visualize and localize lesions in adults with known hepatocellular carcinoma (HCC)
NDA	205637	Bunavail (buprenorphine/naloxone) Full Waiver	Maintenance treatment of opioid dependence

Entyvio (vedolizumab) Partial Waiver/Deferral/Plan



(b) (4)

- BLA 125476 seeks marketing approval for Entyvio (vedolizumab) for the treatment of ulcerative colitis.
- The application has a PDUFA goal date of May 20, 2014.
- The application triggers PREA as directed to a new active ingredient.
- *PeRC Recommendations:*
 - The PeRC agreed with the Division on a partial waiver in pediatric patients aged birth to less than 5 years because studies would be impossible or highly impractical.
 - The Division should ask the sponsor to incorporate this grounds for a partial waiver into the iPSP.
 - The PeRC agreed with the Division on a deferral in pediatric patients aged 6 to less than 17 years because adult studies have been completed and the product is ready for approval.



(b) (4)

Lipiodol (ethiodized oil) Full Waiver

- NDA 9190/S-024 seeks marketing approval for Lipiodol (ethiodized oil) for selective intra-arterial use for computed tomography (CT) of the liver to visualize and localize lesions in adults with known hepatocellular carcinoma (HCC).
- The application has a PDUFA goal date of April 4, 2014.
- The application triggers PREA as directed to a new indication.
- *PeRC Recommendations:*
 - The PeRC agreed with a full waiver because studies would be impossible or highly impractical.

Bunavail (buprenorphine/naloxone) Full Waiver

- NDA 205637 seeks marketing approval for Bunavail (buprenorphine/naloxone) for maintenance treatment of opioid dependence.
- The application has a PDUFA goal date of June 17, 2014.
- The application triggers PREA as directed to a new dosage form.
- *PeRC Recommendations:*
 - The PeRC agreed with a waiver in pediatric patients aged 5 weeks to 16 years because studies would be impossible or highly impractical. The PeRC agreed with the Division's review of the incidence of chronic opioid dependence in the adolescent population as presented. There appears to be a decreasing incidence of opioid dependence in the adolescent population, making studies impossible or highly impracticable.
 - The PeRC agreed with a waiver in pediatric patients aged less than 5 weeks because the product would be unsafe in this age group. The safety issue in this age group should be incorporated into labeling.

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/s/

JANE E INGLESE
01/24/2014



NDA 205637

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

BioDelivery Sciences International
801 Corporate Center Drive
Suite 210
Raleigh, NC 27607

ATTENTION: Adrian Hepner, MD, PhD
Vice President, Clinical Research and Regulatory Affairs

Dear Dr. Hepner:

Please refer to your New Drug Application (NDA) dated August 6, 2013, received August 7, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Buprenorphine and Naloxone Buccal Film, (b)(4) 2.1 mg/0.348 mg, 4.2 mg/0.696 mg, and 6.3 mg/1.044 mg.

We also refer to your correspondence, dated and received October 25, 2013, requesting review of your proposed proprietary name, Bunavail. We have completed our review of the proposed proprietary name, Bunavail and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your October 25, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Lisa Skarupa, Senior Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2219. For any other information regarding this application, contact Matthew Sullivan, Senior Regulatory Project Manager, in the Office of New Drugs at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
01/23/2014

From: Sullivan, Matthew
To: [Renee Boerner \(RBoerner@bdsi.com\)](mailto:RBoerner@bdsi.com)
Cc: [Andrew Finn](#); [Adrian Hepner](#)
Subject: NDA 205637
Date: Thursday, December 05, 2013 5:20:00 PM

Renee –

Can you address these items for us please?

1. Provide the controls to ensure that the mucoadhesive layer will consistently adhere to wet buccal mucosa. These controls can include manufacturing controls e.g. [REDACTED] (b) (4) [REDACTED] /or testing for mucoadhesion of the finished products.
2. Provide data to demonstrate that the buprenorphine cannot be separated from the naloxone by either physical means e.g. peeling the buprenorphine layer from the naloxone layer or by means of differential extraction. We note the following:
 - a. The data in the first two figures on Page 82 of the Pharmaceutical Development Report show that naloxone can be extracted in [REDACTED] (b) (4) while buprenorphine is not extracted.
 - b. The dissolution profiles on Page 75 of the Pharmaceutical Development Report show that naloxone dissolves between [REDACTED] (b) (4) [REDACTED]
[REDACTED]
[REDACTED]

Would it be possible that extraction could be accomplished by dipping the film into a basic solution to remove the naloxone, yielding a buprenorphine-only film, or would the film dissolve?

Thanks,
Matt

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

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/s/

MATTHEW W SULLIVAN
12/05/2013



NDA 205637

INFORMATION REQUEST

BioDelivery Sciences International
Attention: Renee Boerner, PhD
Senior Director, Regulatory Affairs
801 Corporate Center Drive, Suite 210
Raleigh, North Carolina 27607

Dear Dr. Boerner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bunavail (buprenorphine and naloxone) buccal film, (b)(4) 2.1/ 0.35, 4.2/ 0.7, 4.3/ 1.04 mg bup/nal.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

-  (b)(4)

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
12/02/2013

From: Sullivan, Matthew
To: [Renee Boerner \(RBoerner@bdsi.com\)](mailto:RBoerner@bdsi.com)
Subject: N205637
Date: Wednesday, November 27, 2013 12:30:00 PM

Renee –

Can you point us to this Final Study Report file (if it's in the NDA), or if it's not, please submit it as soon as you can?

On page 81 of the Pharmaceutical Develop document is the following statement "All data is summarized in the final Study Report "In Vitro Extraction Study of BEMA Buprenorphine-Naloxone (BNX) Buccal (b) (4) Films" and a summary of key results are provided herein."

Thanks,
Matt

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

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/s/

MATTHEW W SULLIVAN
11/27/2013



NDA 205637

**FILING COMMUNICATION -
NO FILING REVIEW ISSUES IDENTIFIED**

Biodelivery Sciences International
Suite 210
801 Corporate Center Dr
Raleigh, NC 27607

Attention: Renee Boerner, PhD
Senior Director, Regulatory Affairs

Dear Dr. Boerner:

Please refer to your New Drug Application (NDA) dated August 6, 2013, received August 7, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for BEMA buprenorphine NX (buprenorphine and naloxone) buccal (b)(4) film.

We also refer to your amendments dated August 22, and September 3, 23, and 24, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 7, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by May 11, 2014.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We do, however, request that you submit the following information:

1. As per 314.54(a)(1)(i), you must provide a master batch record or a proposed master batch record. We note that you have provided executed batch records in your application. Submit a master batch record, or a 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.
3. Include the (b) (4) in Section 3.2.P.1 (Components and Composition), with the note that they are removed during processing. Also include specifications for the (b) (4) in Section 3.2.P.4.
4. In Section 3.2.P.3.3 (Description of the Manufacturing Process and Process Controls), specify when and how the (b) (4) is removed in the manufacturing process.
5. 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.
6. 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.
7. Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
 - 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.
 - 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., ± 10-20% 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.
8. In support of your request for a partial waiver of pediatric studies in children ages (b) (4) through (b) (4), submit an assessment of the pediatric use of pharmacotherapy for opioid dependence for this age group. This should include a report of pediatric use data for

currently marketed buprenorphine/naloxone products, which could include prevalence data, literature review, expert interviews, and review of insurance databases. Additionally, include an assessment of the prevalence of opioid dependence in this age group, including all illicit and prescription opioids, and the proportion of these cases that are treatment-seeking.

9. It may be possible to receive a partial waiver for ages (b) (4) 16, as well, if you provide information that demonstrates that the necessary studies are impossible or highly impracticable due to the low prevalence of patients seeking agonist treatment for opioid dependence in this population. If you think that it would support a waiver for ages (b) (4) 16, you may submit an assessment, as outlined above, for ages 12 through 16 inclusive, rather than only for ages (b) (4) through (b) (4).

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Highlights

1. White space must be present before each major heading in highlights section.
2. Remove the "(b) (4)" section.
3. Insert "2002" as the year of initial U.S. approval.
4. Realign text to minimize white space under *Dosage Forms and Strengths*.
5. For drug products other than vaccines, the verbatim **bolded** statement must be present: **"To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch"**.
6. The Patient Counseling Information Statement must include the following bolded verbatim statement:
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Full Prescribing Information

7. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [see Warnings and Precautions (5.2)]. Remove italics from leading and trailing bracket (i.e., [] instead of [/]).

We request that you resubmit labeling that addresses these issues within two weeks of the date of this letter. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver and a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the request is denied.

If you have any questions, call Matt Sullivan, Senior Regulatory Project Manager, at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BOB A RAPPAPORT
10/16/2013

From: Sullivan, Matthew
To: [Renee Boerner \(RBoerner@bdsi.com\)](mailto:RBoerner@bdsi.com)
Subject: 205637 Information Request
Date: Thursday, September 12, 2013 11:30:00 AM

Hi Renee –

Can you address this for us please?

1. We are not able to find datasets of PK raw data and PK parameters for your PK studies. For Studies BNX-106, -107 and -110, provide the datasets with all PK raw data for your calculation of PK parameters and the final dataset of PK parameters that you used for your statistical analysis.
2. All the datasets should be ready for analysis using WinNonlin.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

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/s/

MATTHEW W SULLIVAN
09/12/2013



NDA 205637

NDA ACKNOWLEDGMENT

Biodelivery Sciences International
Suite 210
801 Corporate Center Dr
Raleigh, NC 27607

Attention: Renee Boerner, PhD
Senior Director, Regulatory Affairs

Dear Dr. Boerner:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: BEMA buprenorphine NX (buprenorphine and naloxone)
buccal (b) (4) film

Date of Application: August 6, 2013

Date of Receipt: August 7, 2013

Our Reference Number: NDA 205637

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 6, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as

ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 205637** submitted on August 6, 2013, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia,
and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan, MS
Chief, Project Management Staff (Acting)
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MATTHEW W SULLIVAN
08/16/2013

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, June 26, 2013 4:31 PM
To: 'Renee Boerner'
Cc: Andrew Finn (AFinn@bdsi.com)
Subject: RE: NDA questions
Attachments: Meeting Minutes (COR-MEET-03) page 31.pdf

Hi Renee –

Sorry for not closing the loop on this with you. We did update our records with this modification, but our archival systems make it difficult to actually reissue new minutes with the correction.

Nonetheless, please include this replacement page 31 in your copy of the meeting minutes.

Thanks,
Matt

From: Renee Boerner [<mailto:RBoerner@bdsi.com>]
Sent: Wednesday, June 26, 2013 3:44 PM
To: Sullivan, Matthew
Cc: Andrew Finn
Subject: RE: NDA questions

Dear Matt,

I am following up on the preNDA meeting minutes for IND 110267. Will we be getting a copy of the revised minutes? The minutes that were forwarded to us in hard copy did not include the modification noted below.

Thank you for your attention.

Kind Regards,
Renee

Renee Boerner, PhD
Senior Director, Regulatory Affairs
BioDelivery Sciences International, Inc.
801 Corporate Center Drive, Suite 210
Raleigh, North Carolina 27607 USA
Phone (919) 582-0295

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From: Sullivan, Matthew [<mailto:Matthew.Sullivan@fda.hhs.gov>]
Sent: Thursday, June 06, 2013 5:00 PM
To: Renee Boerner
Cc: Andrew Finn
Subject: RE: NDA questions

Renee –

If we were to modify the paragraph on page 31 of the minutes to the following, would it address all of your questions?

The Sponsor stated that they used the same formulation in multiple (b) (4) PK studies, and that they studied up to (b) (4) 6.3 mg. (b) (4)

- The Sponsor stated that they have clinical data supporting doses from 2 mg to 32 mg of buprenorphine.

From: Sullivan, Matthew
Sent: Wednesday, June 05, 2013 2:55 PM
To: 'Renee Boerner'
Cc: Andrew Finn
Subject: RE: NDA questions

Renee –

Attached are the minutes from our recent meeting.

With respect to your two questions, we concur with your proposed approach to each.

matt

From: Renee Boerner [<mailto:RBoerner@bdsi.com>]
Sent: Monday, June 03, 2013 8:42 AM
To: Sullivan, Matthew
Cc: Andrew Finn
Subject: NDA questions

Dear Matt,

I have two questions regarding the datafiles which we plan on submitting as part of our upcoming NDA 205637. Our goal is to finish compiling the datafiles for the submission within the next two weeks, so we would appreciate anything you can do to expedite a response on these questions.

- 1) In the additional comments provided as part of the FDA Preliminary comments to our PreNDA meeting held on 02May2013 (reference ID: 3300658), a request was made for site level datasets as part of an OSI piloted risk based model for site selection (page 32). However, because BDSI did not conduct any efficacy studies, we do not believe this request is applicable to our application. Could you please provide feedback on whether the FDA agrees with this assessment?
- 2) Please refer to the attached the data definition file for our BNX-101 clinical study raw dataset. Since CRFs are electronic documents and easily searchable and each data field is listed within associated dataset, the page number of the CRF is not listed in the origin information in the define.pdf file. Is this an acceptable approach?

I am also following up again to try to get the contact name in the General Counsels office and to inquire as to when the formal preNDA meeting minutes will be available.

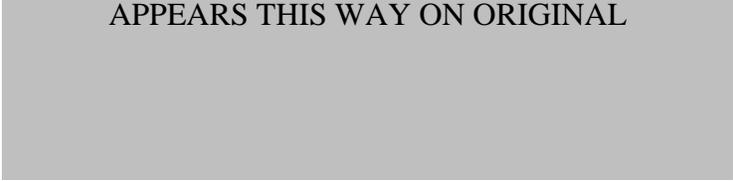
Thank you for your assistance.

Kind Regards,
Renee

Renee Boerner, PhD
Senior Director, Regulatory Affairs
BioDelivery Sciences International, Inc.
801 Corporate Center Drive, Suite 210
Raleigh, North Carolina 27607 USA
Phone (919) 582-0295

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APPEARS THIS WAY ON ORIGINAL



(b) (4)	
	<i>2.1/0.348</i>
<i>8/2</i>	<i>4.2/0.696</i>
	<i>6.3/1.044</i>

Discussion:

The Sponsor stated that they used the same formulation in multiple PK studies, and that they studied up to 6.3 mg. The Sponsor stated that they have clinical data supporting doses from 2 mg to 32 mg of buprenorphine.

The Division also reminded the Sponsor that they will need to submit a biowaiver request in their NDA submission, and inquired if the Sponsor had data supporting conversion between doses other than those which had bioequivalence with Suboxone tablets. The Sponsor stated that they would submit a justification demonstrating that systemic exposures will not be different when switching from Suboxone to their product.

Action Items:

1. The Sponsor will consider additional options for their proprietary name. New proprietary names will be submitted for review.
2. The Sponsor will submit a biowaiver request for their two lower strengths with the NDA submission.

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/s/

MATTHEW W SULLIVAN
06/27/2013



IND 110267

MEETING MINUTES

BioDelivery Sciences International, Inc.
801 Corporate Center Dr, Suite 210
Raleigh, NC 27607

Attention: Renee Boerner, PhD
Director, Regulatory Affairs

Dear Dr. Boerner:

Please refer to your Investigational New Drug Application (IND) submitted March 18, 2011, received March 18, 2011, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BEMA Buprenorphine NX (buprenorphine and naloxone buccal (b) (4) film).

We also refer to the meeting between representatives of your firm and the FDA on May 2, 2013. The purpose of the meeting was to discuss your upcoming NDA submission for BEMA Buprenorphine NX.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan, MS
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Meeting Minutes
BDSI Carton Mock-ups

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: May 2, 2013, 1:30pm
Meeting Location: White Oak 22, Room 1311

Application Number: IND 110267
Product Name: BEMA buprenorphine NX
Indication: Treatment of opioid dependence
Sponsor/Applicant Name: BioDelivery Sciences International, Inc.

Meeting Chair: Ellen Fields, MD, MPH, Clinical Team Leader, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Minutes Recorder: Matthew Sullivan, MS, Senior Regulatory Project Manager, DAAAP

FDA Attendees	Title
Bob A. Rappaport, MD	Director, DAAAP
Rigoberto Roca, MD	Deputy Director, DAAAP
Celia Winchell, MD	Clinical Team Leader, DAAAP
Ellen Fields, MD, MPH	Clinical Team Leader, DAAAP
Elizabeth Kilgore, MD	Medical Officer, DAAAP
Olen Stephens, PhD	CMC Lead, Office of New Drug Quality Assessment (ONDQA)
Xiaobin Shen, PhD	CMC Reviewer, ONDQA
Adam Wasserman, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Gary Bond, PhD	Pharmacology/Toxicology Reviewer, DAAAP
Yun Xu, PhD	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCP II)
Janice Derr, PhD	Statistical Team Leader, Division of Biometrics II (DB II)
Yan Zhou, PhD	Statistical Reviewer, DB II
Matthew Sullivan, MS	Senior Regulatory Project Manager, DAAAP
James Tolliver, PhD	Controlled Substance Staff
JP Gong, MD	Medical Officer, CSS
Jason Bunting, PharmD	Risk Management Analyst, Office of Surveillance and Epidemiology, Division of Risk Management (OSE/DRISK)
Reema Mehta, PharmD	Risk Management Team Leader, OSE/DRISK
Jamie Wilkins Parker, PharmD	Team Leader, Office of Surveillance and Epidemiology, Division of Medication Error and Prevention (OSE/DMEPA)
Vicky Borders-Hemphill	Safety Evaluator, OSE/DMEPA
Doug Warfield	CDER eData team

Sponsor Attendees	Title
Renee Boerner, PhD	Senior Director, Regulatory Affairs
Niraj Vasisht, PhD	Senior Vice President, Product Development
Andrew Finn, PharmD	Executive Vice President, Product Development
Mark Sirgo, PharmD	President and Chief Executive Officer
(b) (4)	BDSI Pharmacokinetic Consultant
	BDSI Opioid Dependence Consultant
	BDSI Toxicology Consultant
	BDSI Clinical Consultant
	Contract Legal Counsel for BDSI

BACKGROUND

BioDelivery Sciences International, Inc. (BDSI), requested a Pre-NDA meeting on February 5, 2013, which the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) granted on February 15, 2013. A meeting package in support of the meeting was submitted on March 18, 2013.

BDSI intends to submit their NDA for buprenorphine and naloxone, for the treatment of opioid dependence, as soon as July 2013. This application will be submitted under section 505(b)(2), and BDSI plans to reference Suboxone sublingual tablet (NDA 020733) as the listed drug.

The questions from the March 18, 2013, meeting package are included below in italic font, and our responses are shown in bold font. Discussion is presented in normal font.

Preliminary responses were sent to BDSI on April 29, 2013, and they provided brief written comments on May 1, 2013. These brief written comments are included below the question to which they pertain, and are shown in italic font.

DISCUSSION

Following introductions and a brief opening statement by the Sponsor, the discussion focused on the Sponsor's questions that were included in the March 18, 2013, meeting package.

Question 1 *During the development of this product, all studies and relevant discussions with the FDA have reflected BDSI's intention to use Suboxone sublingual tablet as the reference listed drug for its 505(b)(2) application. The existence of citizen's petition (Docket # FDA-2011-P-0869) filed 12-02-2011, which may have direct bearing on our upcoming 505(b)(2) application, was referenced at a Meeting between FDA and BDSI on 07FEB2012 (Meeting Minutes 02/28/2012) and the outcome specifically questioned by BDSI for planning purposes. The outcome of*

the FDA's decision was unresolved and BDSI proceeded with the development program as documented in the minutes. BDSI believes that any decision regarding this petition by FDA in the future should not apply to the review of and action on BDSI's upcoming 505(b)(2) submission. Does FDA concur?

FDA Response:

We are not able to comment on the substance or timing of the Agency's action on a pending Citizen Petition.

BDSI May 1, 2013, brief written response:

Discussion required.

Discussion:

The Sponsor stated that resolution of the Citizen Petition is critical to their business strategy. The Division acknowledged this issue, but reiterated that we are not able to provide any additional information. The Sponsor asked if the Division could provide a point of contact in the Office of Regulatory Policy, which the Division stated that we would do in a post-meeting note.

Post-Meeting Note:

We were informed that you may reach the appropriate personnel in the Office of Regulatory Policy at (301) 796-3601. We reiterate, however, that FDA will not comment on the substance or timing of the Agency's action on a pending Citizen Petition.

Question 2 Does the Agency agree to a priority review for the NDA if the individual packaged units include a track and trace system with the ability to track diverted drug?

FDA Response:

A Priority Designation may be granted if preliminary estimates indicate that the drug product has the potential to provide, in the treatment, prevention, or diagnosis of a disease, one of the following:

- 1. Safe and effective therapy where no satisfactory alternative therapy exists; or**
- 2. A significant improvement compared to marketed products (approved, if approval is required), including nondrug products or therapies. Significant improvement is illustrated by the following examples:**
 - a. Evidence of increased effectiveness in treatment, prevention, or diagnosis of disease;**
 - b. Elimination or substantial reduction of a treatment-limiting drug reaction;**
 - c. Documented enhancement of patient compliance; or**

- d. **Evidence of safety and effectiveness in a new subpopulation. Although such evidence can come from clinical trials directly comparing a marketed product with the investigational drug, a priority designation can be based on other scientifically valid information.**

The ability to track and trace diverted drug does not satisfy any of the criteria listed above and would not support a priority review.

*BDSI May 1, 2013, brief written response:
No discussion required.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 3 Is the format and content of the eCTD NDA submission acceptable?

FDA Response:

From a technical standpoint, the proposed format for the planned NDA is acceptable. However, the CDER electronic submissions group (ESUB) would prefer (b)(4) submit an eCTD sample prior to submitting the NDA submission to ensure proper placement of documents (e.g., FDA does not use module 5.3.7) and successful linking of cross-application.

*BDSI May 1, 2013, brief written response:
No discussion required. We would like to clarify that the datasets are traditional format and not CDISC or SDTM, in contrast to what was originally stated in the Appendix 1 of the pre-NDA meeting package.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 4 Can the Agency confirm that the NDA will be stored on the same server as the IND so that appropriate cross references can be made?

FDA Response:

Yes, both your upcoming NDA and IND 110267 will be stored on the same server. Please note the following additional comments.

- 1. As long as your documents are Part 11 compliant, hard copy documents with actual signatures would not need to be submitted.**
- 2. Include a technical point of contact in your cover letter.**
- 3. Provide a linked reviewer's aid/ reviewer's guide in module m1.2, as a separate document from the cover letter, to briefly describe where**

information can be found throughout the application.

4. **Options for cross referencing information submitted to another application would be to either place a cross reference document under module 1.4.4 (cross reference to other applications), or use cross application links. To use the first option (placing a cross reference document in m1.4.4), a PDF document would be placed in m1.4.4 (cross reference to other applications) with a description of what is being cross referenced, and where those original documents resides. Provide hyperlinks to those documents in order to assist reviewers.**
5. **To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server, and the applications need to include the appropriate prefix in the href links (e.g., nda, ind, stn). Also, when cross application links are used, it is strongly recommended that a cross reference document be placed in 1.4.4 , in case any of the links don't work. In the leaf titles of the documents, it is recommended that the leaf title indicate the cross reference and application number (e.g., Cross Ref to ind012345). The cross reference information in the leaf titles allows the reviewer to know that the document resides in another application and what application is being referenced.**
6. **Prior to using cross application linking in an application, we recommend that you submit an "eCTD cross application links" sample to ensure you are able to successfully use cross application links, except if applicant has done cross application linking before.**
7. **To submit an eCTD cross application links sample, you would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. Refer to the Sample Process web page which is located at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm> for instructions.**
8. **For archival purposes, submit a pdf file of the labeling document submitted in Word. Also, when you submit Word documents, make sure the leaf title includes "word", so reviewers can quickly identify the Word version of the document.**
9. **Submitting placeholder documents stating that there is no information or data to report is not necessary (e.g., 2.1; 3.1) and it is not our preferred approach. In eCTD submissions, it is understood that if there is no information to report, the sponsor will not provide placeholder documents under a particular subheading in the eCTD XML backbone. The only exception is for ANDAs being submitted to The Office of Generic Drugs (OGD). OGD does prefer a placeholder document leaf reference stating there is no information to report for those items listed in the ANDA Checklist.**
10. **The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in a tabular format, linked to the referenced studies in m5.**

- 11. Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of 4.3, Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study's STF, including case report forms (CRFs).**
- 12. Regarding use of the m5-3-7 heading element, FDA does not use module 5.3.7 CRFs. Instead, CRFs should be referenced under the appropriate study STF to which they belong, organized by site as per the specifications and tagged as "case report form". Do not use 5.3.7 as a heading element in the index.xml.**
- 13. Submitting in SDTM tabulation and legacy analysis format is acceptable. Please note, however, that traceability should exist between your CRFs, SDTM, and analysis datasets. If an intermediate dataset exists between CRFs and SDTM that enables or allows traceability, please also submit those data in the "legacy" folder, as indicated in the Study Data Specifications document.**

*BDSI May 1, 2013, brief written response:
No discussion required.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 5 Is the proposal for (b)(4) exclusivity acceptable?

FDA Response:

Decisions regarding exclusivity are made post-approval by the Exclusivity Board, not the review Division. However, generally speaking, a 505 (b)(2) application may be granted 3 years of Waxman-Hatch exclusivity if one or more of the clinical investigations, other than BA/BE studies, are essential to approval of the application and was conducted or sponsored by the applicant (21 CFR 314.50(j);314.108(b)(4) and (5)).

If you do not intend to submit additional clinical studies in support of your 505(b)(2) application, then your product will not be eligible for exclusivity.

BDSI May 1, 2013, brief written response:

Discussion required. We would like to confirm that the BNX-201 safety study satisfies the Waxman Hatch (b)(4) exclusivity requirement.

Discussion:

The Sponsor stated that they understood that the safety data from Study BNX-201 would be required for approval, and therefore would make the product (b)(4) of

marketing exclusivity. The Division stated that we would discuss the issue after the meeting and include a post-meeting note with additional information.

Post-Meeting Note:

We concur that the safety data from Study BNX-201 is required for filing your application. However, decisions regarding exclusivity are made by the Exclusivity Board at the time of approval.

Question 6 Is the proposed pediatric drug development plan requesting waivers for neonates, infants, and children acceptable?

FDA Response:

You propose the following rationale for requesting a waiver for neonates and infants:

- 1. Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed;**
- 2. There is evidence strongly suggesting that the drug product would be ineffective or unsafe in that age group.**

In general, this appears acceptable; however, you must define the specific age range for your waiver request.

You propose the following rationale below for requesting a waiver for children:

Population of children who require treatment for opioid dependence is too small, rendering the necessary studies impossible or impracticable to conduct.

In general, this also appears acceptable; however, you must define the specific age range for your waiver request.

*BDSI May 1, 2013, brief written response:
No discussion required.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 7 Is it acceptable to defer the study plan for adolescents to post approval?

FDA Response:

Your rationale for a deferral request for adolescents is reproduced below. In general, it appears acceptable; however, you must define a specific age range for your deferral request.

Deferral Request

- 1. According to "Results from the 2010 National Survey on Drug Use and**

Health: Summary of National Findings”, NSDUH Series H-41, HHS Publication No. (SMA) 11-4658, Rockville, MD: Substance Abuse and Mental Health Services Administration, 2011, in 2010, “among youths aged 12 to 17, there were 1.2 million (4.8%) who needed treatment for an illicit drug use problem”.

- 2. This data suggests that there is a large enough population to justify performing studies in the adolescent group. The justification for deferral is to allow more time to collect human safety data as only limited human safety data is currently available on the use of BEMA Buprenorphine NX in the intended population.**

*BDSI May 1, 2013, brief written response:
No discussion required.*

Discussion:

There was no discussion beyond the Division’s initial written response.

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: (b) (4) 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, brief written response:

Please refer to the revised package label examples. We believe this approach addresses the Agency’s concerns, but provides less confusion and will prevent dosing errors. Does the Agency agree with this approach?

Discussion:

The Sponsor stated that they believe that medication errors and difficulty prescribing may occur if they are required to use three significant digits, particularly since this is a combination product, (b) (4) [See attachments at end of document.]

The Division responded that the proposed proprietary name (*Bunavail*) was acceptable. (b) (4)

Question 9 The draft labeling presents the proposed presentation of our PK data. Is this presentation acceptable?

FDA Response:

We cannot comment on the acceptability of the proposed PK language for the label at this time. The acceptability is dependent on review of the PK data submitted in the NDA.

*BDSI May 1, 2013, brief written response:
No discussion required.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 10 The draft labeling presents the proposed presentation of our clinical safety data. Is this presentation acceptable?

FDA Response:

Your proposal to include the adverse event table for Suboxone, and an adverse event table for other buprenorphine products that also appears in the Suboxone label is reasonable. Regarding the adverse event table for Suboxone you must use the established name of the drug product, not the tradename in the table that will appear in the BNX label. As a general approach, ensure that the annotated label submitted with the NDA notes *all* sources of data included in the label.

Be aware that inclusion of adverse event tables from the Suboxone label will not allow you to promote any comparative claims between your product and the other buprenorphine products.

BDSI May 1, 2013, brief written response:

We drafted the BEMA Buprenorphine NX PI based on guidance provided at our Type A meeting to use the Suboxone tablet PI, but believe that including the adverse events from the Suboxone tablet PI will lead to confusion as such a listing is not customary in a PI. We would like to clarify if it is necessary to include the bup/nal (Suboxone) adverse event tables in our PI.

Discussion:

The Sponsor stated that the adverse event table is potentially confusing and proposed deleting it from the package insert. The Division stated that it is not uncommon to keep

adverse events from one product in the package insert for another product when the NDA being reviewed is based on a 505(b)(2) application. The Sponsor stated their understanding, and commented that they would maintain the table in the package insert.

Question 11 The draft labeling presents the proposed conversion scheme for patients to find the correct dose. Is the conversion scheme acceptable?

FDA Response:

If the conversion scheme you propose for the label was utilized in Study 201, or you provide strong scientific evidence for the proposed conversion based on pharmacokinetic data, it may be appropriate to include in the label; however, final determination will be made upon the completion of the review of the data.

BDSI May 1, 2013, brief written response:

No discussion necessary. We propose to use our PK data based on the BE exposure for buprenorphine demonstrated in Clinical Study BNX-110 for our conversion scheme. We are not pursuing labeling for dose equivalent to Suboxone tablet 32mg, but only included this in our BNX-201 study to address FDA concerns.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 12 The draft labeling presents the proposed presentation of adverse event percentage cutoffs and adverse event tables. Is this presentation acceptable?

FDA Response:

You propose to present Adverse Reactions (ARs) which occurred in 12-week Study 201 as $\geq 5\%$ in an AR table and a listing of ARs which occurred $\geq 1\%$. This appears acceptable but will ultimately be dependent upon review of the data.

BDSI May 1, 2013, brief written response:

No discussion required.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 13 Are the package colors shown in Appendix 6 acceptable?

FDA Response:

The final acceptability of packaging labels and labeling, including layout, will be determined as part of the NDA review. However, the color scheme that you have proposed at this time seems to adequately differentiate between your strengths.

*BDSI May 1, 2013, brief written response:
No discussion required.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 14 Is it acceptable to follow the Suboxone film REMS plan?

FDA Response:

On February 22, 2013, the Agency approved the shared REMS for Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD). It is expected that your product will require the components of the BTOD REMS program. Therefore, we encourage you to contact the Buprenorphine Products Manufacturers Group (BPMG) to ensure the appropriate integration of your product into the BTOD REMS program.

*BDSI May 1, 2013, brief written response:
No discussion required.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 15 Are the proposed REMS assessments acceptable?

FDA Response:

The Agency cannot determine if the proposed REMS assessment is acceptable until the formal REMS submission is received. A complete review of the REMS will be completed during the review of your NDA.

*BDSI May 1, 2013, brief written response:
No discussion required.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 16 Regarding the literature review to be included in Module 2.5, is it sufficient to update only the literature references for hepatotoxicity and pediatric overdose?

FDA Response:

In the literature review, submit any literature that you believe would assist the reviewer during the NDA review process. This may include references for

hepatotoxicity and pediatric overdose. Also provide links in the ISS to any safety related issues for which you are providing literature references.

BDSI May 1, 2013, brief written response:

No discussion required. We understand the response and will provide literature references for hepatotoxicity, pediatric overdose, and any other literature that will assist in the review of the NDA.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 17 Does the Agency have any comments on the proposed buprenorphine hydrochloride or naloxone hydrochloride dihydrate drug substance release specifications for the NDA submission?

FDA Response:

The adequacy of your drug substance specifications will be determined during the NDA review. However, we have the following preliminary comments for each drug substance.

Buprenorphine hydrochloride

- 1) Your acceptance criterion for appearance include (b) (4) (b) (4) " You may consider revising it to more accurate words such as "... free from visible foreign particulates" (b) (4)
- 2) For specifications such as "identification by IR," report the results as "consistent with reference standard" rather than (b) (4) " Similarly, report results quantitatively where possible, rather than (b) (4) ."
- 3) Replace the identification test "(b) (4)" with "HPLC analysis retention time" that is obtained in the assay test or justify your decision to use the titration test.
- 4) We note that you do not test for heavy metals. Provide appropriate justifications for omission of this testing or add heavy metal testing to the drug substance specifications. You may reference a DMF if it includes such justifications.
- 5) (b) (4)
Note that every drug substance batch is still expected to be tested with a subset of the full release specifications. This comment also applies to your naloxone hydrochloride drug substance.

Naloxone hydrochloride

1) Refer to comments regarding heavy metal testing and other release testing comments as noted for buprenorphine hydrochloride.

*BDSI May 1, 2013, brief written response:
No discussion required.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 18 Is the cGMP manufactured (b) (4) blue ink (FD&C #1), which is generally recognized as safe, acceptable for ink marking BEMA Buprenorphine NX films?

FDA Response:

Based on its composition, (b) (4) blue ink appears acceptable. Include appropriate safety justifications in your NDA submission.

BDSI May 1, 2013, brief written response:

No discussion required. The (b) (4) blue ink is composed of ingredients in FDA approved database as shown in Table 23 of the meeting package. We will provide safety justification in the NDA submission.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 19 Is the proposed alphanumeric BEMA Buprenorphine NX dosage form ink marking system acceptable?

FDA Response:

It is not clear what you are asking, other than if the marking can be letters and numbers. It appears reasonable to mark only one side in order to indicate the orientation of the film for application. The marking should also clearly indicate dosage and other useful information.

BDSI May 1, 2013, brief written response:

No discussion required.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 20 Is the primary packaging system acceptable?

FDA Response:

The adequacy of your primary packaging system will be determined during the NDA review in the context of compatibility and stability data. Provide letters of authorization to Drug Master Files (DMFs) for the components of the container closure system if appropriate.

*BDSI May 1, 2013, brief written response:
No discussion required.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 21 Does the Agency have any comments on the proposed BEMA Buprenorphine NX drug product release specifications for the NDA submission?

FDA Response:

We cannot comment on the release specifications at this time, as their adequacy can only be determined upon review of the data. However, see our general comments below.

- 1. There is only one set of regulatory specifications that you should designate in your NDA submission. Your drug product must meet this set of specifications throughout the claimed product shelf life. However, it is permissible that you maintain an internal set of release specifications. In your application, this internal set of release specifications can be discussed as part of your overall control strategy.**
- 2. Additionally, refer to our comments to Question 22.**

*BDSI May 1, 2013, brief written response:
No discussion required.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 22 Does the Agency have any comments on the proposed BEMA Buprenorphine NX drug product stability specifications for the NDA submission?

FDA Response:

We cannot comment on the stability specifications at this time, as their adequacy can only be determined upon review of the data. However, see our general comments below.

1. **The acceptance criterion for appearance should include a requirement for legible and clear prints; the product should have no smears or smudges from the print markings.**
2. **Your proposed acceptance criteria for assay will require justification with respect to safety and efficacy to allow the proposed wide range.**
3. **Microbial burden [REDACTED] ^{(b) (4)} tests should be included or their omissions appropriately justified.**
4. **The acceptance criteria of total impurities, related impurities, and degradants should be based on actual data and appropriately justified.**
5. **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. Alternatively, include a film strength and integrity testing for your stability specifications.**

*BDSI May 1, 2013, brief written response:
No discussion required.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 23 Does the Agency agree with the proposed specification limits used for the related substances and impurities?

FDA Response:

The adequacy of your proposed specification limits for the related substances and impurities in the drug substance and drug product will be determined upon review of the data. Note that the evaluation is conducted in consideration of the relevant ICH guidelines, toxicology considerations, and release/stability data in the NDA.

*BDSI May 1, 2013, brief written response:
No discussion required.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 24 Does the Agency agree that the planned extraction studies for BEMA Buprenorphine NX drug product are sufficient for the dosage form?

FDA Response:

No, we do not agree that the planned extraction studies are sufficient, as you have not provided full protocols. Detailed protocols are needed in order for Controlled Substance Staff (CSS) to provide an assessment. However, based on the information included in the meeting package, we have the following advice:

- 1. For in vitro studies the highest dosage strength should be used, namely 6.3/1.044 mg (buprenorphine HCl/naloxone HCl) instead of the 4.2/0.696 dosage strength.**

BDSI May 1, 2013, brief written response:

4.2 mg BNX was selected because of its bioequivalence to the 8mg Suboxone tablet which was used as a comparator in the initial extraction study. All dose strengths of BNX are (b) (4) different sizes; therefore, the 4.2 mg BNX is representative of what would be expected with 6.3 mg BNX.

Discussion:

The Division thanked the Sponsor for providing full details on the extraction studies and noted that the Sponsor's response to item Number 1 was acceptable.

- 2. Provide details in your protocol regarding the solvent extraction studies, including volume of solvents to be used, agitation conditions, and extraction temperature. In addition, periodic sampling should continue until all the buprenorphine is extracted. All samples should be analyzed for buprenorphine and naloxone. In the event that high levels of buprenorphine are extracted within (b) (4) minutes, examine shorter extraction times.**

BDSI May 1, 2013, brief written response:

Details on the extraction conditions used are provided in the attached protocol. The selection of the time points was based on the fact that this is an IR product. (b) (4) minutes was picked based on the robustness of the dissolution method.

Discussion:

The Division noted that some solvents have a rapid release and that, if extraction is significant (e.g., greater than 50%) at (b) (4) minutes, the Sponsor should consider performing additional analyses at time points earlier than (b) (4) minutes.

- 3. Add (b) (4) to your list of solvents to be tested in the extraction studies.**

BDSI May 1, 2013, brief written response:

We can include (b) (4) extractions.

Discussion:

The Division noted that the response was acceptable.

- 4. Conduct extraction studies with the various solvents at an elevated temperature, as well as room temperature. The elevated temperature should be higher than $(b)(4)$ °C as you have proposed. Temperatures close to the boiling point for each individual solvent (e.g. 95 °C for water) should be maintained during the entire extraction period.**

BDSI May 1, 2013, brief written response:

An elevated temperature of $(b)(4)$ °C was used to have a consistent elevated temperature across the solvents. We will conduct additional extractions near the boiling point using a soxhlet extraction apparatus

Discussion:

The Division noted that the response was acceptable.

- 5. Provide a rationale for the use of films cut in half for the extraction studies. If the cutting of films is expected to increase the release of buprenorphine, then cutting the film in more pieces should be considered.**

BDSI May 1, 2013, brief written response:

We will perform additional studies to assess the release of a tampered product (i.e. cutting, crushing and grinding).

Discussion:

The Division stated that the additional surface area gained by cutting a thin film in half would be negligible, so the Sponsor should consider alternative means of physically manipulating the film product (e.g. crushing, grinding, multiple cutting).

- 6. An examination of the Internet reveals an interest among potential drug abusers in finding ways to manipulate buprenorphine/naloxone products for purposes of separating and isolating the buprenorphine from the naloxone. As such, your in vitro studies should examine methods to separate buprenorphine from naloxone by taking advantage of differential solubility in various solvents, for example, and as a function of solvent temperature.**

BDSI May 1, 2013, brief written response:

Based on FDA comments, differential solubility from individual solvents that selectively extract buprenorphine or naloxone will be provided at the time of the NDA.

Discussion:

The Division noted that the response was acceptable.

- 7. Assess methods for preparing solutions suitable for intravenous injection. Such preparations should be of low volume (1, 2, 5 mL), with sufficient buprenorphine, and preferably low naloxone. Water as a solvent should be examined at room temperature and elevated temperature (60° - 95°C) for extraction from intact or cut strips. In addition, this assessment should include looking at methods to isolate buprenorphine (see item 6, above) with subsequent reconstitution in small volumes of water for injection.**

BDSI May 1, 2013, brief written response:

The product injection potential is being evaluated in the study (b) (4) °C at multiple time points. Elevated temperatures are not warranted since (b) (4) is a lower critical solution temperature (b) (4).

Discussion:

The Division stated that any abuse by the IV route is a concern, and that the additional steps recommended in the initial response should be followed. The Sponsor stated that the final protocol would incorporate additional test procedures, such as utilizing warm and cold solvents.

- 8. Explore possible methods for the preparation of a sample suitable for intranasal abuse.**

BDSI May 1, 2013, brief written response:

Intranasal abuse by means of grinding or crushing will be addressed as indicated in the response to item 5. Intranasal abuse by means of solution will be addressed as indicated in the response to item 7.

Discussion:

The Division noted that the response was acceptable.

- 9. A more detailed methodology is needed to examine abuse by inhalation. According to information provided in the briefing package, buprenorphine HCl and naloxone HCl have melting points of 272° C and 200-205° C, respectively. In light of these melting temperatures it is improbable that any vapor, particularly buprenorphine vapor, will be detected if, as proposed, the "product" is heated to (b) (4) C. Consider subjecting the product (buprenorphine HCl and naloxone HCl) to differential scanning calorimetry plus thermogravimetric analysis over a temperature range of at least 200° to 300° C, in order to look for phase transitions shifts and possible decomposition.**

BDSI May 1, 2013, brief written response:

The vaporization study (inhalation abuse potential) was conducted at (b)(4)°C (not at (b)(4)°C as incorrectly stated in the meeting package) which is sufficient to allow vaporization of both buprenorphine and naloxone.

Discussion:

The Division stated that vaporization data above (b)(4)°C would be useful, and that it should include a degradation profile (e.g., differential scanning calorimetry).

10. For all in vitro studies, provide information on the number of replicates, indicate how results will be expressed, and include the statistical protocol to be followed for analyzes of the data.

BDSI May 1, 2013, brief written response:

We will take these recommendations under consideration.

Discussion:

The Division noted that the response was acceptable.

Discussion necessary. We thank the FDA for providing details to the planned extraction study. The protocol for the extraction study which has already been conducted is provided. Responses to some of the FDA advice are provided above. BDSI plans to include results from the advice and recommendations made by the FDA as warranted for the NDA submission. Can the NDA be amended if CSS comes back with additional questions?

Discussion:

The Division stated that, although they provided comments on the details of the extraction studies, it was not clear why the Sponsor is proposing to complete these specific studies. The Sponsor stated that they had intended to conduct these studies because the drug product is known to be diverted, and that they felt that it was a requirement for approval. The Division stated that if the Sponsor was not seeking any abuse-deterrent language, then no extraction studies would be required.

Question 25 Is submission of the NDA with 6 m of stability data acceptable, with submission of an additional 3 months data (9 months total) at the 120-day safety update?

FDA Response:

No, we do not agree to your proposal to submit the NDA with 6 months of stability data followed by an additional 3 months of data at the 120-day safety update. The NDA must be complete at the time of submission, so if your plan is to submit a total of 12 months of stability data, these data must be included in the initial NDA

submission.

BDSI May 1, 2013, brief written response:

Discussion required. We would like to address Q25 and Q26 together. We understand that any additional data need to be submitted as an amendment to the NDA and will be reviewed subject to timeliness of the submission, the extent of submitted data, and the available resources.

We would like to clarify that we plan to submit the NDA with 6 months of data on three registration batches, (no additional data at 120 day safety update) and accept expiration dating based on the 6 month data. We would like clarification on whether this is sufficient for submission.

Discussion:

The Division stated that 12 months of stability data are likely necessary for filing the application. The Division inquired if the Sponsor felt that having a shorter expiry would be a commercially viable product, to which the Sponsor responded that they would have to consider that issue in the context of a greater business decision.

Post-Meeting Note:

If the NDA is submitted with less than 12 months of stability data, ONDQA will review the stability information during the course of the review and recommend an appropriate shelf life based on the available data.

Question 26 What is the mechanism for providing ongoing stability data generated during the review cycle and what is the impact on the review timeline?

FDA Response:

Additional stability data (along with the updated stability summary and plots as needed) may be submitted as an amendment to your NDA. While every effort will be made to review the stability updates, the review will depend on the timeliness of the submission, the extent of submitted data, and the available resources. The expiration dating period that is granted will be commensurate to the stability data that are reviewed.

BDSI May 1, 2013, brief written response:

Discussion required. We acknowledge that stability data will not be submitted as part of the 120-day safety update. We also interpret the response to mean that a stability amendment would have no impact on the review should we submit one. Please confirm

Discussion:

There was no discussion beyond the Division's initial written response.

Question 27 Does the Agency agree with the justifications and calculations used for determining the relevant exposure margins?

FDA Response:

The justifications and calculations used for converting the relevant exposure margins for buprenorphine from the Suboxone label are acceptable.

However, naloxone exposure margins are not described in the Suboxone label. Unless you have conducted a bridging toxicokinetic study to identify naloxone exposures expected from the buprenorphine/naloxone dietary study or have a right to reference the study from the Sponsor, safety margins based on such data cannot be described in the BEMA Buprenorphine NX label. We note that as this information is not described in the listed drug label it is not necessary that this be incorporated into the BEMA Buprenorphine NX label.

*BDSI May 1, 2013, brief written response:
No discussion necessary.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 28 Does the Agency agree that no additional nonclinical studies are required to qualify the excipients?

FDA Response:

Excipients that are not present in Agency-approved chronic use oral products at doses greater than or equal to that in BEMA Buprenorphine NX may require qualification. We will notify you of any excipients that are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration or are not exempted at proposed levels in 21 CFR.

*BDSI May 1, 2013, brief written response:
No discussion necessary.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 29 Should qualification of impurities be necessary, does the Agency agree with the proposed plan?

FDA Response:

No, we do not agree. In order to qualify impurities for a chronic indication, in addition to genotoxic potential, a 90-day study should be conducted in the species most likely to maximize the potential to detect the toxicity of any impurity/impurities. In addition, *in silico* assessment for potential

genotoxicity/carcinogenicity should include both a knowledge-based assessment (e.g., DEREK) and a statistics-based assessment (e.g., MultiCASE). We are not clear of your strategy here regarding *in silico* assessment and qualification testing; therefore, please clarify. Qualification data must be submitted with the NDA.

*BDSI May 1, 2013, brief written response:
No discussion necessary.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 30 Is the proposed nonclinical data package acceptable?

FDA Response:

We note that the clinical exposures to BEMA Buprenorphine provided in the PIND meeting package are within those of the reference drug, Suboxone and, with adequate monitoring for local toxicity in clinical trials, nonclinical studies to support the drug product during clinical development will not be necessary except as needed to address impurities which exceed ICH guidelines or the presence of novel excipients by identity, route, level, or duration. Also refer to our response to Question 33 as to adequate monitoring of local toxicity in clinical trials.

BDSI May 1, 2013, brief written response:

We would like to address after the discussion of Question 33. Does the response we provided on the oral mucosal assessments performed in BNX-201 eliminate the need for a nonclinical study?

Discussion:

The Division stated that the clinical data appear to be sufficient, but that the Sponsor should include the training program used in BNX-201 in the NDA filing so that the Division can fully review it.

Question 31 Does the Agency agree that the data from BNX-110 has satisfied the buprenorphine bioequivalence requirement?

FDA Response:

Based on your meeting package, your data from Study BNX-110 suggested equivalent buprenorphine exposure between your proposed 4.2/0.696 mg film and Suboxone 8/2 mg tablet. We will review the data submitted in your NDA to draw a final conclusion.

*BDSI May 1, 2013, brief written response:
No discussion necessary.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 32 Does the Agency agree that the BNX-110 and BNX-106 data justifies the acceptability of the biowaiver for the (b) (4) mg bup/nal dosage?

FDA Response:

The submission of bioequivalence (BE) and/or bioavailability (BA) information for lower strength(s) of your proposed product will be waived if all the following requirements are met:

- 1. Inclusion of the biowaiver request as part of the NDA submission;**
- 2. The lower strength (s) and higher strength product have the same dosage form;**
- 3. There is BA/BE data for a higher strength;**
- 4. The lower strength (s) product is proportionally similar in its active and inactive ingredients to the higher strength product for which there is an acceptable BE study; and**
- 5. Dissolution profile comparisons between all lower strengths not tested in the dose proportionally study or BE study (e.g., (b) (4) 2.10/0.348 strengths) and the higher strengths should meet the f2 similarity requirements in the QC proposed dissolution medium.**

Note that we do not grant biowaivers of the required BA/BE studies during the IND stage. Our final recommendation on granting the biowaiver will be provided during NDA review. Therefore, you should include all supporting information in your NDA submission.

*BDSI May 1, 2013, brief written response:
No discussion necessary.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 33 Does the Agency agree that BNX-201 has adequately assessed local toxicity at the site of film application?

FDA Response:

The most recent protocol submitted for Study 201, Amendment 2, dated September 15, 2012, appears to incorporate some, but not all, of the recommendations from our correspondence on August 29, 2012. Preliminary comments from the Division of Dermatology and Dental Products (DDDP) regarding your September, 15, 2012, amended protocol include the following:

- 1. The protocol has been modified to include oral assessments at Days 1, 7, 14,**

- 28, 56 and 84 (end of treatment). We recommend that an assessment be added at 2 days after applying the product as the greatest likelihood of oral irritation will be in the first two days of use.**
- 2. We advised that exclusion Criterion 13 should be modified so that, “Any clinically significant abnormality of the buccal mucosa which could impact drug absorption,” requires assessment by a dentist. The amended protocol does not specify that an initial oral assessment must be conducted by a dentist.**
 - 3. As you were previously advised, the WHO Oral Toxicity Scale was developed principally to assess toxicity associated with cancer treatments (e.g., oral mucositis). The 0-4 scale for toxicities reflects increasing severity of signs. You are using the WHO Oral Toxicity Scale to identify observed signs in the proposed study. The WHO Toxicity Scale should not be mentioned, since it is intended to describe a range of toxicities that goes well beyond that which would be expected for this product. Rather, the terms “normal,” ”redness,” ”swelling or raised lesions,” or “other (describe)” could be selected by the reporter. Certainly ulceration or bleeding (which could be reported as “other”), and probably swelling would be cause to discontinue a subject from the study. Your amended protocol uses a modified WHO Toxicity Scale which is not acceptable.**

Therefore, based upon the comments from DDDP, the oral mucosal assessments are not adequate.

BDSI May 1, 2013, brief written response:

With regard to 1):

- The FDA advice letter dated 29AUG2012 specified assessing subjects for oral irritation at day 1, 3, 7 and 14 days. BDSI did not receive any comments indicating a 2 day assessment was necessary. Since the protocol window for oral assessments was +/- 3 days, an interim time point between 0/1 and 7 days was not included. With the exception of the 2/3 day time point, all requested evaluation time points were assessed.*
- The protocol text was modified as follows:*
 - Schedule of Assessment (Table 4)*
 - Oral examination on Days -30 to -1, 0/1, 7, 14, 28, 56, 84/ET.*
- As noted in [Table 1](#), only 1 abnormal observation out of 209 was observed at day 7.*

With regard to 2):

- We believe that properly trained physicians are capable of identifying significant abnormalities of the buccal mucosa that could impact drug absorption.*
- A board certified dentist designed the training program for Clinical Study BNX-201 and trained the physician investigators and physician subinvestigators on the oral exam. The protocol, methods and standards of exam were consistent with the*

council of interstate testing agency for dental licensure in the US. (Please see the attached training program used at the investigators meeting and subsequent Webex reviews on oral mucosal evaluation with reference pictures from the UNC Dental School curriculum).

- *The protocol text was modified with the following requirement:*
 - *Oral examination by a trained Investigator or Sub-Investigator (Days 7, 14, 28, 56, and 84)*

With regard to 3):

- *We used the specific terms requested by the FDA, but incorrectly referred to it in the protocol amendment as a modified WHO Oral Toxicity Scale. The terms used clearly distinguish our oral examination scale from the WHO Oral Toxicity Scale. Please excuse our incorrect reference to the WHO Toxicity Scale and note that the clinical study report will correct this mistake.*

With regard to the comment that oral mucosal assessments are not adequate:

Mucosal evaluation data are summarized in Table 1 and demonstrate both the rigor of the examinations and the absence of any clinically meaningful mucosal related adverse events.

Table 1

	<i>Subjects with Abnormal Oral Examination Results (Safety Population)</i>							
	<i>Screening</i>	<i>Baseline</i>	<i>Day 7</i>	<i>Day 14</i>	<i>Day 28</i>	<i>Day 56</i>	<i>Day 84</i>	<i>Early Termination</i>
<i>N</i>	249	249	209	204	219	206	199	36
<i>Normal</i>	232	241	208	204	215	206	199	35
<i>Abnormal</i>	17	8	1	0	4	0	0	1
<i>Erythema</i>	2	5	0	0	3	0	0	0
<i>Swelling/Raised lesions</i>	13	2	1	0	1	0	0	0
<i>Ulceration</i>	1	0	0	0	0	0	0	1
<i>Bleeding</i>	0	0	0	0	0	0	0	0
<i>Other</i>	1	1	0	0	0	0	0	0

It should be noted that:

- *Each exam was divided into an assessment of 4 quadrants of the mouth.*
- *Exams were performed in all 249 subjects at screening and baseline and abnormalities were identified in 20 subjects.*
- *One mouth ulcer was observed at screening that had resolved at baseline.*
- *No bleeding or other abnormalities were observed at baseline that would have either altered drug absorption or introduced a risk to the subject.*
- *Over 1000 oral examinations were performed during the study drug administration period (post baseline).*

- *Over the 12-week study period, 6 subjects had an abnormal oral exam including:*
 - *4 observations with erythema,*
 - *1 observation with swelling or raised lesions, and*
 - *1 observation with an ulcer.*
- *Note that the primary observation was erythema that neither persisted nor progressed in severity.*

Importantly, there were no subjective reports of irritation from participating subjects.

The absence of changes in the oral mucosa evaluations over the course of the study is indicative of the oral safety of the BEMA technology and the BNX product specifically.

Discussion:

The Sponsor provided a summary of the training that each health care practitioner passed before being able to perform oral examinations. The Division stated that the concern had been expressed by the Division of Dermatology and Dental Products, so this Division could not provide immediate comments on the acceptability of the training program or the assessment scale that was utilized. The Division noted that an additional non-clinical study to quantify the local toxicity was likely not necessary. The Division also noted that examination by physicians would likely be adequate, but whether the evaluations of oral toxicity in Study BNX-201 were adequate will be determined upon review of the data.

Question 34 Does the Agency concur that no additional clinical pharmacology studies are required to support a 505(b)(2) NDA for BEMA Buprenorphine NX in the proposed indication?

FDA Response:

We are increasingly aware of the need to provide information about the effects of temperature and pH on bioavailability for drugs that are delivered transmucosally. Provide information about the effects of temperature or pH on transmucosal bioavailability of buprenorphine in general, or your product specifically, and propose wording for labeling to reflect that information in your NDA submission.

BDSI May 1, 2013, brief written response:

No discussion necessary. Clinical study BNX-107 was conducted to evaluate the effects of pH on the bioavailability.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 35 Does the Agency concur that no clinical efficacy studies are required to support a 505(b)(2) NDA for BEMA Buprenorphine NX in the proposed indication?

FDA Response:

If bioequivalence is established between BEMA Buprenorphine NX and the listed drug, then no clinical efficacy studies are required.

*BDSI May 1, 2013, brief written response:
No discussion necessary.*

Discussion:

There was no discussion beyond the Division's initial written response.

Question 36 Does the Agency concur that no additional clinical safety information is required to support a 505(b)(2) NDA for BEMA Buprenorphine NX in the proposed indication?

FDA Response:

In prior advice from the Agency, you were informed that, for a 12-week study, at least 200 completers, including patients taking up to 32mg buprenorphine (Suboxone) per day would be required. Although the proposed dosing range is for opioid dependent patients on 16 to 24mg of Suboxone, in prior Agency advice you were advised that, since some patients are maintained on 32mg of buprenorphine per day, Study 201 should permit enrollment of these patients. You report that Study BNX-201 includes 249 subjects, 198 of whom completed the 12-week study, and that 8 patients were enrolled who were taking 32mg/day Suboxone. Whether data from 8 patients treated with the 32mg dose are sufficient to permit evaluation of the highest dose will be determined upon review of the data and will depend on the safety profile of BNX.

Additional safety data may be required if your proposed to-be-marketed doses are higher than those studied in the 12-week study.

*BDSI May 1, 2013, brief written response:
Discussion required. We would like to clarify that we are not pursuing marketing of a BEMA Buprenorphine NX dose providing equivalent exposure to the 32 mg buprenorphine Suboxone tablet*

Discussion:

There was no discussion beyond the Division's initial written response.

ADDITIONAL COMMENTS

BIOPHARMACEUTICS

- 1. We have the following advice regarding the dissolution method information that should be provided in your NDA.**

- a. **Solubility data for the drug substances covering the physiological pH range**
 - b. **Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product – If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified.**
 - c. **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.**
 - d. **Complete dissolution profile data (individual, mean, SD, profiles) for your product – The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product’s label claim).**
 - e. **Data to support the discriminating ability of the selected dissolution 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 and 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 the capability of the selected dissolution method to reject batches that are not bioequivalent.**
 - f. **Supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).**
2. **Your proposed dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ min is considered rather permissive and should be supported by data. Note that for the selection of the dissolution acceptance criterion of your product, the following points should be considered:**
- a. **The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value).**
- Submit the mean and individual dissolution data (tabulated and graphical form) of all the batches used in setting the dissolution acceptance criterion for both components of your proposed**

product.

- b. The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.**
- c. The selection of the specification time point should be where Q^{(b) (4)} % dissolution occurs.**

CHEMISTRY, MANUFACTURING AND CONTROL (CMC)

Your dosage form should be presented as "buccal film" rather than "buccal (b) (4) film."

BDSI May 1, 2013, brief written response:

Discussion required. We would like to know the rationale for changing from buccal (b) (4) film to buccal film?

Discussion:

There was no discussion beyond the Division's initial written response.

CLINICAL

We note that the doses of BNX used in the safety and pharmacokinetic studies are not the same as the proposed marketed doses. Provide clarification at the meeting as to why you are not planning to market the doses you studied.

BDSI May 1, 2013, brief written response:

Background information:

The final formulation chosen was a 6:1 buprenorphine to naloxone ratio. The dose strengths of the BNX 6:1 formulation which were used in the individual clinical studies are summarized by study in Table 2.

- This formulation was first evaluated in dose linearity study BNX-106. The results indicated a linear increase in buprenorphine exposure over a BNX dose range of 0.875 to 5.25 mg of buprenorphine and suggested that a 3.5 mg dose would be bioequivalent to the 8 mg Suboxone tablet.*
- Study BNX-103 demonstrated that the buprenorphine exposure from a 3.5 mg BNX dose had comparable bioavailability to an 8 mg Suboxone tablet.*
- Based on the comparable bioavailability of buprenorphine in the BNX-103 study of 3.5 mg BNX strength to the 8mg Suboxone tablet, a dose conversion ratio was developed and used in evaluating the safety of the formulation for mucosa related adverse events and control of*

opioid dependence in the BNX-201 safety study. Investigators were able to titrate patients to symptom control if necessary (~33%) thus allowing for comparable plasma concentrations between the BNX and the patients prior treatment with Suboxone.

- The retention of subjects in the BNX-201 study (79%) along with the low percentage of subjects (21 subjects, 8%) with urines positive for non-prescribed opioids demonstrate the effectiveness of buprenorphine in this study.

Table 2

	BNX Dose Strengths (6:1 formulation; mg buprenorphine/naloxone)				
Study	0.875/0.145	3.5/0.58	4.2/0.696	5.25/0.87	6.3/1.044
BNX-106	X	X		X	
BNX-103		X			
BNX-201		X		X	
BNX-110			X		
BNX-107			X		X

- Based on the results from pharmacokinetic study BNX-103 and the dose linearity demonstrated in the BNX-106 study, we estimated that a ^(b)₍₄₎ % increase in dose would provide bioequivalent buprenorphine exposure to the Suboxone tablet. Thus a dose of 4.2 mg of BNX was compared to Suboxone 8 mg tablet in BNX-110. In addition, the Suboxone film was included for future reference. The results demonstrated that the 4.2 mg dose of BNX is BE to the 8 mg Suboxone tablet, with respect to buprenorphine.
- The 4.2 mg dose was used in the BNX 107 PK study to evaluate the effect of low and high pH liquids on absorption and for a comparison of the dose proportionality to a higher 6.3 mg dose.

Rationale for doses being recommended for marketing:

Study BNX-201 demonstrated safety in the opioid dependent population for BNX across the Suboxone dose range of 8 – 32 mg buprenorphine. In BNX-110, we established buprenorphine bioequivalence of the 4.2 mg BNX dose strength with the 8 mg Suboxone tablet. This is the rationale for our recommendation.

Based on the BE results, we will be marketing the BNX doses shown in Table 3 as compared to the corresponding Suboxone tablet doses.

Table 3

Current Suboxone tablet dose (mg buprenorphine/naloxone)	Conversion BEMA Buprenorphine NX Bioequivalent Dose (mg buprenorphine/naloxone)

(b) (4)	
	2.1/0.348
8/2	4.2/0.696
	6.3/1.044

Discussion:

The Sponsor stated that they used the same formulation in multiple (b) (4) PK studies, and that they studied up to (b) (4) mg. (b) (4)

(b) (4) The Sponsor stated that they have clinical data supporting doses from 2 mg to 32 mg of buprenorphine.

The Division also reminded the Sponsor that they will need to submit a biowaiver request in their NDA submission, and inquired if the Sponsor had data supporting conversion between doses other than those which had bioequivalence with Suboxone tablets. The Sponsor stated that they would submit a justification demonstrating that systemic exposures will not be different when switching from Suboxone to their product.

Action Items:

1. The Sponsor will consider additional options for their proprietary name. New proprietary names will be submitted for review.
2. The Sponsor will submit a biowaiver request for their two lower strengths with the NDA submission.

OTHER IMPORTANT INFORMATION

SUBMISSIONS UNDER 505(b)(2)

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach

will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.

- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[see *Warnings and Precautions (5.2)*]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

ADDITIONAL STANDARD PRE-NDA COMMENTS

The following comments are shared with all Sponsors at the Pre-NDA stage, and any specific comment may or may not apply to your upcoming NDA submission.

Nonclinical Comments

1. Include a detailed discussion of the nonclinical information in the published literature in your NDA submission and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.
2. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 draft guidance for industry, *Applications Covered by Section 505(b)(2)*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408, available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>).

Note that you may only rely on the Agency's finding of safety and/or effectiveness as it is reflected in the approved labeling for the listed drug(s). You may not reference data in the Summary Basis of Approval or other FDA reviews obtained via the Freedom of Information Act or publically posted on the CDER website to support any aspect of your development program or proposed labeling of your drug product. Reviews are summary data only and do not represent the Agency's previous finding of safety and effectiveness.

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). Establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

3. The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label.
4. New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance for industry, *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients*.

As noted in the document cited above, "the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently **proposed level of exposure, duration of exposure, or route of administration.**" (emphasis added).

5. Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in ICHQ3A(R2) and ICHQ3B(R2) guidances at the time of NDA submission.

Adequate qualification would include:

- a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies; e.g., one point mutation assay and one chromosome

aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

- b. Repeat dose toxicology of appropriate duration to support the proposed indication.
6. Genotoxic, carcinogenic or impurities that contain a structural alert for genotoxicity must be either reduced to NMT 1.5 mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative in vitro bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICHS2A guidance document titled “Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals.” Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.
 7. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICHQ3A and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.
 8. The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation as outlined in the FDA Guidance for Industry titled “Container Closure Systems for Packaging Human Drugs and Biologics.” The evaluation of extractables and leachables from the drug container closure system or from a transdermal patch product must include specific assessments for residual monomers, solvents, polymerizers, etc.). Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds.

The safety assessment should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents “Container Closure Systems for Packaging Human Drugs and Biologics” and “Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation.” Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf.

9. Failure to submit adequate impurity qualification, justification for the safety of new excipient use, or an extractable leachable safety assessment at the time of NDA submission can result in a Refusal-to-File or other adverse action.

Chemistry, Manufacturing and Control (CMC) Comments

1. Include a well documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.
2. Provide a list of all manufacturing and testing facilities and their complete addresses in alphabetical order, and a statement about their cGMP status. For all sites, provide a name contact and address with telephone number and facsimile number at the site. Clearly specify the responsibilities (e.g., manufacturer, packager, release tester, stability tester etc.) of each facility, the site CFN numbers and designate which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.
3. Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming to this in the NDA cover letter.
4. Provide summary stability data on a parameter-by-parameter basis (instead of only on a batch to batch basis), and in addition, provide graphical plots of critical parameters and trending parameters. The graphical plots should indicate the proposed acceptance criteria, and they should include both mean and individual data points.

The Abuse Potential section of the NDA is submitted in the eCTD as follows:

Module 1: Administrative Information and Prescribing Information

1.11.4 Multiple Module Information Amendment

This section should contain:

- A summary, interpretation and discussion of abuse potential data provided in the NDA.
- A link to a table of contents that provides additional links to all studies (nonclinical and clinical) and references related to the assessment of abuse potential.
- A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA.

Module 2: Summaries

2.4 Nonclinical Overview

This section should include a brief statement outlining the nonclinical studies performed to assess abuse potential.

2.5 Clinical Overview

This section should include a brief statement outlining the clinical studies performed to assess abuse potential.

Module 3: Quality

3.2.P.1 Description and Composition of the Drug Product

This section should describe any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).

3.2.P.2 Description and Composition of the Drug Product

This section should describe the development of any components of the drug product that were included to address accidental or intentional misuse.

Module 4: Nonclinical Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

These sections should contain study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.

4.2.3.7.4 Dependence

This section should include:

- A complete discussion of the nonclinical data related to abuse potential.
- Complete study reports of all preclinical abuse potential studies.

Module 5: Clinical Study Reports

5.3.5.4 Other Study Reports

This section should contain complete study reports of all clinical abuse potential studies.

5.3.6.1 Reports of Postmarketing Experience

This section should include information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product

General Clinical Comments

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP 6010.3R).

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - Important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 – Clinical Pharmacology- Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.
3. Section 7.5.1 Dose Dependency for Adverse Events
4. Section 7.5.2 Time Dependency for Adverse Events
5. Section 7.5.3 Drug-Demographic Interactions
6. Section 7.5.4 Drug-Disease Interactions
7. Section 7.5.5 Drug-Drug Interactions
8. Section 7.6.4 – Overdose, Drug Abuse Potential, Withdrawal and Rebound

Sites for Inspection

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested, as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

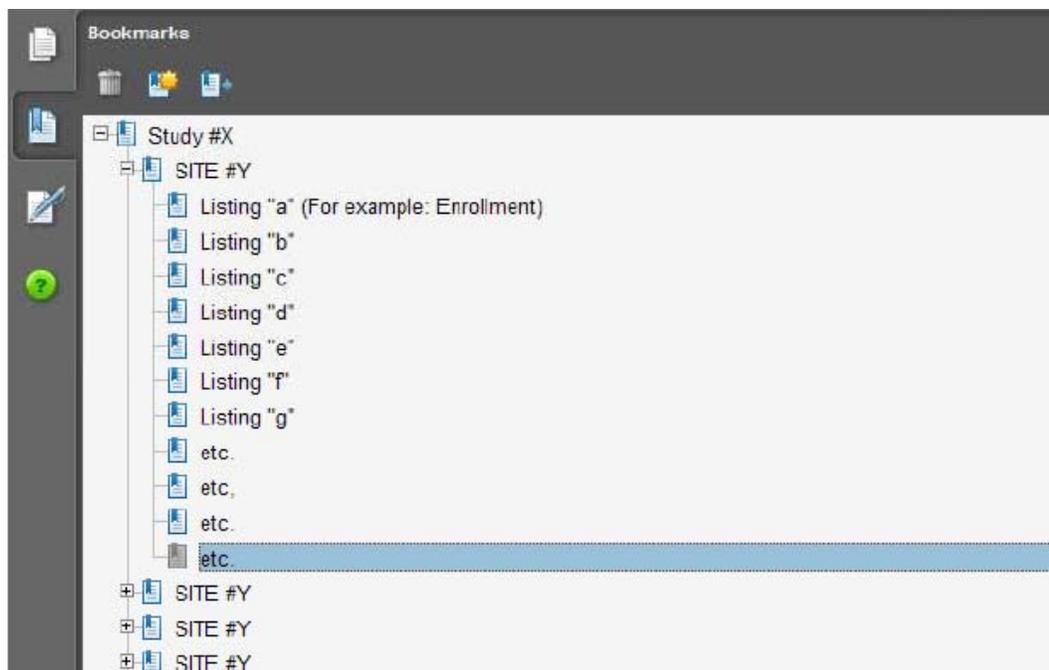
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Subpart 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

- I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**
1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Number of subjects screened for each site by site
 - b. Number of subjects randomized for each site by site, if appropriate
 - c. Number of subjects treated who prematurely discontinued for each site by site
 3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
 - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
 - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
 - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
 - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
 4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
 - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
 - b. Subject listing for treatment assignment (randomization)
 - c. Subject listing of drop-outs and subjects that discontinued with date and reason
 - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 3 study using the following format:



III. Request for Site Level Dataset

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Subpart 1, “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions” for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Subpart 1

1. Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1. Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2. Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYT L	DOMAIN	SPON NO	SPONN AME	IND	UNDE RIND	ND A	BL A	SUPPN UM	SIT EID	ARM	ENR OLL	SCREE N	DISCO NT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FI
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	

Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	4
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	4
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	2
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	2
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Subpart 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item1	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

Common PLR Labeling Errors

Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions)
7. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
8. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

9. Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
10. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
11. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]
12. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
13. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
14. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
15. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Contents (Table of Contents):

16. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
17. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
18. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
19. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
20. When a subsection is omitted, the numbering does not change. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

- 8.1 Pregnancy
- 8.3 Nursing Mothers (not 8.2)
- 8.4 Pediatric Use (not 8.3)
- 8.5 Geriatric Use (not 8.4)

21. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI):

22. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>
24. Do not refer to adverse reactions as “adverse events.” Refer to the guidance for industry, *Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.
25. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
26. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)].
28. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference

[See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

29. Since SPL Release 4 validation does not permit the inclusion of the Medication Guide as a subsection, the Medication Guide or Patient Package Insert should not be a subsection under the Patient Counseling Information section. Include at the end of the Patient Counseling Information section without numbering as a subsection.
30. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
32. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. See guidance for industry, *Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements*. The same applies to PPI and MG.
33. For fictitious examples of labeling in the new format, refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>
34. For a list of error-prone abbreviations, symbols, and dose designations, refer to the Institute of Safe Medication Practices’ website, <http://www.ismp.org/Tools/abbreviationslist.pdf>

SPL Submission

Structured product labeling (SPL) must be submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); guidance for industry, *Providing Regulatory Submissions in Electronic Format — Content of Labeling*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>], you are required to submit to FDA prescribing and product information (i.e., the package insert) in SPL format. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance.

Integrated Summary of Effectiveness

Please refer to the guidance for industry, *Integrated Summary of Effectiveness*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>

Please refer to guidance for industry, *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

CDER Data Standards Reference Guide/Checklist

The following resources are intended to assist submitters in the preparation and submission of standardized study data to CDER.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

Dataset Comments

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

The integrated safety dataset that must include the following fields/variables:

- a. A unique patient identifier
- b. Study/protocol number
- c. Patient's treatment assignment
- d. Demographic characteristics, including gender, chronological age (not date of birth), and race
- e. Dosing at time of adverse event
- f. Dosing prior to event (if different)
- g. Duration of event (or start and stop dates)
- h. Days on study drug at time of event
- i. Outcome of event (e.g., ongoing, resolved, led to discontinuation)
- j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).

- k. Marker for serious adverse events
 - l. Verbatim term
- 2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the verbatim term taken from the case report form.
- 3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.
- 4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.
- 5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
- 6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the *ICH MedDRA Term Selection: Points to Consider* document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.
- 7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.
- 8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
- 9. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.

10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.
11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.
13. All datasets must contain the following variables/fields (in the same format and coding):
 - a. Each subject must have one unique ID across the entire NDA
 - b. Study number
 - c. Treatment assignment
 - d. Demographic characteristics (age, race, gender, etc.)
14. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. A listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.
15. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.
16. For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.

17. With reference to the table on the following page, note that the HLGT and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

Unique Subject Identifier (USUBJID)	Sequence Number (ASEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferr ed Term High Level Term (HLT)	High Level Group Term (HLGT)	Syst em Organ Clas s (SOC)	Seco ndary System Organ Class 2 (SOC 2)	Seco ndary System Organ Class 3 (SOC 3)	Seco ndary System Organ Class 4 (SOC 4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW W SULLIVAN
06/05/2013



IND 110267

MEETING MINUTES

BioDelivery Sciences International, Inc.
801 Corporate Center Dr, Suite 210
Raleigh, NC 27607

Attention: Renee Boerner, PhD
Director, Regulatory Affairs

Dear Dr. Boerner:

Please refer to your Investigational New Drug Application (IND) submitted March 18, 2011, received March 18, 2011, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BEMA Buprenorphine NX (buprenorphine and naloxone buccal (b) (4) film).

We also refer to the meeting between representatives of your firm and the FDA on February 7, 2012. The purpose of the meeting was to discuss your future 505(b)(2) NDA submission and results from your recent pharmacokinetic program.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan, MS
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 7, 2012
TIME: 1:30 pm to 2:30 pm
LOCATION: FDA White Oak Campus
Building 22, Room 1313
APPLICATION: IND 110267
PRODUCT: BEMA buprenorphine NX buccal (b) (4) film
PROPOSED INDICATION: Treatment of opioid dependence
SPONSOR: BioDelivery Sciences International, Inc
TYPE OF MEETING: Type A
MEETING CHAIR: Rigoberto Roca, MD, Deputy Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
MEETING RECORDER: Matthew Sullivan, MS, Senior Regulatory Project Manager, DAAAP

FDA Attendees	Title
Bob A. Rappaport, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, MD	Deputy Director, DAAAP
Celia Winchell, MD	Clinical Team Leader, DAAAP
Pamela Horn, MD	Medical Officer, DAAAP
Ramesh Raghavachari, PhD	CMC Lead, ONDQA
Yun Xu, PhD	Clinical Pharmacology Team Leader Division of Clinical Pharmacology II (DCP II)
Sheetal Agarwal, PhD	Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II (DCP II)
Lori Love, MD, PhD	Medical Officer, Controlled Substance Staff
Matthew Sullivan, MS	Senior Regulatory Project Manager, DAAAP
BDSI Attendees	Title
Renee Boerner, PhD	Director, Regulatory Affairs
Susan Kerls	Associate Director, Clinical and Regulatory Science
Andrew Finn, PharmD	Executive Vice President, Product Development
Niraj Vasisht	Senior Vice President, Product Development
Mark Sirgo, PharmD	President and Chief Executive Officer
(b) (4)	Consultant

Following introductions and a brief opening statement by the Sponsor, the discussion focused on the Sponsor's questions that were included in the December 22, 2011, meeting package. Preliminary comments were sent to the Sponsor on February 3, 2012.

The Sponsors questions are in italics and the Division's responses are in bold text. Discussion is in normal text.

Question 1 Assuming the results for the low dose of the BNX-103 study are as depicted in Table 5, does the Agency agree that the low dosage BNX product (b) (4) satisfies the equivalent exposure requirement with respect to the corresponding dose of Suboxone sublingual tablet for a 505(b)(2) submission?

FDA Response:

No, we do not agree that this satisfies the equivalent exposure requirement for the following reasons:

- 1. You must demonstrate equivalent exposure (based on 90% confidence interval) with respect to buprenorphine between your product and the reference product. Lower naloxone exposure, when used as intended, would be acceptable because the naloxone is expected to play a role only when the product is not used as intended. However, the ability of the product to perform as expected with respect to precipitation of withdrawal under conditions of misuse is a review issue and would depend on the data and the justification provided in the NDA. Also see our response to Question 3.**
- 2. If exposure for buprenorphine or naloxone is higher than the reference product (C_{max} and AUC values), then additional safety data will be required.**
- 3. If your product demonstrates lower buprenorphine exposure than the reference product, you will need to provide additional efficacy data.**

Additional comments related to proposed study BNX-103:

- 1. Based on your expected PK data from study BNX-103 for all the three proposed strengths, it appears that buprenorphine C_{max} values for your low and high strength products will exceed that of the reference, low (2/0.5) and high (8/2) strength Suboxone SL tablets, respectively. If patients use multiple strips of your product to achieve a higher dose, including doses recommended in labeling (e.g., 16 mg buprenorphine – 24 mg buprenorphine), they will be exposed to much higher buprenorphine concentrations as compared to the reference Suboxone SL tablets. Therefore, you need to provide additional safety data to support the higher buprenorphine concentrations for all proposed strengths of your product. When demonstrating the safety profile with these strips to address higher buprenorphine exposure, we recommend that you use the maximum number of strips to be employed to achieve the desired dose as intended in product's final label (e.g., 4 low strength strips to achieve a dose equivalent to 8/2 mg of Suboxone SL tablet or 3 high-strength strips to achieve a dose equivalent to**

24/6 mg of Suboxone SL tablet). The safety data required will depend on the actual PK results. You may need to collect clinical data to evaluate the potential for acute overdose and the effects of chronic exposure, depending on the PK profile of your product. In general, C_{max} values that exceed the product you are referencing raise concern for acute overdose and AUC values that exceed the product you are referencing raise concern for the effects of chronic use.

2. Based on your expected PK data from study BNX-103 it appears that naloxone C_{max} values for your (b) (4) strength, and naloxone C_{max} and AUC values for your (b) (4) strength will exceed that of the reference 2/0.5 and 8/2 mg Suboxone SL tablets respectively. For the higher naloxone C_{max} values, you need to provide additional safety data demonstrating that the higher naloxone exposures do not lead to opioid withdrawal symptoms in patients.
3. Based on your expected PK data from study BNX-103 for the (b) (4) strength, it appears that naloxone C_{max} values will be similar and AUC values will be lower as compared to the reference 8/2 mg Suboxone SL tablet. As indicated earlier, lower naloxone exposure, when used as intended, is acceptable because naloxone is expected to play a role only when the product is not used as intended.
4. The responses above are based on the hypothetical result you proposed for study BNX-103. If the final study result is different from what you proposed in the package, our responses may change accordingly.
5. In addition, we refer you to our responses to Question 13 and Question 17 from the January 18, 2011, Pre-IND meeting.

Discussion:

The Sponsor stated that, based upon the response to Question 3, they plan on using a 6:1 ratio for both the high dose ((b) (4) mg) and the low dose ((b) (4) mg) of BEMA Buprenorphine / Naloxone (BNX). The Sponsor also noted that a naloxone dose of (b) (4) mg had produced an aversive effect in the precipitated withdrawal study, and asked the Division if the proposed (b) (4) mg in the low dose was acceptable. The Division stated that the level of naloxone would be acceptable as long as it remained at (b) (4) mg or above.

The Sponsor stated that opioid dependent patients on 16 to 24 mg of Suboxone would be enrolled in the 12-week safety study, and that approximately 300 subjects would be enrolled to ensure at least 200 completers at the end of 12 weeks.

The Division noted that the Sponsor can only reference the range of buprenorphine exposure with the ethanolic solution included in the Suboxone label. Thus, although an innovator could conceivably have access to data on a broader range of doses studied, the Sponsor of a 505(b)(2) application would only be able to reference the information in the label in support of the safety of the exposures observed with their product. The Division also stated that it cannot confirm that 300 patients would be adequate to ensure 200 completers through 12 weeks, because it will

depend on how many complete their dose level and how different the buprenorphine PK is from the reference drug.

The Sponsor stated that the protocol would include oxygen saturation monitoring and adverse event monitoring. Additionally, local toxicity would be assessed by dental hygienists. The Division suggested that the Sponsor submit the protocol with ample lead time prior to initiation of the trial so that the Division could include dental experts in the review.

The Sponsor inquired if published literature of clinical trials which were funded by NIDA were able to be referenced in a 505(b)(2) submission, even though they might include a proprietary tradename. The Division responded that it may be possible, but that it is not clear whether these studies would be in the public domain. If they were conducted under a Cooperative Research and Development Agreement, they may be considered proprietary. The Division advised that the Sponsor should submit the article(s) in question, and the Division would assist in determining if it was able to be included in a 505(b)(2) submission.

The Division stated that, since some patients are maintained on 32 mg of buprenorphine per day, which is outside of the labeled dosing (but included in widely-disseminated treatment guidelines created by organizations other than FDA or the manufacturer), the study should permit enrollment of these patients. The Sponsor stated that they would consider this request.

The Sponsor sought agreement that their planned safety study supported the excursion from bioequivalence from the referenced product, and that the study was acceptable as the pivotal study supporting the NDA. The Division stated that it was acceptable, as long as the maximum number of strips to be applied at once and the possible combinations of strips which comprise labeled doses are included in the study. The Sponsor stated that they have experience with dosing a maximum of (b)(4) films at once in the Onsolis development program.

Question 2 Assuming the results for the high dose ((b)(4) mg) of the BNX-103 study are as depicted in Table 7, does the Agency agree that the high dosage BNX product ((b)(4) mg) satisfies the equivalent exposure requirement with respect to the corresponding dose of Suboxone sublingual tablet for a 505(b)(2) submission?

FDA Response:

No, we do not agree. See our response to Question 1.

Discussion:

The Sponsor stated that they no longer intend to pursue the (b)(4) ratio of the high strength dosage ((b)(4)) and, therefore, there was no need for additional discussion.

Question 3 If the projected naloxone exposure at the (b) (4) mg dose is unacceptable, and the results for the high dose ((b) (4) mg) of the BNX-103 study are as depicted in Table 7, does the Agency agree that the high dosage BNX product ((b) (4) mg) satisfies the equivalent exposure requirement with respect to the corresponding dose of Suboxone sublingual tablet for a 505(b)(2) submission?

FDA Response:

No, we do not agree. See our response to Question 1.

Additional comment related to the precipitated withdrawal brief study report:

On face, the dose of naloxone and the 7.5:1 ratio of buprenorphine to naloxone used in the precipitated withdrawal study appear to contribute to the aversive effects of injected buprenorphine and naloxone when compared to injecting buprenorphine alone. The 3.25:1 ratio appeared to be more aversive than the 7.5:1 ratio. Additionally, it appears from the draft study report that a 0.1 mg dose of naloxone, given in conjunction with a 0.75 mg dose of buprenorphine, can produce aversive effects when injected by a subject dependent on a full opioid agonist. These results appear to be supportive of the utility of the naloxone contained in the low dose strength ((b) (4) mg) of your product, as well as the proposed 6:1 ratio in your high dose strength ((b) (4) mg). However, further review of the full study report will take place as part of the NDA review.

Discussion:

See discussion to Question 1.

General Discussion:

The Division stated that the proposed relative bioavailability study between the strip and the listed drug for both low strength and high strength is acceptable. In addition, the Sponsor needs to evaluate dose proportionality between low strength and high strength strips in order to warrant that multiple low strength strips will obtain the same exposure as an equivalent dose of high strength strip.

The Division inquired about the difference between low and high strength strips. The Sponsor clarified that they are compositionally proportional and differ only in size. The Division stated that the Sponsor may have the option to request a biowaiver for some of the PK studies. If the Sponsor chooses this pathway, then they need to submit a biowaiver request with an adequate justification.

The Sponsor sought clarification as to whether or not the plasma concentration of conjugated naloxone needed to be included in the NDA submission. The Division responded that the Office of Generic Drugs requires both conjugated and unconjugated drug concentration be measured, so a similar request is made of 505(b)(2) applicants. The Division also clarified that considering the point that naloxone is included in the formulation in an attempt to deter abuse, the Sponsor does not need to demonstrate bioequivalence to the listed drug in terms of naloxone exposure.

The Division noted that it would try to include a Post-Meeting Note containing the rationale for requiring both conjugated and unconjugated naloxone. The Division also noted that it would be open to discussion of this requirement if the Sponsor believes that measuring conjugated drug concentration is not needed for this product.

Post-Meeting Note:

Naloxone is only minimally absorbed via the oral route as it is rapidly converted to the glucuronide conjugate. The systemic exposure of unconjugated naloxone is much lower compared to the conjugated drug. Therefore, we usually require measurement of the conjugated drug concentration as well as the unconjugated drug. As noted during the meeting, you can submit a rationale for our review if you do not plan to measure the conjugated drug concentration.

The Sponsor stated that they are aware of a Citizens Petition which has been filed with the Agency and may have bearing on their 505(b)(2) submission. The Division responded that it was not aware of the specifics in the Citizens Petition at this time, but that it would try to find out whether the Sponsor's application would be affected. The Division stated that they would try to include a Post-meeting note to this effect.

Post-Meeting Note:

The Division has begun a discussion with the Office of Regulatory Policy regarding this Citizens Petition. However, no decisions have been made with respect to the merits of this Petition. We will communicate any decisions with you as soon as we are able.

Action Items:

1. The Sponsor will enroll a sufficient number of opioid-dependent patients in the 12-week safety study such that at least 200 complete all 12 weeks. The inclusion criteria should permit patients taking up to 32 mg a day of buprenorphine.
2. The Sponsor will assess their products for dose-proportionality and ensure that the drug exposure is equivalent regardless of whether the subject uses high dose strips or an equivalent dose comprised of lower dose strips.
3. The Division will try to address the two Post-Meeting Notes listed above.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW W SULLIVAN
02/28/2012



PIND 110267

MEETING MINUTES

BioDelivery Sciences International, Inc.
801 Corporate Center Dr, Suite 210
Raleigh, NC 27607

Attention: David T. Wright, PhD, RAC
Vice President, Regulatory Affairs

Dear Dr. Wright:

Please refer to your Pre-Investigational New Drug Application (PIND) file for BEMA buprenorphine NX (buprenorphine and naloxone).

We also refer to the meeting between representatives of your firm and the FDA on January 18, 2011. The purpose of the meeting was to discuss your IND submission and drug development program.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan, MS
Senior Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

SPONSOR MEETING MINUTES

MEETING DATE: January 18, 2011

TIME: 2:30 pm to 3:30 pm

LOCATION: FDA White Oak Campus
Silver Spring, MD

APPLICATION: PIND 110267

PRODUCT: BEMA buprenorphine NX (buprenorphine and naloxone)

INDICATIONS: Treatment of opioid dependence

SPONSOR: BioDelivery Sciences International

TYPE OF MEETING: Type B

MEETING CHAIR: Celia Winchell, MD, Clinical Team Leader, Division of Anesthesia and Analgesia Products (DAAP)

MEETING RECORDER: Matthew Sullivan, MS, Regulatory Project Manager, DAAP

FDA Attendees	Title
Bob A. Rappaport, MD	Division Director, Division of Anesthesia and Analgesia Products (DAAP)
Rigoberto Roca, MD	Deputy Division Director, DAAP
Celia Winchell, MD	Clinical Team Leader, DAAP
Pamela Horn, MD	Clinical Reviewer, DAAP
Suresh Doddapaneni, PhD	Clinical Pharmacology Team Leader, DAAP
Sheetal Agarwal, PhD	Clinical Pharmacology Reviewer, DAAP
Adam Wasserman, PhD	Pharmacology/Toxicology Supervisor, DAAP
Gary Bond, PhD	Pharmacology/Toxicology Reviewer, DAAP
Ramesh Raghavachari, PhD	CMC Lead ONDQA
Stephen Sun, MD	Medical Officer, CSS
Matthew Sullivan, MS	Regulatory Project Manager, DAAP
BioDelivery Sciences	Title
David Wright, PhD, RAC	Vice President, Regulatory Affairs (BDSI Delegation Head)
Renee Boerner, PhD	Director, Regulatory Affairs
Niraj Vasisht, PhD	Senior Vice President, Product Development
Susan Kerls	Associate Director, Clinical and Regulatory Science
Andrew Finn, PharmD	Executive Vice President, Product Development

Meeting Objective(s): To discuss questions related to the IND submission and development plans for BEMA buprenorphine NX.

Opening Discussion: Following introductions, the discussion focused on the Sponsor's questions that were included in the October 29, 2010, meeting package. Written comments were sent to the Sponsor on January 14, 2011, and are shown in bold text. The Sponsor's questions are shown below in italic text, and the discussion is shown in normal text.

Quality (Chemistry, Manufacturing and Controls) Questions

Question 1 Does the Agency have any concerns regarding naloxone hydrochloride dihydrate drug substance produced by [REDACTED] (b)(4) ?

Division Response:

Based on the limited information provided, we have no additional comments.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 2 Does the Agency have any comments on the proposed naloxone hydrochloride dihydrate drug substance release specifications for the initial IND submission?

Division Response:

Your proposal is acceptable for the initial IND submission.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 3 Will any additional characterization of the naloxone hydrochloride dihydrate drug substance be required for the NDA submission?

Division Response:

For the NDA, the characterization requirements will depend upon the review of the DMF referenced in your application. We expect you to follow ICH guidances Q3A and Q6A for both your drug substances.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 4 Does the Agency have any comments on the proposed BEMA Buprenorphine NX drug product release and stability specifications for the initial IND submission?

Division Response:

Based on the limited information provided, we have no additional comments for the IND submission.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 5 Will any additional characterization of the BEMA Buprenorphine NX drug product be required for the NDA submission?

Division Response:

Based on the limited information provided, your strategy for characterizing the drug product appears to be acceptable.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 6 Does the Agency have any comments on the proposed BEMA Buprenorphine NX dosage form color and ink marking system?

Division Response:

We recommend that you develop a drug product that would be user friendly to the patient and that would not cause any confusion during administration, particularly with respect to product's transparency, markings, and proper positioning in the buccal area.

Discussion:

The Sponsor stated that they are planning to maintain a uniform color throughout the product, partially to hinder attempts to separate the buprenorphine layer from the naloxone layer. The Sponsor also stated that the product would be opaque and the ink marking would not be visible on the unmarked side of the product. Additionally, the Sponsor stated that the mucoadhesive layer will stick to the buccal mucosa, but the other side will not. The Division reiterated its concern that patients may not be able to easily identify the correct side of the product to place in contact with the oral mucosa. The Sponsor stated that the product would not work if it were applied backwards, and that they understood the Division's concern and will work to address it.

Question 7 Does the Agency have any comments on the proposed extraction study for BEMA Buprenorphine NX drug product?

Division Response:

We can not provide meaningful comments until the formulation, manufacturing process, and the physical dimensions of the drug product are decided. However, you must provide data demonstrating that your product releases sufficient naloxone under conditions of misuse to precipitate withdrawal in persons dependent on full agonist opioids.

Information should be obtained on how much drug substance might be released and any changes that could take place in the rate of release of the drug from the final drug product if it is misused either intentionally or unintentionally. The effects of changes in pH, temperature, and solvent polarity on disruption or destruction of the drug product matrix should be evaluated. Additional experimental variables may include exposure times to the solvent, agitation, varying the surface area (such as from intact to being ground, crushed, or cut up into pieces), and ease of crushing tablets or destroying the dosage form matrix.

Discussion:

The Division advised that the extraction study will need to measure not only the ratio of buprenorphine to naloxone that was extracted, but also the total extracted doses. The Division noted that, while the ratio of buprenorphine to naloxone is important, there may also be a level of naloxone below which withdrawal would not be precipitated under conditions of misuse (i.e. intravenous injection) for those dependent on full-agonist opioids. The Division clarified that, while the literature shows that there is some blunting of euphoria when buprenorphine and naloxone are injected together, the best evidence for abuse deterrence for buprenorphine/naloxone combination products comes from the aversive reaction experienced by those who are dependent on full-agonist opioids when they inject buprenorphine and naloxone. The Division further noted that, if the nominal dose of naloxone in some of the strengths developed is below the level which is known to produce withdrawal when administered parenterally in combination with buprenorphine, behavioral pharmacology studies may be necessary to show that the product will be aversive under conditions of misuse in this population. The Sponsor asked if increasing the amount of naloxone in the lowest strength product (and therefore lowering the buprenorphine:naloxone ratio) would be acceptable. The Division replied that it may be acceptable, but if the buprenorphine:naloxone ratio in the formulation is different than 4:1, it would affect their ability to reference Suboxone. The Sponsor also asked whether a product containing only buprenorphine could be acceptable at the lowest doses. The Division advised that such a product would be acceptable if supported by appropriate evidence of safety and effectiveness and appropriate management of the risks of abuse. However, the Division cautioned that there was a possibility that such a product may not be well-accepted by prescribers.

Nonclinical Questions

Question 8 Does the Agency have any comments on the design and/or duration of the proposed 28-day buccal toxicity study for BEMA Buprenorphine NX in the proposed indication?

Division Response:
See our response to Question 10.

Discussion
See discussion related to Question 10.

Question 9 Does the Agency agree that the proposed 28-day buccal toxicity study can be conducted in parallel with the proposed clinical development of BEMA Buprenorphine NX?

Division Response:
See our response to Question 10.

Discussion
See discussion related to Question 10.

Question 10 Does the Agency agree that no additional nonclinical studies are required to support a 505(b)(2) NDA for BEMA Buprenorphine NX in the proposed indication?

Division Response:
Provided clinical exposures to BEMA Buprenorphine NX are within that of the listed drug, Suboxone, and with adequate monitoring for local toxicity in clinical trials, nonclinical studies to support the drug product during clinical development will not be necessary except as needed to address impurities which exceed ICH guidelines or the presence of novel excipients by identity, route, level, or duration.

In the absence of sufficient safety support of novel excipients from prior inclusion in approved products, information from literature or other sources, a chronic 9-month buccal study will need to be conducted using a placebo BEMA patch.

Should you conduct the proposed 28-day buccal study in the dog we have the following recommendations:

- 1. Ideally, if a single test dose is to be used, the final clinical formulation should be employed; otherwise, use multiple doses that meet or exceed the proposed clinical level of active pharmaceutical ingredients per cm² of disc.**

- 2. Include recovery groups, primarily for the purpose of observing reversibility of local toxicity.**

See Additional Comments section for further recommendations.

Discussion:

The Sponsor noted that all of the excipients in the product are listed in the FDA Inactive Ingredient Database, and that the expected exposures are less than those listed for route, dose, and total daily dose.

Clinical Questions

Question 11 Does the Agency have any comments related to the design or conduct of the clinical pharmacology studies described in the clinical development plan summary?

Division Response:

Please note that the following comments are based on the review of the brief summaries of studies provided in the package. Additional comments may be forthcoming if full protocols are submitted to the IND.

- 1. Design your pivotal BA/BE study(s) to demonstrate equivalent exposure for both buprenorphine and naloxone with respect to Cmax and AUC between your product and the listed product.**
- 2. Quantify the plasma level of buprenorphine's metabolite, norbuprenorphine.**
- 3. Evaluate the time it takes for the product to completely release buprenorphine when applied to the buccal mucosa as intended.**
- 4. Multiples of the two proposed strengths would need to be used to achieve intermediate doses. Address the feasibility and the dose-proportionality of intermediate doses (for instance, equivalent to 12 mg of Suboxone) with your product which is substantially different from the reference (in terms of route of administration and dosage form).**
- 5. The Agency is in agreement with your proposal to evaluate effect of ingested liquids on the pharmacokinetics of buprenorphine. Extend the plasma sampling duration to 48 hours and quantify the pharmacokinetics of naloxone and norbuprenorphine in addition to buprenorphine levels. Clarify whether the fed part of the study is intended to characterize the typical food effect, because the food effect characterization may not be needed.**
- 6. Data from the proposed TQT study BNX-150 is not required to be submitted with the NDA submission. Since the systemic exposure from your product is intended to be similar to Suboxone, labeling language related to QT prolongation may be applied to your product as well. If QT prolongation potential with the sublingual products is still open at the time of regulatory action on your NDA, you may have to submit these data as a post marketing requirement. However, based on your judgment, if you wish to conduct this**

study now and submit the data along with the NDA submission, the Agency is willing to provide feedback on the study design when a draft protocol is available.

Discussion:

The Sponsor requested that the Division clarify Item 1 regarding the design of BA/BE studies. The Division replied that the study should be designed such that BE analysis can be conducted for both the buprenorphine and naloxone moieties, including norbuprenorphine and unconjugated and total naloxone. Achieving BE is a requirement for the buprenorphine moiety; however, lower naloxone exposure with your product may be acceptable when the product is used as intended. The Sponsor acknowledged that they understood this requirement.

With respect to Item 4, the Sponsor stated that they plan to study intermediate doses in a cross-over design. The Division stated that this was acceptable. The Division also encouraged the Sponsor to develop a 16 mg dose, as it's the recommended dose. (b) (4)

Regarding Item 5, the Sponsor stated that they would reconsider the necessity of the food effect characterization.

Question 12 Does the Agency have any comments related to the design or conduct of the proposed initial clinical pharmacology study BNX-101?

Division Response:

Based on the brief study summary provided, BNX-101 appears to be a pilot study intended to guide formulation selection. We recommend that you extend the plasma sampling duration to 48 hours and also quantify (b) (4) plasma levels.

Discussion:

The Division clarified that the recommendation to assess (b) (4) in the pilot study is not a requirement, but that this assay would provide additional supportive data for the bioequivalence comparison. The Sponsor stated that they plan to measure total plus free naloxone and asked the Division if this was acceptable, to which the Division replied that it was acceptable.

Post-meeting note:

Upon further internal discussion, the Division recommends conducting BE analysis on both the unconjugated and total naloxone, individually.

Question 13 Compared to Suboxone sublingual tablets, does the Division agree that the clinical basis of approval for a BEMA Buprenorphine NX 505(b)(2) NDA in the proposed indication could be:

- a similar bioavailability for buprenorphine (i.e., similar Cmax and AUC); and*
- b lower than or equal to systemic exposure to naloxone (i.e., $\leq C_{max}$ and $\leq AUC$)?*

Division Response:

No. You have to demonstrate equivalent exposure (based on 90% confidence interval) with respect to buprenorphine between your product and the reference product. Lower naloxone exposure, when used as intended, would be acceptable because the naloxone is expected to play a role only when the product is not used as intended. However, the ability of the product to perform as expected with respect to precipitation of withdrawal under conditions of misuse is a review issue and would depend on the data and the justification provided in the NDA.

You propose to label your product for [REDACTED] (b) (4) maintenance use (as either Subutex and Suboxone are used). The product could be labeled for [REDACTED] (b) (4) use only if there is no detectable systemic exposure to naloxone. See response to Question 17.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 14 Does the Agency concur that no additional clinical pharmacology studies are required to support a 505(b)(2) NDA for BEMA Buprenorphine NX in the proposed indication?

Division Response:

Because there are no adequate and well-controlled studies of Suboxone as [REDACTED] (b) (4), we recommend that you develop [REDACTED] (b) (4) buprenorphine/naloxone buccal strips for [REDACTED] (b) (4) maintenance treatment of opioid dependence, respectively, similar to Subutex and Suboxone. You would have to demonstrate BE of your products to their respective approved counterparts to be able to effectively utilize their approved labels as references. If you wish to pursue buprenorphine/naloxone product for [REDACTED] (b) (4) maintenance treatments, you would have to provide data from adequate and well controlled study(s) establishing its use for [REDACTED] (b) (4). Also see our response to Question 17.

In addition, see our responses to Questions 11, 12 and 13.

Discussion:

[REDACTED] (b) (4)

(b) (4)

Question 15 Does the Agency concur that no clinical efficacy studies are required to support a 505(b)(2) NDA for BEMA Buprenorphine NX in the proposed indication?

Division Response:

If equivalent exposure is demonstrated between your product and the reference product (including similar T_{max} values) for both buprenorphine and naloxone, then a clinical efficacy study is not required to support labeling similar to that of Suboxone sublingual film, which represents the Agency's most current thinking on the labeling of a combination buprenorphine/naloxone product. However, clinical data in support of efficacy of the proposed product will be needed if equivalent exposure is not demonstrated and significant PK differences exist between your product and the reference.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 16 Does the Agency concur that no additional clinical safety information (i.e., other than the information from the proposed clinical pharmacology studies) is required to support a 505(b)(2) NDA for BEMA Buprenorphine NX in the proposed indication?

Division Response:

If exposure for buprenorphine or naloxone is higher than the reference product (C_{max} and AUC values), then additional safety data will be required.

Irrespective of the systemic exposure of buprenorphine or naloxone of your product, additional safety data will need to be submitted addressing the potential for local toxicity. Subjects will need to be examined by a professional qualified to perform

examinations of the buccal mucosa and assess evidence of local toxicity. Safety data must be collected in at least 200 patients for a minimum of 12 weeks.

Discussion:

There was no discussion beyond the Division's initial written response.

Regulatory Questions

Question 17 Does the Agency have any comments on the proposed indication: treatment of opioid dependence (i.e., (b) (4) maintenance treatment)?

Division Response:

(b) (4)
If the product delivers detectable naloxone (b) (4), then the following indication is acceptable: "for the maintenance treatment of opioid dependence". (b) (4)
(b) (4)

Be informed that maintaining a 4:1 ratio of buprenorphine:naloxone is not sufficient to ensure that the product will perform as intended under conditions of misuse (i.e., that it will precipitate withdrawal in persons dependent on full agonists). Therefore, it is also essential that an adequate naloxone dose be maintained in your product to ensure that the naloxone component performs as intended. Studies of the lowest doses of the product under conditions of misuse may be needed to demonstrate this.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 18 Although the planned BEMA Buprenorphine NX cannot reference Suboxone (buprenorphine and naloxone) sublingual film, can the recently approved prescribing information for this product be considered the Agency's current thinking on labeling for buprenorphine and naloxone products in this indication?

Division Response:

Yes, the recently approved prescribing information for this product should be considered the Agency's current thinking on labeling for buprenorphine and naloxone products in this indication.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 19 Does the Agency agree that the 30AUG2010 approval of Suboxone sublingual film for maintenance treatment of opioid dependence is not an impediment to approval of BEMA Buprenorphine NX for treatment of opioid dependence within the normal 10 month PDUFA timeframe?

Division Response:

We agree that the August 30, 2010, approval of Suboxone sublingual film for maintenance treatment of opioid dependence is not an impediment to approval of BEMA Buprenorphine NX for treatment of opioid dependence within the normal 10 month PDUFA timeframe.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 20 Can the Agency share any thoughts on risk management plans for BEMA Buprenorphine NX in the proposed indication, eg, would a Risk Evaluation and Mitigation Strategy (REMS) be based on a Medication Guide without specific Elements to Assure Safe Use?

Division Response:

We refer you to the REMS for Suboxone sublingual film (NDA 022410) in planning your REMS.

Discussion:

There was no discussion beyond the Division's initial written response.

Question 21 Would the Division consider a priority review for the NDA submission?

Division Response:

You have indicated that your rationale for this request is as follows:

One of BDSI's key objectives in the development of BEMA Buprenorphine NX for treatment of opioid dependence is to establish that the absolute bioavailability of buprenorphine from BEMA Buprenorphine NX is greater than from Subutex/Suboxone (together with lower systemic exposure to naloxone). We believe that bioequivalence for buprenorphine will be established between the products using lower buprenorphine doses in BEMA Buprenorphine NX. Based on current data, BEMA Buprenorphine NX films containing (b) (4) mg buprenorphine/naloxone should be approximately bioequivalent to Suboxone tablets containing 8/2 mg buprenorphine/naloxone. Thus, from a public health standpoint, BEMA Buprenorphine NX may be less appealing for misuse, abuse, addiction, and overdose following extraction of buprenorphine due to the lower buprenorphine content. In essence, this property is a corollary to the priority review criterion "documented enhancement of patient compliance.

Based on the information you have provided, we do not anticipate that the NDA submission will receive a priority review. Diverted units of existing tablet products are commonly divided into smaller doses for abuse; therefore, simply providing a smaller number of milligrams per dose does not represent a clear improvement over the existing product. Moreover, the low dose of naloxone in the product may impair the product's ability to perform as expected under conditions of misuse.

Discussion:

The Sponsor stated that the bioavailability of their product would be higher than that of the referenced product, so there would be less buprenorphine needed to achieve the same effect. Because there was less buprenorphine available to be abused or diverted, the Sponsor claimed that this would represent a public health benefit. As such, the Sponsor stated that fast-track designation and priority review would be appropriate.

The Division replied that it is unlikely that this product would qualify for either of these programs, based on the above rationale. The Division also clarified that granting fast-track designation and priority review are separate from each other. Because existing tablets on the market are currently known to be divided and abused in doses as small as 1 mg (which can produce a euphoric effect) and the amount of buprenorphine expected to be available in the BEMA buprenorphine NX product is within the range that is currently abused, the Division stated that there would be no clear public health benefit. The Division additionally noted that the route of administration influences the subjective experience of users irrespective of dose.

The Sponsor stated that they would like to demonstrate that their product can't be snorted, dissolved or injected. The Division responded that these types of claims are abuse-deterrence claims. The Division stated that it would consider data collected from robust studies which support the assertion that the BEMA buprenorphine NX product is more tamper-resistant than the reference product at the time of filing.

ADDITIONAL COMMENTS

- 1. The granting of orphan designation is performed by the Office of Orphan Products. Subutex received orphan drug designation on June 15, 1994, and Suboxone received orphan drug designation on October 27, 1994, prior to the 2000 Drug Addiction Treatment Act and the institution of office-based opioid-dependence treatment with buprenorphine products.**
- 2. If orphan designation is not granted, you will be obliged to fulfill the pediatric requirements under the Pediatric Research Equity Act (PREA).**
- 3. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at**

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at **<http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-voll.pdf>**).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You must establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

4. Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the published domain impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.
5. The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label.
6. New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance document: Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the CDER web page at the following **<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>**.

As noted in the document cited above, “the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration.” (emphasis added).

7. Any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as described in ICHQ3A(R2) and ICHQ3B(R2) guidances at the time of NDA submission.

Adequate qualification would include:

- a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies; e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - b. Repeat dose toxicology of appropriate duration to support the proposed indication.
8. Genotoxic, carcinogenic or impurities that contain a structural alert for genotoxicity must be either reduced to NMT 1.5 mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative *in vitro* bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICHS2A guidance document titled “Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals.” Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.
 9. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICHQ3A and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.
 10. Failure to submit adequate impurity qualification or justification for the safety of new excipient use may result in a Refusal-to-File or other adverse action.

Discussion:

With respect to Comment 4, the Sponsor inquired if they could submit a summary of the reference product for the IND, with the remainder of the nonclinical summary being presented with the NDA. The Division stated that this was acceptable.

Post-meeting Note:

We note that, due to increased bioavailability with your drug product, your total daily dose may be lower than the referenced drug product yet provide comparable exposure levels. Most of the nonclinical data in the referenced drug product labeling includes exposure margins that are based on body surface extrapolations. Exposure margins are necessary to put the nonclinical findings into clinical perspective. Adjusting the body surface area exposure margins based on total daily dose alone would imply a greater safety margin, which would be inaccurate and misleading if the actual exposure with your product is comparable to the referenced drug product. For your eventual product labeling, you will need to take this into consideration and either propose adequate language that is scientifically accurate, clinically meaningful, and not misleading or provide actual exposure data to revise the safety margins. The latter may require animal toxicokinetic studies that mimic the dosing regimen employed in the studies cited in the referenced product labeling. We encourage further discussion of this issue prior to NDA submission.

General Discussion:

The Division reminded the Sponsor that they would be subject to the Pediatric Research Equity Act (PREA) unless they received Orphan Drug designation. The Sponsor stated that they understood.

The Sponsor then stated that their plan is to submit 9 months of real-time and 6 months of accelerated stability data with the NDA submission. The Division stated that this was acceptable, but that the expiry would be based upon data available at the time of submission.

Action Items:

1. The Sponsor will develop their lowest dose BEMA buprenorphine NX product with the level of naloxone in mind. Additional behavioral pharmacology studies may be necessary to confirm that the dose of naloxone adds meaningfully to the product.
2. The Sponsor will submit a clinical protocol to study induction. Efficacy should be assessed at multiple timepoints throughout the study. The study should be designed so that approximately 200 subjects complete the study.
3. The Sponsor will design their pivotal BA/BE study(s) to demonstrate equivalent exposure for buprenorphine and naloxone with respect to C_{max} and AUC between BEMA buprenorphine NX and the listed product.

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/s/

MATTHEW W SULLIVAN
02/10/2011