

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207932Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207932

SUPPL #

HFD # 170

Trade Name Belbuca

Generic Name buprenorphine

Applicant Name Endo Pharmaceuticals, Inc.

Approval Date, If Known October 23, 2015

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)

b) 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:

c) Did the applicant request exclusivity?

YES NO

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

d) 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# 205637	Bunavail
NDA# 021306	Butrans Transdermal System
NDA# 022410	Suboxone film
020732	Subutex tablets
018401	Buprenex

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#

NDA#

NDA#

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:

Protocol EN3409-307

A Phase 3, double-blind, placebo-controlled, multicenter, randomized withdrawal study to evaluate the analgesic efficacy, safety, and tolerability of BEMA® buprenorphine in opioid-experienced subjects with moderate to severe chronic low back pain requiring around-the-clock opioid analgesia for an extended period of time

Protocol EN3409-308

A Phase 3, double-blind, placebo-controlled, multicenter, randomized withdrawal study to evaluate the analgesic efficacy, safety, and tolerability of BEMA® buprenorphine in opioid-naive subjects with moderate to severe chronic low back pain requiring around-the-clock opioid analgesia for an extended period of time

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"):

Protocol EN3409-307

A Phase 3, double-blind, placebo-controlled, multicenter, randomized withdrawal study to evaluate the analgesic efficacy, safety, and tolerability of BEMA® buprenorphine in opioid-experienced subjects with moderate to severe chronic low back pain requiring around-the-clock opioid analgesia for an extended period of time

Protocol EN3409-308

A Phase 3, double-blind, placebo-controlled, multicenter, randomized withdrawal study to evaluate the analgesic efficacy, safety, and tolerability of BEMA® buprenorphine in opioid-naive subjects with moderate to severe chronic low back pain requiring around-the-clock opioid analgesia for an extended period of time

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 # 72428 YES !
! NO
! Explain:

Investigation #2
IND # 72428 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:

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: Spiros Nicols, PharmD, MBA

Title: Regulatory Project Manager

Date: October 22, 2015

Name of Office/Division Director signing form: Sharon Hertz, MD

Title: Director, Division of Anesthesia, Analgesia, and Addiction Products

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

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

/s/

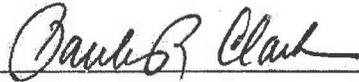
SPIROS NICOLS
10/23/2015

SHARON H HERTZ
10/23/2015

1.3. Administrative Information

3. DEBARMENT CERTIFICATION

Endo Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Paula R. Clark

Senior Director, Regulatory Affairs Liaison

December 16, 2014

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 207932 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: Belbuca Established/Proper Name: buprenorphine Dosage Form: buccal film		Applicant: Endo Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Spiros Nicols, PharmD, MBA		Division: Division of 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: October 1, 2015</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>October 23, 2015</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.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 5 (New manufacturer)
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input checked="" 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 | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: [CST SharePoint](#))

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: 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)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ 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) Approval October 23, 2015
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 checked="" type="checkbox"/> Patient Package Insert <input checked="" 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> 	Acceptability letter February 6, 2015. Review of proprietary name January 30, 2015
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> March 6, 2015 DMEPA: <input checked="" type="checkbox"/> April 24, 2015, August 6, 2015, September 1, 2015, September 4, 2015 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> July 30, 2015, October 21, 2015, October 23, 2015 OPDP: <input type="checkbox"/> None SEALD: <input checked="" type="checkbox"/> March 6, 2015 CSS: <input checked="" type="checkbox"/> July 27, 2105 Product Quality <input type="checkbox"/> None Other: <input checked="" type="checkbox"/> None Pediatric Labeling Review October 20, 2015, Pediatric and Maternal Health Review September 29, 2015
Administrative / Regulatory Documents	

<ul style="list-style-type: none"> ❖ RPM Filing Review⁴/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 	<p>March 17, 2015</p> <p><input type="checkbox"/> Not a (b)(2) October 14, 2015</p>
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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
<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
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>February 17, 2015</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
<ul style="list-style-type: none"> ❖ 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, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	Several
<ul style="list-style-type: none"> ❖ 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) 	Several
<ul style="list-style-type: none"> ❖ 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>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	

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

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
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 October 23, 2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None October 22, 2015
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 3 total October 23, 2015
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	September 9, 2015
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input 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>)	September 10, 2015
❖ 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 August 27, 2015
❖ Risk Management	October 23, 2015, October 21, 2015
• 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>)	October 22, 2015
• 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>)	<input type="checkbox"/> None October 23, 2015, October 22, 2015
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested July 22, 2015 and July 23, 2015
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 type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None October 7, 2015

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 September 11, 2015
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None September 17, 2015
❖ 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 type="checkbox"/> None requested August 6, 2015. Note included above on page 5 entry
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input type="checkbox"/> None September 11, 2015
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input type="checkbox"/> None
❖ 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>	Septmeber 11, 2015
<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"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • 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>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<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

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/s/

SPIROS NICOLS
10/28/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Friday, September 18, 2015 1:37 PM
To: 'Clark, Paula'
Subject: RE: EXTERNAL: NDA 207932 Belbuca Information Request

Importance: High

Dear Paula,

Our Medical Officer apologizes for the following error:

Can you let them know that in the left hand columns, the > signs are supposed to be ≥ signs (didn't copy correctly when I transferred it between documents).

Thanks,

Sincerely,

Spiros

From: Clark, Paula [<mailto:Clark.Paula@endo.com>]
Sent: Friday, September 18, 2015 12:18 PM
To: Nicols, Spiros
Cc: Sullivan, Matthew
Subject: RE: EXTERNAL: NDA 207932 Belbuca Information Request

Thank you!

Paula Clark

Senior Director, Regulatory Affairs Liaison

Endo 1400 Atwater Drive, Malvern, PA 19355

484-216-7397 (b) (6) mobile

clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]
Sent: Friday, September 18, 2015 12:05 PM
To: Clark, Paula
Cc: Sullivan, Matthew
Subject: RE: EXTERNAL: NDA 207932 Belbuca Information Request

Dear Paula,

This table was generated by FDA. The origin of the data is from the data set submitted by Endo and referenced by our Medical Officer in the IR.

Sincerely,

Spiros

From: Clark, Paula [<mailto:Clark.Paula@endo.com>]
Sent: Friday, September 18, 2015 11:54 AM
To: Nicols, Spiros
Cc: Sullivan, Matthew
Subject: RE: EXTERNAL: NDA 207932 Belbuca Information Request

Hi – my team members are asking if this table was generated by FDA or Endo.

Thanks.

Paula Clark

Senior Director, Regulatory Affairs Liaison
Endo 1400 Atwater Drive, Malvern, PA 19355
484-216-7397 (b) (6) mobile
clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]
Sent: Friday, September 18, 2015 11:00 AM
To: Clark, Paula
Cc: Sullivan, Matthew
Subject: EXTERNAL: NDA 207932 Belbuca Information Request
Importance: High

Dear Paula,

I have received an information request from our Medical Officer/Clinical Reviewer. I have copied and pasted her request below. She has kindly asked that this information be communicated by Monday. Can you please contact Matt Sullivan when this information is available as I will be on leave next week. I have cc'd Matt.

Hi Spiros,

I have done some tabulations of ECG data and they do not match exactly with what the firm reported in their clinical study reports. Can you send them an IR and ask for a response by Monday?

Please evaluate all values in these tabulations for accuracy and explain any discrepancies that you identify. These values were generated from the updated ADEG dataset of the ISS submitted 4/15. The highlighted values appear to conflict with those reported in the clinical study reports for studies 307 and 308.

Table 1: QTcF tabulations studies 307, 308, and 309

	Open-label buprenorphine^[1] N=2065	Double-blind^[2] buprenorphine N=483	Double-blind placebo N=488
ECG 450 msec +	32 (1.5%)	(b) (4)	(b) (4)
ECG change >10 msec from	414 (20%)	(b) (4)	(b) (4)

baseline			
ECG change >30 msec from baseline	75 (4%)	(b) (4)	(b) (4)
ECG change >60 from baseline	5 (0.2%)	0	(b) (4)

¹All open-label periods of studies 307, 308, and 309

² Studies 307 and 308

Table 2: QTcF tabulations by dose level during double-blind period of studies 307 and 308

	Buprenorphine						Placebo N=488
	150 N=68	300 N=97	450 N=140	600 N=43	750 N=42	900 N=93	
ECG 450 msec +	0	2 (2%)	(b) (4) (4%)	1 (2%)	4 (10%)	(b) (4)	(b) (4)
ECG change >10 msec from baseline	(b) (4)						(b) (4)
ECG change >30 msec from baseline	(b) (4)						(b) (4)

If you have any questions please let me know.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
 Regulatory Health Project Manager
 DAAAP, ODE II, FDA, CDER
 10903 New Hampshire Ave Bldg 22, Rm 3111
 Silver Spring, MD 20993
 Office: 240.402.5988

^[1] All open-label periods of studies 307, 308, and 309

^[2] Studies 307 and 308

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/s/

SPIROS NICOLS
10/26/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Monday, October 19, 2015 10:48 AM
To: 'Clark, Paula'
Subject: NDA 207932 Label (PI, MG, IFU)
Attachments: Belbuca Package Insert-2015-10-12.docx; Belbuca-IFU_2015-10-12.doc; Belbuca-MG_2015-10-12.doc

Dear Paula,

Please find the attached labeling that the Division has reviewed in Tracked Changes format.

Please let me know if you have questions.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

From: Clark, Paula [<mailto:Clark.Paula@endo.com>]
Sent: Thursday, October 15, 2015 9:58 AM
To: Nicols, Spiros
Subject: RE: EXTERNAL: NDA 207932 Belbuca FDA Form 356h

Hi Spiros:

Thanks I will speak to our operations team to ensure that it is corrected.

As FYI, please also note that next week I will be in the White Oak area for a different Division FDA meeting (takes place on Wednesday; we are in preparation at a Hotel in Silver Spring on Tuesday). I will be watching for any emails you may send regarding Belbuca and will be checking voicemail as well; that's not an issue.

I will be remote if I need to gather the team to review labeling (package insert) comments. I know I have been asking – but do you have any idea if we may get return comments on our edits/changes to the package insert from the Division before Tuesday?

Thanks!

Paula Clark
Senior Director, Regulatory Affairs Liaison
Endo 1400 Atwater Drive, Malvern, PA 19355

484-216-7397 (b) (6) mobile
clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]
Sent: Thursday, October 15, 2015 9:50 AM
To: Clark, Paula
Subject: EXTERNAL: NDA 207932 Belbuca FDA Form 356h

Dear Paula,

Endo revised the FDA 356h form to include our requirement for "Relied Upon Product" in Box 20 to NDA 020732 instead of ANDA 78633 on 13 February, however, subsequent to that submission all submissions have retained the ANDA 78633 in Box 20 (at least 26 March through 14 September). Please address this request when you are able to. Let me know if you require further clarification.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

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/s/

SPIROS NICOLS
10/26/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Wednesday, October 21, 2015 2:35 PM
To: 'Clark, Paula'
Cc: Brown, Wendy
Subject: RE: EXTERNAL: NDA 207932 Belbuca ER/LA Blueprint
Attachments: risk-manage-rem-s-support_July 2015.doc

Importance: High

Dear Paula,

This additional information attachment and the below should be helpful to your team.

The Agency has reviewed your supporting document submission and finds the changes acceptable. The attached document incorporates those changes in the most recent version of the ER/LA Opioid Analgesic REMS supporting document.

Thanks!

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

From: Clark, Paula [mailto:Clark.Paula@endo.com]
Sent: Wednesday, October 21, 2015 2:05 PM
To: Nicols, Spiros
Cc: Brown, Wendy
Subject: RE: EXTERNAL: NDA 207932 Belbuca ER/LA Blueprint

Thank you. Will share with our REMs team.

Kind regards,

Paula Clark
Senior Director, Regulatory Affairs Liaison
Endo 1400 Atwater Drive, Malvern, PA 19355
484-216-7397 (b) (6) mobile
clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]
Sent: Wednesday, October 21, 2015 1:26 PM
To: Clark, Paula
Cc: Brown, Wendy
Subject: RE: EXTERNAL: NDA 207932 Belbuca ER/LA Blueprint

Dear Paula,

Please see the below reply to your question from my colleague.

DRISK does not share the supporting document (SD) with Sponsor companies. Endo is a member of the RPC and should have access to the most recent version of the SD. Endo just needs to submit the current version of the SD with the proposed changes (addition of “Belbuca” and “buprenorphine-containing buccal films”) included.

DRISK has reviewed Endo’s submission from 12/23/2014 and we are ok with the changes they made to the SD.

If need further clarity please let me know.

On a related matter, for tomorrow’s teleconference we will be calling you shortly after 1:35 and not at 1:30.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

From: Clark, Paula [<mailto:Clark.Paula@endo.com>]
Sent: Wednesday, October 21, 2015 10:14 AM
To: Nicols, Spiros
Cc: Brown, Wendy
Subject: RE: EXTERNAL: NDA 207932 Belbuca ER/LA Blueprint

Dear Spiros:

I have forwarded this to our REMS team for rapid review – do have a quick question.

Should we expect to see an updated REMS supporting document, assuming that it was also changed not only with pending Belbuca, but also with the approval of Morphabond?

Thanks and kind regards,

Paula Clark

Senior Director, Regulatory Affairs Liaison

Endo 1400 Atwater Drive, Malvern, PA 19355

484-216-7397 (b) (6) mobile

clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]
Sent: Wednesday, October 21, 2015 9:33 AM
To: Clark, Paula
Cc: Brown, Wendy
Subject: EXTERNAL: NDA 207932 Belbuca ER/LA Blueprint
Importance: High

Dear Paula,

I am sending you the attached ER/LA Blueprint for Endo's review. The Division requests that you review as soon as possible and have send back to us by tomorrow afternoon. I have included comments from the Office of Surveillance and Epidemiology immediately below.

COMMENTS FOR THE APPLICANT

The Office of Surveillance and Epidemiology (OSE), DRISK has completed the review of ER/LA Opioid Analgesic REMS document, appended materials submitted on December 23, 2014. DRISK has the following comments, below, in response to the Sponsor's proposal, including redlined/highlighted changes to the ER/LA Opioid Analgesic REMS document and appended materials.

1. Update the *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics* as described in the attached redlined document. Note this verison is the most recently approved ER/LA Opioid Analgesic REMS approved on October 2, 2015 which includes Morphabond's ® product specific information. This document must be aligned with any changes, if any, made to the Belbuca Prescribing Information.
2. The "Most Recent Modification" date on the REMS document must be changed to "XX/XXXX" as indicated in the redlined, attached REMS document when resubmitted to the Agency. If this product is approved, this date will be updated by the Agency to reflect the approval date.
3. Resubmission and Format Instructions:
 - a. Resubmission Requirements and Instructions: Submit the revised proposed ER/LA Opioid Analgesic REMS for Belbuca with appended materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.
 - b. Format Request: As noted previously, please submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. Please also submit for the Agency's review mocked up PDF versions of all the materials and webpages which show the intended layout and graphic design of each.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

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/s/

SPIROS NICOLS
10/26/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Wednesday, October 21, 2015 1:27 PM
To: 'Clark, Paula'
Cc: Brown, Wendy
Subject: RE: EXTERNAL: NDA 207932 Belbuca ER/LA Blueprint

Dear Paula,

Please see the below reply to your question from my colleague.

DRISK does not share the supporting document (SD) with Sponsor companies. Endo is a member of the RPC and should have access to the most recent version of the SD. Endo just needs to submit the current version of the SD with the proposed changes (addition of “Belbuca” and “buprenorphine-containing buccal films”) included.

DRISK has reviewed Endo’s submission from 12/23/2014 and we are ok with the changes they made to the SD.

If need further clarity please let me know.

On a related matter, for tomorrow’s teleconference we will be calling you shortly after 1:35 and not at 1:30.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

From: Clark, Paula [<mailto:Clark.Paula@endo.com>]
Sent: Wednesday, October 21, 2015 10:14 AM
To: Nicols, Spiros
Cc: Brown, Wendy
Subject: RE: EXTERNAL: NDA 207932 Belbuca ER/LA Blueprint

Dear Spiros:

I have forwarded this to our REMS team for rapid review – do have a quick question.

Should we expect to see an updated REMS supporting document, assuming that it was also changed not only with pending Belbuca, but also with the approval of Morphabond?

Thanks and kind regards,

Paula Clark

Senior Director, Regulatory Affairs Liaison

Endo 1400 Atwater Drive, Malvern, PA 19355

484-216-7397 (b) (6) mobile

clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]
Sent: Wednesday, October 21, 2015 9:33 AM
To: Clark, Paula
Cc: Brown, Wendy
Subject: EXTERNAL: NDA 207932 Belbuca ER/LA Blueprint
Importance: High

Dear Paula,

I am sending you the attached ER/LA Blueprint for Endo's review. The Division requests that you review as soon as possible and have send back to us by tomorrow afternoon. I have included comments from the Office of Surveillance and Epidemiology immediately below.

COMMENTS FOR THE APPLICANT

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the document 508 compliant. Please also submit for the Agency's review mocked up PDF versions of all the materials and webpages which show the intended layout and graphic design of each.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

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SPIROS NICOLS
10/26/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Wednesday, October 21, 2015 9:33 AM
To: 'Clark, Paula'
Cc: Brown, Wendy
Subject: NDA 207932 Belbuca ER/LA Blueprint
Attachments: Belbuca_ERLA Opioid REMS Complete_TC.doc

Importance: High

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Paula,

I am sending you the attached ER/LA Blueprint for Endo's review. The Division requests that you review as soon as possible and have send back to us by tomorrow afternoon. I have included comments from the Office of Surveillance and Epidemiology immediately below.

COMMENTS FOR THE APPLICANT

The Office of Surveillance and Epidemiology (OSE), DRISK has completed the review of ER/LA Opioid Analgesic REMS document, appended materials submitted on December 23, 2014. DRISK has the following comments, below, in response to the Sponsor's proposal, including redlined/highlighted changes to the ER/LA Opioid Analgesic REMS document and appended materials.

1. Update the *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics* as described in the attached redlined document. Note this version is the most recently approved ER/LA Opioid Analgesic REMS approved on October 2, 2015 which includes Morphabond's ® product specific information. This document must be aligned with any changes, if any, made to the Belbuca Prescribing Information.
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Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

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/s/

SPIROS NICOLS
10/26/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Thursday, October 22, 2015 12:34 PM
To: 'Clark, Paula'
Subject: RE: EXTERNAL: RE: NDA 207932; 1:35 PM Teleconfernece - Confirmation if teleconference is required

Dear Paula,

Thanks! All of your emails to me have been received. Thank you for the ER/LA Blueprint. This must be submitted through the gateway.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

From: Clark, Paula [<mailto:Clark.Paula@endo.com>]
Sent: Thursday, October 22, 2015 12:23 PM
To: Nicols, Spiros
Subject: RE: EXTERNAL: RE: NDA 207932; 1:35 PM Teleconfernece - Confirmation if teleconference is required

HI - I have just left you a voicemail.

I have provided you with responses to all your emails today.

Note:

- We feel the teleconference can be cancelled.
- We have sent the Blueprint back and also copied Wendy at 11:19 today
- We acknowledge receipt of the information on labeling and have no further comment regarding language in section 5.7
- We acknowledge the query below and will send the Division information on how we arrived at 1590 – but I also have requested from you what number the Division has arrived at so we can get help with the discrepancy.
- **Please kindly acknowledge this email as I am concerned you are not receiving responses.**
- I believe we have fulfilled all requests with the exception of #2 below.

With kind regards,

Paula Clark

Senior Director, Regulatory Affairs Liaison

Endo 1400 Atwater Drive, Malvern, PA 19355

484-216-7397 (b) (6) mobile

clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]

Sent: Thursday, October 22, 2015 11:49 AM

To: Clark, Paula

Subject: EXTERNAL: RE: NDA 207932; 1:35 PM Teleconfernece - Confirmation if teleconference is required

Importance: High

Dear Paula,

Please see the below correspondence that I sent earlier this hour in which our Team Leader is asking if Endo still would like to cancel after reviewing the below information.

Dear Paula,

Please see the below response from our Medical Officer/Cross Disciplinary Team Leader regarding your most recent email earlier this morning.

Please let the company know that we want to keep the language as proposed (i.e., using the word recommended and not (b) (4)) because the QT effect still needs to be defined (i.e., through the PMR)

If they want to cancel the meeting, please let them know about our other two issues with labeling:

1. The image quality of the figures in section 14 need to be improved
2. They need to clarify the highlighted number below. We cannot reproduce it

Effects on Cardiac Electrophysiology

QTc prolongation with BELBUCA has been observed. Of the 1590 patients that were treated with BELBUCA in controlled and open-label chronic pain trials at doses up to 900 mcg every 12 hours, 2% demonstrated a prolongation of QTcF to a post-baseline value between 450 - 480 msec during therapy.

You will note that you have satisfied our request for no. 1 (image quality).

Sincerely,

Spiros

From: Clark, Paula [<mailto:Clark.Paula@endo.com>]

Sent: Thursday, October 22, 2015 11:41 AM

To: Nicols, Spiros

Subject: NDA 207932; 1:35 PM Teleconfernece - Confirmation if teleconference is required

Dear Spiros:

Can you kindly let us know if our teleconference will be held this afternoon so I know if we need to open the teleconference telephone lines or not.

If the teleconference is required, provided below are the Endo participants:

Sue Hall, Executive Vice President, Chief Scientific Officer, Global Head of R&D

Craig Paterson, MD, Chief Medical Officer

Paula Clark, Senior Director, Regulatory Affairs

With kind regards,

Paula Clark

Senior Director, Regulatory Affairs Liaison

Endo 1400 Atwater Drive, Malvern, PA 19355

484-216-7397 (b) (6) mobile

clark.paula@endo.com



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/s/

SPIROS NICOLS
10/26/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Thursday, October 22, 2015 11:28 AM
To: 'Clark, Paula'
Subject: RE: NDA 207932; Belbuca - Teleconference today - Endo Response

Importance: High

Dear Paula,

Please see the below response from our Medical Officer/Cross Disciplinary Team Leader regarding your most recent email earlier this morning.

Please let the company know that we want to keep the language as proposed (i.e., using the word recommended and not (b) (4)) because the QT effect still needs to be defined (i.e., through the PMR)

If they want to cancel the meeting, please let them know about our other two issues with labeling:

1. The image quality of the figures in section 14 need to be improved
2. They need to clarify the highlighted number below. We cannot reproduce it

Effects on Cardiac Electrophysiology

QTc prolongation with BELBUCA has been observed. Of the 1590 patients that were treated with BELBUCA in controlled and open-label chronic pain trials at doses up to 900 mcg every 12 hours, 2% demonstrated a prolongation of QTcF to a post-baseline value between 450 - 480 msec during therapy.

You will note that you have satisfied our request for no. 1 (image quality).

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

From: Clark, Paula [mailto:Clark.Paula@endo.com]
Sent: Thursday, October 22, 2015 9:43 AM
To: Nicols, Spiros
Subject: NDA 207932; Belbuca - Teleconference today - Endo Response

Dear Spiros:

We greatly appreciate the collaborative dialogue and want to continue in that spirit. The proposed language regarding QTc is informative, balanced and certainly more interpretable for prescribers. Without belaboring the issue further, we are very willing to accept the proposed language and respectfully ask if we could substitute the words (b) (4)

as opposed to "is recommended" (b) (4)

The language would subsequently read:

5.7 QTc Prolongation

BELBUCA has been observed to prolong the QTc interval in some subjects participating in clinical trials. Consider these observations in clinical decisions when prescribing BELBUCA to patients with hypokalemia, hypomagnesemia, or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Periodic electrocardiographic (ECG) monitoring (b) (4) in these patients. Avoid the use of BELBUCA in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval. [see *Dosage and Administration (2.3)*, *Adverse Reactions (6.1)*, and *Clinical Pharmacology (12.2)*].

Again, we appreciate your willingness to work with us on this matter and also want to be considerate of the timing close to the PDUFA date. We would very much appreciate your consideration of our proposal for a minor change."

In addition, we understand the requirement for the PMR as described below and have no further questions at this time. We can supply you with tentative dates if required.

Therefore, in respect to the Division's time, from our perspective we do not feel a teleconference is needed if these are the only remaining issues.

We look forward to your response.

Thank you and regards,

Paula Clark

Senior Director, Regulatory Affairs Liaison

Endo 1400 Atwater Drive, Malvern, PA 19355

484-216-7397 (b) (6) mobile

clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]

Sent: Thursday, October 22, 2015 7:47 AM

To: Clark, Paula

Subject: EXTERNAL: NDA 207932 Teleconference today

Importance: High

Dear Paula,

The language below is what the Division has proposed and will be the subject for a portion of the teleconference.

5.7 QTc Prolongation

BELBUCA has been observed to prolong the QTc interval in some subjects participating in clinical trials. Consider these observations in clinical decisions when prescribing BELBUCA to patients with hypokalemia, hypomagnesemia, or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Periodic electrocardiographic (ECG) monitoring is recommended in these patients. Avoid the use of BELBUCA in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval. [see *Dosage and Administration (2.3)*, *Adverse Reactions (6.1)*, and *Clinical Pharmacology (12.2)*].

In addition we the Division will require a multiple ascending dose study, please see below in preparation for our tcon.

On further consideration, we are going to require a multiple ascending dose study and a thorough QT study for Belbuca. The text of the PMRs follow below. We can discuss in more detail on the telecon this afternoon the rationale for these PMRs.

####-# Conduct a multiple ascending dose clinical trial in adults to determine the maximum tolerated dose of BELBUCA without co-administration of naltrexone to inform the dosing for a thorough QT (tQT) trial of BELBUCA.

The timetable you submitted on DATE states that you will conduct this trial according to the following schedule:

Final Protocol Submission: MM/YY
Study Completion: MM/YY
Final Report Submission: MM/YY

####-# Conduct a thorough QT trial in adults without naltrexone co-administration to assess the risk of QT prolongation with BELBUCA. This trial will provide information on the conduction effects of BELBUCA on the heart, specifically cardiac repolarization, at therapeutic and suprathreshold dose regimens. The tQT trial may be conducted as part of the required multiple ascending dose trial (PMR #####-#).

The timetable you submitted on DATE states that you will conduct this trial according to the following schedule:

Final Protocol Submission: MM/YY
Study Completion: MM/YY
Final Report Submission: MM/YY

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

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/s/

SPIROS NICOLS
10/26/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Friday, October 23, 2015 12:45 PM
To: 'Clark, Paula'
Cc: Sullivan, Matthew
Subject: NDA 207932 Belbuca Package Insert
Attachments: Belbuca Package Insert-sent to Endo 10-23-15.docx

Importance: High

Dear Paula,

Please find the attached PI for a final quick review by Endo. Let us know if you have any concerns.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

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SPIROS NICOLS
10/26/2015

Nicols, Spiros

From: Clark, Paula <Clark.Paula@endo.com>
Sent: Friday, October 23, 2015 11:10 AM
To: Nicols, Spiros
Cc: Chapman, Tara
Subject: RE: EXTERNAL: URGENT Please submit ALL of the associated REMS documents via the Gateway not just the Blueprint

Ok – I will submit all of them.

Thanks.

Paula

Paula Clark

Senior Director, Regulatory Affairs Liaison

Endo 1400 Atwater Drive, Malvern, PA 19355

484-216-7397 (b) (6) mobile

clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]
Sent: Friday, October 23, 2015 11:07 AM
To: Clark, Paula
Cc: Chapman, Tara
Subject: EXTERNAL: URGENT Please submit ALL of the associated REMS documents via the Gateway not just the Blueprint
Importance: High

Dear Paula,

There were changes that Endo made to multiple documents not only the Blueprint. We need a complete submission of all the REMS documents via the Gateway. If you have any questions let me know.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

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SPIROS NICOLS
10/26/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Friday, September 18, 2015 11:00 AM
To: 'Clark, Paula'
Cc: Sullivan, Matthew
Subject: NDA 207932 Belbuca Information Request

Importance: High

Dear Paula,

I have received an information request from our Medical Officer/Clinical Reviewer. I have copied and pasted her request below. She has kindly asked that this information be communicated by Monday. Can you please contact Matt Sullivan when this information is available as I will be on leave next week. I have cc'd Matt.

Hi Spiros,

I have done some tabulations of ECG data and they do not match exactly with what the firm reported in their clinical study reports. Can you send them an IR and ask for a response by Monday?

Please evaluate all values in these tabulations for accuracy and explain any discrepancies that you identify. These values were generated from the updated ADEG dataset of the ISS submitted 4/15. The highlighted values appear to conflict with those reported in the clinical study reports for studies 307 and 308.

Table 1: QTcF tabulations studies 307, 308, and 309

	Open-label buprenorphine ^[1] N=2065	Double-blind ^[2] buprenorphine N= 483	Double-blind placebo N=488
ECG 450 msec +	32 (1.5%)	(b) (4)	(b) (4)
ECG change >10 msec from baseline	414 (20%)	(b) (4)	(b) (4)
ECG change >30 msec from baseline	75 (4%)	(b) (4)	(b) (4)
ECG change >60 msec from baseline	5 (0.2%)	0	(b) (4)

¹All open-label periods of studies 307, 308, and 309

² Studies 307 and 308

Table 2: QTcF tabulations by dose level during double-blind period of studies 307 and 308

	Buprenorphine						Placebo N=488
	150 N=68	300 N=97	450 N=140	600 N=43	750 N=42	900 N=93	
ECG 450 msec +	0	2 (2%)	^(b) ₍₄₎ (4%)	1 (2%)	4 (10%)	^(b) ₍₄₎	^(b) ₍₄₎
ECG change >10 msec from baseline	^(b) ₍₄₎						^(b) ₍₄₎
ECG change >30 msec from baseline	^(b) ₍₄₎						^(b) ₍₄₎

If you have any questions please let me know.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
 Regulatory Health Project Manager
 DAAAP, ODE II, FDA, CDER
 10903 New Hampshire Ave Bldg 22, Rm 3111
 Silver Spring, MD 20993
 Office: 240.402.5988

^[1] All open-label periods of studies 307, 308, and 309

^[2] Studies 307 and 308

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SPIROS NICOLS
10/19/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Tuesday, August 04, 2015 1:46 PM
To: 'Clark, Paula'
Subject: RE: EXTERNAL: NDA 207932 Belbuca Information Request from Clinical Reviewer

Dear Paula,

Thank you very much for clarifying.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue Building 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988
Spiros.Nicols@fda.hhs.gov

From: Clark, Paula [<mailto:Clark.Paula@endo.com>]
Sent: Tuesday, August 04, 2015 8:25 AM
To: Nicols, Spiros
Subject: RE: EXTERNAL: NDA 207932 Belbuca Information Request from Clinical Reviewer

Dear Spiros:

The information we have provided regarding this request is summarized in section 12.5.5. in the CSRs respectively in Module 5 of the NDA.

Let me know if you need anything further.

Paula

Paula Clark
Senior Director, Regulatory Affairs Liaison
Endo 1400 Atwater Drive, Malvern, PA 19355
484-216-7397 (b) (6) mobile
clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]
Sent: Monday, August 03, 2015 4:00 PM

To: Clark, Paula

Subject: EXTERNAL: NDA 207932 Belbuca Information Request from Clinical Reviewer

Importance: High

Dear Paula,

I have been advised of another Information request from our Medical Officer/Clinical Reviewer. Please see the below request:

Please provide the location of the summary and discussion of the results of the prospective suicidal ideation and behavior assessments collected using the C-SSRS in controlled Phase 3 studies 307 and 308.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue Building 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988
Spiros.Nicols@fda.hhs.gov

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SPIROS NICOLS
10/19/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Wednesday, September 02, 2015 2:38 PM
To: 'Clark, Paula'
Subject: NDA 207932 Belbuca August 25, 2015 amendment: Revised Container Label and Carton

Importance: High

Dear Paula,

Thank you for your August 25, 2015 amendment: Revised Container Label and Carton.

Please see the below recommendation from the Division of Medication Error Prevention and Analysis.

The revised container label for the 600 mcg strength is unacceptable from a medication error perspective.

We recommend the Sponsor revise the presentation of the expiration date on the 600 mcg container label from (b) (4) to "MMYYYY" to mitigate the risk for confusion

Please let me know if you need further clarification.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

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SPIROS NICOLS
10/13/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Thursday, August 20, 2015 1:03 PM
To: 'Clark, Paula'
Subject: NDA 207932 Belbuca Recommendations for container labeling

Dear Paula,

Please find the following comments to be conveyed regarding the container labeling provided to the Division by the Division of Medication Error Prevention and Analysis:

The revised carton labeling is acceptable from a medication error perspective. The revised container labels are unacceptable from a medication error perspective. We recommend the Sponsor revise the presentation of the expiration date on the container labels from [REDACTED] ^{(b) (4)} to “MMMYYYY” to mitigate the risk for confusion.

Sincerely,

Spiros

Spiros Nicols PharmD MBA RPh
Regulatory Health Project Manager
DAAAP, ODE II, FDA, CDER
10903 New Hampshire Ave Bldg 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988

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SPIROS NICOLS
10/13/2015

Nicols, Spiros

From: Travis, James
Sent: Monday, June 22, 2015 7:24 AM
To: Nicols, Spiros
Cc: Cooner, Freda; Meaker, Katherine B; Horn, Pamela; Lloyd, Joshua
Subject: IR Request

Spiros,
We have the following IR for the sponsor.

James E. Travis, Ph.D.
FDA/CDER/OTS/OB/DBII
WO Bldg 21, Rm 3660
Office: (240) 402-4601

Conduct additional racial subgroup analyses in studies EN3409-307 and EN3409-308 taking the findings below into consideration. You should also include an exploration of any factors (e.g., gender, age, geographic region) that may be confounded with Race and an exploration of rescue medication usage patterns. Explain the treatment differences observed in the Black/African American subgroup.

- Note that you analyze the data from individual study using an analysis of covariance (ANCOVA) model with the subjects who had observed pain scores during Week 12. We observed that using this analysis the estimated treatment benefit in the Black/African American subgroup is substantially less than that of the White subgroup in the opioid experienced subjects (Study 307) and roughly comparable between the two subgroups in the opioid naïve population (Study 308).
- When the data are re-analyzed using either a Mixed-Model with Repeated Measures (MMRM) or using the imputation method specified for the primary analysis, both of which take into account the observed pain scores for subjects who discontinue from the study, we found that the estimated treatment benefit for Black/African American patients is substantially less in both studies than the estimated treatment benefit for White patients.
- The disposition patterns by race shows, in the opioid experienced study (307), approximately the same completion rate in both the treatment and placebo arms for the Black/African American subgroup compared to a 50% dropout rate in the White placebo arm. In the opioid naïve study (308) a higher dropout rate in the treatment arm than the placebo arm can be observed.

Repeat the additional analyses with the below changes to the data.

- Study EN3409-307:
 - Two subjects (1022-7028 and 1051-7017) discontinued from the study for reasons classified as protocol violation/other were imputed using multiple imputation in the primary analysis. These subjects are reclassified as withdrawn due to adverse events and should be imputed using screen observation carried forward.
- Study EN3409-308:
 - Six subjects (1006-8004, 1006-8013, 1019-8033, 1055-8011, 1064-8010, 1013-8049) were withdrawn from the study for reasons classified as protocol violation/other and were imputed using multiple imputation in the primary analysis. These subjects are reclassified as withdrawn due to adverse events and should be imputed using screen observation carried forward.

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SPIROS NICOLS
06/24/2015

Nicols, Spiros

From: Clark, Paula <Clark.Paula@endo.com>
Sent: Monday, May 18, 2015 12:57 PM
To: Nicols, Spiros
Subject: FW: EXTERNAL: Information Request please
Attachments: SAS programs requested by FDA (20150518).zip

Dear Spiros:

Attached are the requested SAS programs as requested this morning in the zip file attached.

These will also be submitted formally through the gateway.

Provided below is a TOC as well for the reviewer to access easily, which will also be included in the gateway submission.

Table of Content – FDA Requested Items

307		
Table Number	Program Name	Table Title
Table 14.2.14.1	t-pnc-itt-gender-e.sas	Table 14.2.14.1 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by Gender in Double-blind Treatment Phase ITT Population (Subjects at Site 1008 Excluded)
Table 14.2.14.3	t-pnc-itt-age-exc8.sas	Table 14.2.14.3 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by Age Group in Double-blind Treatment Phase ITT Population (Subjects at Site 1008 Excluded)
Table 14.2.14.9	t-pnc-itt-race-e.sas	Table 14.2.14.9 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by Race in Double-blind Treatment Phase ITT Population (Subjects at Site 1008 Excluded)
Table 14.2.14.10	t-pnc-itt-race.sas	Table 14.2.14.10 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by Race in Double-blind Treatment Phase ITT Population

308

Table Number	Program Name	Table Title
Table 14.2.14.1	t-pnc-itt-gender-e.sas	Table 14.2.14.1 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by Gender in Double-blind Treatment Phase ITT Population (Subjects at Site 1008 Excluded)
Table 14.2.14.3	t-pnc-itt-age-exc8.sas	Table 14.2.14.3 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by Age Group in Double-blind Treatment Phase ITT Population (Subjects at Site 1008 Excluded)
Table 14.2.14.7	t-pnc-itt-race-e.sas	Table 14.2.14.7 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by Race in Double-blind Treatment Phase ITT Population (Subjects at Site 1008 Excluded)
Table 14.2.14.8	t-pnc-itt-race.sas	Table 14.2.14.8 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by Race in Double-blind Treatment Phase ITT Population

ISE

Table Number	Program Name	Table Title
Table 14.2.5.1	t-pnc-itt-comb.sas	Table 14.2.5.1 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by the Combined Dose Group and Prior Opioid Experience in Double-blind Treatment Phase ITT Population

Table 14.2.6.1	t-pnc-itt-gender.sas	Table 14.2.6.1 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by Gender in Double-blind Treatment Phase ITT Population
Table 14.2.7.1	t-pnc-itt-age.sas	Table 14.2.7.1 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by Age Group in Double-blind Treatment Phase ITT Population
Table 14.2.7.5	t-pnc-itt-race.sas	Table 14.2.7.5 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by Race in Double-blind Treatment Phase ITT Population
Table 14.2.7.6	t-pnc-itt-race-s.sas	Table 14.2.7.6 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by Race in Double-blind Treatment Phase ITT Population (EN3409-307 and EN3409-308)
Table 14.2.7.7	t-pnc-itt-race-e.sas	Table 14.2.7.7 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by Race in Double-blind Treatment Phase ITT Population [Subjects at Site 1008 Excluded]
Table 14.2.7.8	t-pnc-itt-race-s-e.sas	Table 14.2.7.8 Descriptive Statistics of Weekly Change from Baseline in Average Numeric Rating Scale (NRS) Pain Intensity by Race in Double-blind Treatment Phase ITT Population (EN3409-307 and EN3409-308) [Subjects at Site 1008 Excluded]

Please let me know if you require anything further.

Paula Clark

Senior Director, Regulatory Affairs Liaison
Endo 1400 Atwater Drive, Malvern, PA 19355
484-216-7397 (b) (6) mobile
 clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]
Sent: Monday, May 18, 2015 9:56 AM
To: Clark, Paula
Subject: EXTERNAL: Information Request please

Dear Paula,

I have been contacted by our Biometrics reviewer and he informed me of the following information request:

Please submit the SAS program files which correspond to the analyses presented in the following tables of the clinical study reports:

Study 307/308:

Subgroup Analyses from the original study report (Tables 14.2.14.1, 14.2.14.3)

Racial Subgroup Analyses from submission dated 1/27/2015 (Tables 14.2.14.9-10 (Study 307), Tables 14.2.14.7-8 (Study 308))

ISE:

Subgroup Analyses from the original study report (Tables 2.5.1, 2.6.1, 2.7.1)

Racial subgroup Analyses from submission dated 1/27/2015 (Tables 14.2.7.5-14.2.7.8)

Sincerely,

Spiros

Spiros Nicols PharmD, RPh, MBA
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue Building 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988
Spiros.Nicols@fda.hhs.gov

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SPIROS NICOLS
05/18/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Tuesday, May 12, 2015 3:41 PM
To: 'Clark, Paula'
Subject: NDA 207932 Belbuca Information Request from Medical Officer Subject 1045-8014 study 308

Dear Paula,

I have received a question pertaining to Study 308 from our Clinical Reviewer. Please see below:

Could you ask the Sponsor which treatment subject 1045-8014 from study 308 received and ask for an explanation for the difference in treatment group between the narrative and the CSR body and datasets? In the SAE narrative it states that the subject was in the buprenorphine group and in the dataset and CSR body it says the subject was in the placebo group.

Sincerely,

Spiros

Spiros Nicols PharmD, RPh, MBA
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue Building 22, Rm 3111
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SPIROS NICOLS
05/13/2015

Nicols, Spiros

From: Clark, Paula <Clark.Paula@endo.com>
Sent: Wednesday, May 13, 2015 11:33 AM
To: Nicols, Spiros
Subject: RE: EXTERNAL: NDA 207932 Belbuca Information Request from Medical Officer Subject 1045-8014 study 308

Dear Spiros:

Response for Reviewer:

We reviewed the narrative versus the datasets and CSR body for subject 1045-8014. Please note the SAE narrative is in error; the CSR and datasets are correct. The subject was in the placebo group. On page 684 of the narrative, "buprenorphine" was incorrectly stated 3 times and should have reflected "placebo".

Please advise if you require an updated narrative or any further details.

With kind regards,

Paula Clark

Senior Director, Regulatory Affairs Liaison
Endo 1400 Atwater Drive, Malvern, PA 19355
484-216-7397 (b) (6) mobile
clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]
Sent: Tuesday, May 12, 2015 3:41 PM
To: Clark, Paula
Subject: EXTERNAL: NDA 207932 Belbuca Information Request from Medical Officer Subject 1045-8014 study 308

Dear Paula,

I have received a question pertaining to Study 308 from our Clinical Reviewer. Please see below:

Could you ask the Sponsor which treatment subject 1045-8014 from study 308 received and ask for an explanation for the difference in treatment group between the narrative and the CSR body and datasets? In the SAE narrative it states that the subject was in the buprenorphine group and in the dataset and CSR body it says the subject was in the placebo group.

Sincerely,

Spiros

Spiros Nicols PharmD, RPh, MBA
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue Building 22, Rm 3111
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Spiros.Nicols@fda.hhs.gov

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SPIROS NICOLS
05/13/2015

Nicols, Spiros

From: Clark, Paula <Clark.Paula@endo.com>
Sent: Friday, April 17, 2015 1:13 PM
To: Nicols, Spiros
Subject: Clinical Information Request for NDA 207932 Belbuca

Please see our responses to your questions from the email dated April 14, 2015. Please let me know if you have any questions arising from our responses.

Thank you.

1. The reason for discontinuation for two subjects at site 1027 in the ADDS dataset for study 307 is listed as “study was terminated at our site”. Explain why the study was terminated at site 1027.

The site’s participation in EN3409-307 was terminated due to suspension of the Principal Investigator’s (PI) medical license for sexual harassment and professional sexual misconduct on 26 Feb 2014. A follow up site audit was conducted by Endo on 29 Apr 2014. This audit was conducted to assess adherence to protocol-specific, GCP, SOP, and Regulatory requirements in the conduct of EN3409-307, EN3409-308, and EN3409-309 and, to identify potential operational/compliance-related GCP risks related to an ongoing disciplinary investigation of the PI by the State of Georgia Medical Board related to allegations of sexual boundary issues. The audit focused on Physician Oversight, Subject Eligibility & Subject Safety, and Data Reliability. There were no critical or major GCP nonconformities; and, there appear to have been no operational practices related to the Georgia State Board of Medicine investigation that compromised Subject Safety or Data Integrity.

2. Describe the context and the actions taken for the 636 subjects that were reported to have positive urine toxicology screen for drugs of abuse in the protocol deviations section of the study 307 clinical study report.

While all these subjects showed positive urine toxicology screen for drugs of abuse (UDS) results, only 6 of these subjects listed had positive UDS results that met exclusion criteria #19: Positive urine toxicology screen for drugs of abuse (non-prescribed amphetamines, benzodiazepines, barbiturates, cannabinoids, or cocaine). For all of the subjects, except the ones listed below, these positive results were expected and/or explainable during Endo’s clinical review of 1) a subject’s prior medications, 2) concomitant medication the subject was allowed to take and/or continue on and 3) all subjects were provided HC/APAP rescue medication during the subject’s participation in the study. The six (6) subjects (see below) with positive UDS that were not expected and/or explainable were excluded from the per protocol population.

1023-7010	Exclusion Criteria #19 in protocol	Positive Urine Toxicology Screen for Drugs of Abuse (non-prescribed amphetamines, benzodiazepines, barbiturates, cannabinoids, or cocaine)
1090-7032	Exclusion Criteria #19 in protocol	Positive Urine Toxicology Screen for Drugs of Abuse (non-prescribed amphetamines, benzodiazepines, barbiturates, cannabinoids, or cocaine)
1027-7018	Exclusion Criteria #19 in protocol	Positive Urine Toxicology Screen for Drugs of Abuse (non-prescribed amphetamines, benzodiazepines, barbiturates, cannabinoids, or cocaine)
1010-7012	Exclusion Criteria #19 in protocol	Positive Urine Toxicology Screen for Drugs of Abuse (non-prescribed amphetamines, benzodiazepines, barbiturates, cannabinoids, or cocaine)
1062-7009	Exclusion Criteria #19 in protocol	Positive Urine Toxicology Screen for Drugs of Abuse (non-prescribed amphetamines, benzodiazepines, barbiturates, cannabinoids, or cocaine)

		amphetamines, benzodiazepines, barbiturates, cannabinoids
1066-7022	Exclusion Criteria #19 in protocol	Positive Urine Toxicology Screen for Drugs of Abuse (non-pr amphetamines, benzodiazepines, barbiturates, cannabinoids

3. Explain the statement in the protocol deviations section of the study 307 clinical study report indicating that the safety labs and ECG for around 300 subjects were not done “per protocol” and how this impacts the safety analyses for the study.

In Study 307, 815 subjects entered into the Open-label Titration Phase. 511 out of 815 subjects were randomized (visit #19). 304 subjects discontinued during the Open-label Titration Phase and therefore did not have a randomization visit. Per the protocol, the baseline visit occurs at randomization. Therefore, 304 subjects would not be expected to have baseline labs or ECGs because they were not randomized and continuing into the next phase of the study.

For the safety analysis, the baseline values are defined as the last available values for safety assessments prior to the Open-label Titration Phase (the analyses for the Open-label Titration Phase) or prior to randomization (the analyses for the Double-blind Treatment Phase). There is no impact on our overall safety conclusion.

4. Explain the statement in the protocol **deviations** section of the study 308 clinical study report indicating that the safety labs for 280 subjects were not done “per protocol” and how this impacts the safety analyses for the study.

In Study 308, 752 subjects entered into the Open-label Titration Phase. 462 out of 752 subjects were randomized (visit #12). 290 subjects discontinued during the Open-label Titration Phase and therefore did not have a randomization visit. Per the protocol, the baseline visit occurs at randomization. Therefore, 290 subjects would not be expected to have baseline labs because they were not randomized and continuing into the next phase of the study.

For the safety analysis, the baseline values are defined as the last available values for safety assessments prior to the Open-label Titration Phase (the analyses for the Open-label Titration Phase) or prior to randomization (the analyses for the Double-blind Treatment Phase). There is no impact on our overall safety conclusion.

5. Explain what the “less than 4 pain score during the last 7 days” protocol deviation was for study 301.

If a subject has fewer than 4 daily pain intensity scores during last 7 days of the double-blind treatment period, it was considered a protocol deviation.

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/s/

SPIROS NICOLS
04/17/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Tuesday, April 14, 2015 7:29 AM
To: 'Clark, Paula'
Subject: Information Request for NDA 207932 Belbuca

Dear Paula,

Our medical officer reviewing clinical data from your submission has requested the following information from Endo.

The reason for discontinuation for two subjects at site 1027 in the ADDS dataset for study 307 is listed as “study was terminated at our site”. Explain why the study was terminated at site 1027.

Describe the context and the actions taken for the 636 subjects that were reported to have positive urine toxicology screen for drugs of abuse in the protocol deviations section of the study 307 clinical study report.

Explain the statement in the protocol deviations section of the study 307 clinical study report indicating that the safety labs and ECG for around 300 subjects were not done “per protocol” and how this impacts the safety analyses for the study.

Explain the statement in the protocol deviations section of the study 308 clinical study report indicating that the safety labs for 280 subjects were not done “per protocol” and how this impacts the safety analyses for the study.

Explain what the “less than 4 pain score during the last 7 days” protocol deviation was for study 301.

If you have any questions, please let me know.

Sincerely,

Spiros

Spiros Nicols PharmD, RPh, MBA
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue Building 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988
Spiros.Nicols@fda.hhs.gov

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/s/

SPIROS NICOLS
04/15/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Thursday, April 02, 2015 7:26 AM
To: 'Clark, Paula'
Subject: RE: EXTERNAL: RE: NDA 207932; Belbuca - Query Regarding Priority Review

Dear Paula,

Our Medical Officer has provided the reason for Endo not receiving a priority review for Belbuca below:

The proposed indication meets the serious condition criterion for priority review designation. However, you have not provided information indicating that the proposed drug would be a significant improvement in safety or effectiveness over available therapies. Available therapies include a transdermal buprenorphine product that is indicated for the treatment of pain, which is the product that is the most similar to your product. To receive a priority review designation, you would have needed to provide information indicating that your product is a significant improvement over transdermal buprenorphine.

Sincerely,

Spiros

Spiros Nicols PharmD, MBA
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue Building 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988
Spiros.Nicols@fda.hhs.gov

From: Clark, Paula [<mailto:Clark.Paula@endo.com>]
Sent: Friday, March 27, 2015 1:26 PM
To: Nicols, Spiros
Subject: RE: EXTERNAL: RE: NDA 207932; Belbuca - Query Regarding Priority Review

Hi – I don't think we would need a teleconference; just the reasoning behind the decision (eg outside of guidance) and email response works, unless the only vehicle to receive response is a teleconference, would it then be a type C meeting?

Thanks very much for any guidance.

Regards,
Paula

Paula Clark
Senior Director, Regulatory Affairs Liaison
Endo 1400 Atwater Drive, Malvern, PA 19355
484-216-7397 (b) (6) mobile

clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]
Sent: Friday, March 27, 2015 1:22 PM
To: Clark, Paula
Subject: EXTERNAL: RE: NDA 207932; Belbuca - Query Regarding Priority Review

Dear Paula,

If you would like to have the Division provide a reason for our Standard Review it is possible to request a teleconference for such a matter.

Sincerely,

Spiros

Spiros Nicols PharmD, MBA
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue Building 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988
Spiros.Nicols@fda.hhs.gov

From: Clark, Paula [<mailto:Clark.Paula@endo.com>]
Sent: Friday, March 27, 2015 8:11 AM
To: Nicols, Spiros
Subject: NDA 207932; Belbuca - Query Regarding Priority Review

Dear Spiros:

Our Leadership have asked Regulatory to gain understanding regarding the Division not granting our request for Priority Review for the Belbuca NDA.

Could you provide to us the reason for Standard Review and for not receiving Priority Review for the NDA.

Thanks and regards,

Paula Clark
Senior Director, Regulatory Affairs Liaison
Endo 1400 Atwater Drive, Malvern, PA 19355
484-216-7397 (b) (6) mobile
clark.paula@endo.com



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/s/

SPIROS NICOLS
04/15/2015

Nicols, Spiros

From: Clark, Paula <Clark.Paula@endo.com>
Sent: Thursday, March 12, 2015 5:31 PM
To: Nicols, Spiros
Subject: RE: EXTERNAL: NDA 207932 Belbuca; Information Request: Microbiology, QT study.

Dear Spiros:

In response to question 1, please note:

Method verification studies for both USP <61> and USP<62> have been performed on buprenorphine hydrochloride (HCl) films. The results demonstrated that the methods are adequate for use in buprenorphine HCl films.

We continue to work on question 2 and will have response prepared early next week.

Please let me know if there are any questions or concerns.

With kind regards,

Paula Clark

Senior Director, Regulatory Affairs Liaison

Endo 1400 Atwater Drive, Malvern, PA 19355

484-216-7397 (b) (6) mobile

clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]
Sent: Wednesday, March 11, 2015 4:15 PM
To: Clark, Paula
Subject: EXTERNAL: NDA 207932 Belbuca; Information Request: Microbiology, QT study.
Importance: High

Dear Paula,

The Division has the following information requests from two review teams (1) Microbiology and (2) Clinical

The information requested is denoted below adjacent to the team number requesting.

- (1) Your application states that microbial limits testing will be performed for release and stability using methods described in USP <61> and USP <62>. State whether method verification studies were performed to ensure that these methods are adequate for use with your drug product.**

(2) In order to assist us with our review, provide the mean steady state maximum exposures (Cmax) for your product at the following doses: 75 ug q12 h, 150 mcg q 12 h, 300 mcg q12h, 450 mcg q12h, 600 mcg q12h, 750 mcg q12h and 900 mcg q12h

Please provide us with the requested information at your earliest convenience. If you have any questions, please let me know.

Sincerely,

Spiros

Spiros Nicols Pharm D MBA
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue Building 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988
Spiros.Nicols@fda.hhs.gov

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/s/

SPIROS NICOLS
03/20/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Wednesday, March 11, 2015 4:15 PM
To: 'Clark, Paula'
Subject: NDA 207932 Belbuca; Information Request: Microbiology, QT study.

Importance: High

Dear Paula,

The Division has the following information requests from two review teams (1) Microbiology and (2) Clinical

The information requested is denoted below adjacent to the team number requesting.

- (1) Your application states that microbial limits testing will be performed for release and stability using methods described in USP <61> and USP <62>. State whether method verification studies were performed to ensure that these methods are adequate for use with your drug product.**
- (2) In order to assist us with our review, provide the mean steady state maximum exposures (Cmax) for your product at the following doses: 75 ug q12 h, 150 mcg q 12 h, 300 mcg q12h, 450 mcg q12h, 600 mcg q12h, 750 mcg q12h and 900 mcg q12h**

Please provide us with the requested information at your earliest convenience. If you have any questions, please let me know.

Sincerely,

Spiros

Spiros Nicols Pharm D MBA
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue Building 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988
Spiros.Nicols@fda.hhs.gov

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/s/

SPIROS NICOLS
03/11/2015

Nicols, Spiros

From: Clark, Paula <Clark.Paula@endo.com>
Sent: Wednesday, March 04, 2015 2:49 PM
To: Nicols, Spiros
Subject: RE: EXTERNAL: Information Request NDA 207932: Buprenorphine HCl Buccal Film
Attachments: FDA Biometric Review Team Information Request (20150304).zip

Dear Spiros: Please note we plan to also submit this information formally through the gateway; however, I am attached the SAS Program files via email (Zip File) as well (attached).

Response regarding sample size re-estimation to follow.

Please contact me with any questions you or the biometrics team may have. We will formally submit through the gateway tomorrow.

Kind regards,

Paula Clark

Senior Director, Regulatory Affairs Liaison
Endo 1400 Atwater Drive, Malvern, PA 19355
484-216-7397 (b) (6) mobile
clark.paula@endo.com



From: Nicols, Spiros [<mailto:Spiros.Nicols@fda.hhs.gov>]
Sent: Monday, March 02, 2015 9:56 AM
To: Clark, Paula
Subject: EXTERNAL: Information Request NDA 207932: Buprenorphine HCl Buccal Film
Importance: High

Dear Paula,

Please see the below information request from our biometrics reviewers.

Please submit the SAS program files which correspond to the analyses presented in the following tables of the clinical study reports:

Study 301

Primary Efficacy Analyses (Tables 14.2.1.1 and 14.2.1.1.1)

Sensitivity Analyses (Tables 14.2.2.1, 14.2.2.2, 14.2.2.3, 14.2.2.4)

Study 307/308

Primary Efficacy Analyses (Tables 14.2.1.1 and 14.2.1.5)

Sensitivity Analyses (Tables 14.2.2.1, 14.2.3.1, 14.2.3.3, 14.2.4.1(307 only), 14.2.4.3(307 only), 14.2.5.1, 14.2.13.1, 14.2.13.3)

Any additional code used to impute the missing data for the primary efficacy analysis

Please provide the DSMB meeting minutes related to the sample size re-estimation discussed in Section 11.4.2.3 of the Complete Study Report for Studies 307 and 308.

At your convenience the Division requests this information to be submitted for our review.

Thank you!

Spiros

Spiros Nicols Pharm D MBA
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue Building 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988
Spiros.Nicols@fda.hhs.gov

From: Nicols, Spiros
Sent: Friday, February 27, 2015 12:38 PM
To: 'Clark, Paula'
Subject: RE: Follow-up - NDA 207932: Buprenorphine HCl Buccal Film

Dear Paula,

This should not be a problem for us. I can send you the 74 day letter via email as a courtesy copy next Friday.

Sincerely,

Spiros

Spiros Nicols Pharm D MBA
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue Building 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988
Spiros.Nicols@fda.hhs.gov

From: Clark, Paula [<mailto:Clark.Paula@endo.com>]
Sent: Friday, February 27, 2015 9:41 AM
To: Nicols, Spiros
Subject: Follow-up - NDA 207932: Buprenorphine HCl Buccal Film

Dear Spiros:

I hope you don't mind my reaching out to you - Just a quick inquiry – with Day 74 fast approaching, can you let me know if you plan on sending Day 74 correspondence as an attachment to an email (copy) with official hard copy in the mail (with day 74 falling on a Saturday). Our team is forming our “Rapid Response Team” and are looking to understand quickly the content of the day 74 letter, once it arrives here in the appropriate timeframe.

Of course my management is keen on understanding how you plan on sending this to us. US mail takes an inordinate long time to get here for FDA letters.

Many thanks in advance and enjoy the weekend.

Paula Clark

Senior Director, Regulatory Affairs Liaison

Endo 1400 Atwater Drive, Malvern, PA 19355

484-216-7397 [REDACTED] (b) (6) mobile

clark.paula@endo.com



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/s/

SPIROS NICOLS
03/06/2015

Nicols, Spiros

From: Horn, Pamela
Sent: Tuesday, March 03, 2015 4:09 PM
To: Nicols, Spiros
Cc: Lloyd, Joshua
Subject: Information Request NDA 207932

Hi Spiros,

The applicant needs to provide the following information in accordance with the guidance for industry Financial Disclosure by Clinical Investigators:

1. Number of investigators/ sub-investigators listed on form 3454 attachment
2. Details of the disclosable financial interest for Dr. [REDACTED] (b) (6) on form 3455 attachment
3. A description of the steps taken to minimize potential bias for Dr. [REDACTED] (b) (6) and Dr. [REDACTED] (b) (6)

Thanks,
Pam

Pamela Horn, MD
Senior Clinical Reviewer
Division of Anesthesia, Analgesia, and Addiction Products
OND/CDER/FDA
301-796-5315

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/s/

SPIROS NICOLS
03/06/2015

Nicols, Spiros

From: Nicols, Spiros
Sent: Wednesday, February 11, 2015 2:08 PM
To: 'Clark, Paula'
Subject: NDA 207932, information request (filing issues)

Dear Paula,

Referring to your NDA 207932 for Belbuca, submitted and received on Dec. 23, 2014, we have identified issues that are potential filing issues, and these need to be addressed immediately.

1. We note that Sections 2.4 and 2.6.1 of the submission state that a safety assessment of all excipients in buprenorphine HCl buccal film is presented in Sections 2.3 and 2.4, respectively. However, this safety assessment does not appear to be included in those sections. Provide the specific section and page number for this safety assessment, or, if it is not present, submit the safety assessment to the NDA immediately. In addition to all of the drug product excipients, this safety assessment must include a safety justification for the levels of the components of the TekPrint SW-9008 blank ink. As we have informed you in previous correspondences prior to your NDA submission, human safety support for the chronic use of excipients in the Belbuca buccal film is required either by nonclinical testing or identification of chronic use of the excipients by an appropriate dose route and dose level in approved human drugs. We cannot file your NDA without this information.
2. The annotated draft labeling for your product references information from (b) (4) in sections for Metabolism and Special Populations/Hepatic Impairment in Section 12.3 Pharmacokinetics. You have not included (b) (4) as one of your listed products for your 505(b)(2) NDA submission, nor have you provided patent certifications for patents under NDA (b) (4). You must either submit new proposed labeling and annotated draft labeling that does not rely upon any prior FDA findings of efficacy or safety for (b) (4) (b) (4), or, provide (1) a corrected Form 356h (Box 20) with (b) (4) as one of your listed products, (2) the appropriate patent certifications for (b) (4), and (3) data/information to establish a bridge between your proposed drug product and the (b) (4) product to demonstrate that reliance on FDA's prior findings for (b) (4) is scientifically justified.
3. Provide a corrected Form 356h (Box 20) that lists NDA 020732 (Subutex), replacing ANDA 078633, as one of your listed products. While Subutex is a discontinued product, NDA 020732 is still the appropriate application as a listed product for your 505(b)(2) NDA. It is acceptable that the ANDA 078633 Roxane product was used in your bioavailability comparison to provide the scientific bridge between Belbuca and Subutex. You should also check the appropriate boxes (all that apply) in Box 20 related to patent certification paragraphs for all listed products. Refer to 21CFR 314.50(i)(1)(i)(A)(1 through 4) (i.e., Paragraph I, II, III, or IV certification).
4. Provide the appropriate patent certification statements in your eCTD tab, 1.3.5.2. "Patent Certifications". These statements pertain to the NDA products upon which you are relying for your 505(b)(2) NDA submission. Refer to 21CFR 314.50(i)(1)(i)(A)(1 through 4) (i.e., Paragraph I, II, III, or IV certification). You have already described your own patents for Belbuca under tab 1.3.5.1, using Form 3542a. Tab 1.3.5.2. does not relate to your own patents.

Please contact me at your earliest convenience to indicate your plans and timing for a submission to NDA 207932 that addresses the above issues.

Sincerely,

Spiros

Spiros Nicols Pharm D MBA
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue Building 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988
Spiros.Nicols@fda.hhs.gov

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/s/

SPIROS NICOLS

02/11/2015

Information request (filing issues).



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207932

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Endo Pharmaceuticals Inc.
1400 Atwater Drive
Malvern, PA 19355

ATTENTION: Paula Clark
Senior Director, Regulatory Affairs

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) dated and received, December 23, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Buprenorphine HCl buccal film, 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg and 900 mcg.

We also refer to your correspondence, dated and received December 23, 2014, requesting review of your proposed proprietary name, Belbuca.

We have completed our review of the proposed proprietary name, Belbuca and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your December 23, 2014, 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 Vaishali Jarral, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4248. For any other information regarding this application, contact Spiros Nicols, Regulatory Project Manager in the Office of New Drugs, at (240) 402-5988.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
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
02/10/2015



IND 072428

ADVICE/INFORMATION REQUEST

Endo Pharmaceuticals, Inc.
1400 Atwater Drive
Malvern, PA 19355

Attention: Paula Clark
Senior Director, Regulatory Affairs

Dear Ms. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for EN3409 (BEMA buprenorphine buccal soluble film). We also refer to your submission dated and received January 16, 2015, containing your Agreed Initial Pediatric Study Plan (iPSP).

We acknowledge your plan to study EN3409 in pediatric patients aged seven to less than seventeen years, and your request for a waiver in ages birth to less than seven years. We have completed our review of the submission, and we confirm our agreement to your Agreed iPSP. We have no further comments on your PSP. A clean copy of the Agreed iPSP is attached for your reference.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;
- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter); if you also send copies of these

reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors 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 (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

If you have any questions, contact Spiros Nicols, PharmD, MBA, Regulatory Project Manager, at (240) 402-5988.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Acting Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Agreed iPSP

29 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

SHARON H HERTZ
02/05/2015

Dear Paula,

With regard to NDA 207932 for Belbuca, the Division did not find analyses of efficacy results by race in the clinical study report or appendices for studies EN3409-307 and EN3409-308 or for the integrated summary of efficacy. In addition we did not find included any analyses of efficacy results by subgroup (gender; age; race) for study BUP-301.

Can you please advise us where this information may be located in the submission or provide the necessary tables?

Sincerely,

Spiros

Spiros Nicols Pharm D MBA
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products

Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue Building 22, Rm 3111
Silver Spring, MD 20993
Office: 240.402.5988
Spiros.Nicols@fda.hhs.gov

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/s/

SPIROS NICOLS

01/23/2015

Information Request, archiving email of January 22, 2015



IND 072428

MEETING MINUTES

Endo Pharmaceuticals, Inc.
1400 Atwater Drive
Malvern, PA 19355

Attention: Paula Clark
Senior Director, Regulatory Affairs

Dear Ms. Clark:

Please refer to your Investigational New Drug Application (IND) submitted December 15, 2005, received December 16, 2005, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for buprenorphine buccal film.

We also refer to the telecon between representatives of your firm and the FDA on July 15, 2014. The purpose of the meeting was to discuss your upcoming NDA submission.

A copy of the official minutes of the telecon 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
Supervisory Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: July 15, 2014 noon to 1pm EDT
Meeting Location: Teleconference
Application Number: IND 072428
Product Name: Buprenorphine Buccal Film
Indication: For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Sponsor/Applicant Name: ENDO Pharmaceuticals, Inc.

CDER Attendees	Title
Bob A. Rappaport, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Sharon Hertz, MD	Deputy Director, DAAAP
Josh Lloyd, MD	Clinical Team Leader, DAAAP
Pam Horn, MD	Clinical Reviewer, DAAAP
Adam Wasserman, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Gary Bond, PhD	Pharmacology/Toxicology Reviewer, DAAAP
Ciby Abraham, PhD	Chemistry, Manufacturing, and Controls (CMC) Reviewer, ONDQA
Julia Pinto, PhD	Chemistry, Manufacturing, and Controls (CMC) Team Lead, ONDQA
Yun Xu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Suresh Naraharisetti, PhD	Clinical Pharmacology Reviewer, OCP
Janice Derr, PhD	Statistical Team Leader, Office of Biostatistics (OB)
Kate Meaker, MS	Statistical Reviewer, OB
Matthew Sullivan, MS	Supervisory Regulatory Health Project Manager

Endo Attendees	Title
Sue Hall, PhD	Executive Vice President, Chief Scientific Officer and Global Head of Research and Development and Quality, Endo Pharmaceuticals Inc.
Paula Clark, BS	Senior Director, Regulatory Affairs, Endo Pharmaceuticals Inc.
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Evan Tzanis, MA	Senior Director, Clinical Development, Head of Biostatistics and Programming, Endo Pharmaceuticals Inc.
Neil Shusterman, MD	Vice President, Pharmacovigilance and Senior Clinical Advisor, Endo Pharmaceuticals Inc.
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Steve Xiang, PhD	Principal Biostatistician, Endo Pharmaceuticals Inc.
David Oakley, RPh, PhD	Director, Pharmaceutical Development, Endo Pharmaceuticals Inc.
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Niraj Vasisht, PhD	Senior Vice President, Product Development and Chief Technical Officer, BioDelivery Sciences International

BACKGROUND

ENDO Pharmaceuticals requested a Pre-NDA meeting on April 21, 2014, which the Division granted in a May 14, 2014, letter. ENDO plans to submit a marketing application under section 505(b)(2) for buprenorphine buccal film, referencing Buprenex and Subutex as the listed drugs. The Sponsor proposes the indication of “management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.”

ENDO submitted a meeting package on May 30, 2014, in support of this meeting. Questions from this meeting package are included below in italics, and the Division responses are shown in bold font. Discussion from the meeting is in normal font.

Preliminary comments were sent to the Sponsor on July 11, 2014, and the Sponsor responded on July 14, 2014, with brief written responses to Questions 1, 2, and 14. These responses are included below the Question to which they apply.

DISCUSSION

Chemistry, Manufacturing, and Controls (CMC)

Question 1 Does the Agency concur that the proposed drug substance specification (Table 8) is sufficient to ensure consistent quality of the drug substance?

Division Response:

The evaluation of the drug substance specifications will be conducted during the NDA review. However, we note that the proposed specification for (b) (4) is (b) (4) ppm, which exceeds the acceptable level of (b) (4) ppm in accordance with the ICH Q3C document *Impurities: Residual Solvents*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073395.pdf> Set residual solvent specifications in accordance with ICH Q3C or provide a justification for the proposed levels.

ENDO July 14, 2014, written response:

Endo acknowledges the Agency's comment that the limit for residual (b) (4) ppm is above ICH Q3C acceptable limit of (b) (4) ppm for (b) (4). Endo will follow ICH Q3C (b) (4) (link below) which allows for adding the amounts of (b) (4) present in each of the components of the drug product (including all excipients and drug substance in the final drug product).

Using the ICH Q3C (b) (4) calculation, the sum of residual (b) (4) amounts in all buprenorphine hydrochloride (HCl) buccal film components is less than (b) (4) ppm, which is the permissible daily exposure (PDE) for the solvent.

Does the Agency agree that following ICH Q3C (b) (4) provides sufficient justification for (b) (4) having a limit of (b) (4) ppm in buprenorphine HCl drug substance?

Discussion:

The Sponsor stated that they intend to utilize the ICH Q3C (b) (4) calculation method. The Division stated that this would be acceptable and that the Sponsor should ensure that the details of the calculation are clearly presented in the NDA submission.

Question 2 Does the Agency concur that the proposed drug product specification (Table 10) is sufficient to ensure consistent quality of the drug product?

Division Response:

Evaluation of the drug product specification will be conducted during the NDA review. However, we note that in the current data, the Assay and Content Uniformity results are on the low end of the currently proposed specifications. Further, we suggest that you test pH and (b) (4) at release and stability for your registration batches.

Additionally, you have not provided sufficient information in the current submission to make a final determination on the acceptability of your proposed dissolution method and dissolution acceptance criterion. We previously provided recommendations in the May 24, 2012, Type C meeting comments regarding the information that should be provided to support your proposed dissolution method and acceptance criterion. This information includes the dissolution method development report, including justification for the selection of your dissolution parameters, and the dissolution method development report.

We also have the following additional recommendation regarding your dissolution test procedures:

After sampling, (b) (4) dissolution medium to maintain sink conditions.

We have the following additional recommendations regarding your proposed acceptance criterion:

1. Clearly identify the clinical and registration batches tested to determine your proposed acceptance criterion.
2. Provide the complete dissolution data (individual, mean, SD) for each batch tested at each time point under the release and stability conditions.

ENDO July 14, 2014, written response:

Endo acknowledges the Agency's feedback on the drug product specification. Endo would like to seek further clarification on the Agency's Meeting Preliminary Comments for assay, dissolution and film color testing.

a) Assay (Proposed Acceptance Criteria: (b) (4)%)

In the pre-NDA briefing book, Endo provided the ranges for the batch analyses/release and stability assay results generated from the registration stability lots and clinical lots. These lots were manufactured at (b) (4) and (b) (4) (commercial drug product manufacturers) and are representative of the to-be-marketed product.

The ranges are provided in the table below (Table 13 in the pre-NDA briefing book, page 40). Individual batch analysis data will be provided in the NDA.

Table 13: Assay

Results	Assay ^a Range (Low % – High %)		Proposed Acceptance Criteria
	(b) (4)	(b) (4)	
Batch Analysis / Release	(b) (4) (n=20 lots)	(b) (4) (n=26 lots)	(b) (4) % label claim
Stability (25°C/60%RH)	(b) (4) (n=14 lots)	(b) (4) (n=14 lots)	
Stability (40°C/75%RH)	(b) (4) (n=14 lots)	(b) (4) (n=14 lots)	

^a Composite assay of 10 films.

The buccal film manufacturing process (b) (4)
 (b) (4) As noted in the pre-NDA briefing book, bilayer films such as buprenorphine hydrochloride (HCl) buccal films are manufactured (b) (4)

(b) (4)

(b) (4)

The same manufacturer and equipment have been utilized for several years and in-process controls have been in place throughout the development of buprenorphine buccal films. During this time, the manufacturing process has been evaluated and modified based on experience gained from manufacturing many clinical batches. Based on this product knowledge, optimization studies were performed and improvements made to the process and enhancements made to the in-process controls prior to registration batch manufacture. The manufacturing process is robust and consistently yields product that meets specifications at release and through shelf life.

Based on the complexity of the buprenorphine film manufacturing process (b) (4), (b) (4), Endo believes that an assay limit of (b) (4) (b) (4) % is appropriate for buprenorphine HCl buccal films and will use these limits for assessing expiry dating for the product and proposing an expiration date in the NDA.

Understanding that the Agency cannot comment specifically on the acceptability of the proposed assay limits without reviewing all of the information to be included in the NDA, what potential issues (if any) does the Agency foresee with regard to approval of the proposed assay limits?

Discussion:

The Sponsor reiterated the complexity in manufacturing buccal film products, specifically (b) (4). The Division responded that an (b) (4)% range for the (b) (4) formulation seemed (b) (4). The Division also noted that the Sponsor had previously stated that a (b) (4)% range would be proposed for the acceptance criteria, but those criteria have now been (b) (4) even further. Additionally, the Division stated that some lots were as (b) (4)% of the labeled claim on stability.

The Sponsor stated that they have not planned on using an (b) (4) during the manufacturing process, and that due to the complexity of the process, some (b) (4) is expected.

The Division stated that a (b) (4) specification range is desirable and that the Sponsor should seek increased consistency in the data, across all batches tested. The Sponsor stated that they are continually working to improve the manufacturing process and would take into account the Division's concerns.

b) Dissolution

In accordance with the Agency's feedback in the May 24, 2012 Type C meeting minutes, Endo has performed the following dissolution studies:

- *Solubility/sink conditions - various dissolution media volumes*
- *Established dissolution profiles using the proposed method and using different pHs*
- *Testing with deliberate changes in conditions to challenge the discriminatory nature of the method*
- *Analytical method validation and robustness testing of HPLC parameters*

Based on the solubility of buprenorphine at pH 4.5 and the dissolution media volume, sink conditions are established for all strengths and maintained throughout the profile testing for this product. The total sample volume removed during profile testing is (b) (4) mL (out of 60 mL).

Since sink conditions are maintained throughout the profile testing without dissolution media replacement, Endo has not been (b) (4) at each dissolution pull time.

The proposed acceptance criterion ($Q = \frac{(b) (4)}{(4)}\%$ at 60 minutes) has been established based on the release and stability data (including registration lot stability through 12 months) generated (b) (4). In the NDA submission, Endo will provide complete dissolution data with clear identification as to the clinical/registration batches used to establish the proposed acceptance criterion.

In response to the Agency's feedback provided in the May 24, 2012 Type C meeting minutes and in pre-NDA Meeting Comments, Endo is requesting that the Agency confirm the following:

- *A single dissolution time point is appropriate for this product since it is an immediate release product*
- *The proposed 60-minute time point is appropriate as it is based on the dissolution profile data and aligns with USP Chapter <1088>*
- *Based on solubility and sink conditions, (b) (4) is not required*

Discussion:

The Sponsor stated that because the proposed product is an immediate-release product, a single point acceptance criterion is proposed. Additionally, the Sponsor proposed that (b) (4) would not be needed due to the solubility and sink conditions.

The Division stated that it was unable to address the comments during the meeting, but would provide a response in a post-meeting note.

Post-Meeting Note:

1. We agree that a single dissolution time point is appropriate for your drug product.
2. We cannot determine if the proposed 60-minute time point is appropriate until we review the requested dissolution information and dissolution data.
3. We concur that (b) (4) is not required. However, ensure that the final dissolution media volume at each time point is used when calculating the percent drug release.

c) Film Color

Endo would like to confirm that the Agency is in agreement with the approach proposed in the pre-NDA briefing book for film color testing:

- *Testing will be performed on representative registration stability lots at both storage conditions (25°C/60%RH through 36 months and 40°C/75%RH through 6 months).*
- *Testing will not be performed on commercial drug product lots.*

Information on the test method, validation and test results (registration stability lots, aged samples) is provided on page 43 and in Appendix J of the briefing book.

Does the Agency agree with Endo's approach for film color testing?

Discussion:

The Sponsor stated that colorimetric tests have been developed and that registration batches would be tested throughout the proposed shelf-life and a specification would be proposed for color. However, the Sponsor noted that it was qualitative, not quantitative, (backing layer – white; mucoadhesive layer – yellow). The Division stated that it was necessary to review the

supportive data to determine whether this approach was acceptable.

Question 3 Does the Agency concur that batch analyses, dissolution data (including dissolution profiles) and stability data (long-term and accelerated conditions) are sufficient to demonstrate a successful site change and that no bioequivalence documentation is required?

Division Response:

We concur that batch analyses, dissolution data and stability data are sufficient to provide for a manufacturing site change during post-approval. Evaluation of the batch analyses, dissolution and stability data will determine if a site change will be approved. Since your drug product is an immediate-release product, it is unnecessary to submit comparative dissolution data at multiple pH conditions. You should submit multi-point dissolution data in the approved dissolution medium per the guidance for industry, *Immediate Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*, available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070636.pdf>.

Discussion:

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

Question 4 Does the Agency concur that the information provided in the briefing package regarding TekPrint SW-9008 Black Ink is sufficient to address the Agency's request included in the Type C Meeting Request Written Responses (see Appendix A, Section 1, Type C Written Responses, Question 3)?

Division Response:

The Master File for the TekPrint SW-9008 Black Ink will be evaluated during the NDA review.

Discussion:

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

Question 5 Does the Agency concur that the information provided sufficiently addresses the Agency's comment in the End of Phase 2 (EOP2; see Appendix A, Section 3, Type B Meeting Minutes) meeting minutes regarding the presence of (b) (4)?

Division Response:

The information presented appears adequate, but a final determination will be made during the NDA review.

Discussion:

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

Nonclinical

Question 6 Based on the summary provided, which describes Endo's plan to file a 505(b)(2) submission utilizing Buprenex and Subutex as referenced drugs, coupled with the findings presented here, does the Agency concur that the proposed nonclinical package is adequate to support the NDA?

Division Response:

The nonclinical package appears adequate. Note that drug substance and drug product specifications, including inactive ingredient content, are NDA review issues. While proposed specifications have appeared acceptable in the past, they will be evaluated during the NDA review. You should express values relative to the final proposed dose levels, and present inactive ingredients as total mg/total drug product (combined film layers). To this end, provide clear, transparent, comprehensive, and adequately documented reporting of such support in your NDA submission. Provide a total daily intake (TDI) under chronic dosing comparison for all excipients. Refer to previous communications for details of specific issues, including any possible need for nonclinical qualification.

Discussion:

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

Clinical Pharmacology

Question 7 Does the Agency agree that the equivalent compositions and comparable bioavailability of the (b)(4) formulations across the dose strengths are sufficient to support the proposed dosing regimen (see section 2.5.3 Dosing Regimen)?

Division Response:

From clinical pharmacology perspective, your proposed formulations (b)(4) appear to have similar bioavailability based on the information provided in your meeting package.

Discussion:

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

Question 8 Does the Agency agree the studies (see Appendix B) represent a complete Clinical Pharmacology package and no additional studies are required?

Division Response:

As discussed during the Jan 13, 2012, Type A meeting, the Agency generally agreed with your study to evaluate the effect of grade 3 oral mucositis using the low potency formulation and reiterated that if there are clinically meaningful changes in PK in the grade 3 mucositis patients, patients with a lower grade mucositis may need to be studied. In addition, you were advised to provide a rationale as to why no additional studies in patients with mucositis would need to be performed on the higher concentration formulation.

Discussion:

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

Clinical

Question 9(i) This NDA submission will include 9 Phase 1 studies (BUP-101, BUP-110, BUP-115, BUP-116, BUP-117, BUP-118, EN3409-120, BUP-121, and BUP-150) (Appendix B) that characterize the pharmacokinetic and biopharmaceutical properties for various buprenorphine HCl buccal formulations. With the exception of 2 studies (BUP-110 and BUP-121), all subjects in the Phase 1 clinical pharmacology studies received concurrent naltrexone to reduce the risk of opioid induced safety adverse reactions including nausea, vomiting and respiratory depression. Study BUP-121 enrolled cancer patients with mucositis who received a single dose of buprenorphine film. Because of the nature of these studies (single dose or limited dosing PK studies), and the concurrent naltrexone block, Endo does not intend to pool data from these Phase 1 studies. Does the Agency concur with the proposal to not pool safety data from Phase 1 studies?

Division Response:

Yes, this approach appears to be acceptable.

Discussion:

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

Question 9(ii) Study BUP-110 (a randomized, crossover, double-blind, placebo-controlled, single-dose study to investigate pharmacokinetics and pharmacodynamics of 2 formulations of BEMA buprenorphine in healthy volunteers) was an early clinical study using an experimental formulation of buprenorphine HCl buccal film ((b) (4)) that was not developed further. This was an IND study conducted by our development partner BDSI and performed in France by (b) (4), a contract research organization (CRO) (b) (4). Our development partner BDSI has informed us that this CRO is no longer operating a business, and with the discontinuation of their operation, key elements of the trial master file (TMF) were not returned to BDSI. This includes raw data sets, analysis datasets, and SAS programs. At the time of submission, if we continue to

be unsuccessful in obtaining this information, Endo will only have the clinical study report (CSR) included in the NDA. Given the nature of the BUP-110 study (single-dose and crossover design), Endo believes that the CSR should be adequate given the purpose of the study and its limited utility to the evaluation of safety and efficacy. Does the Agency concur with the inclusion of only a CSR for study BUP-110?

Division Response:

Yes, on face, submission of a CSR alone appears to be acceptable for this study. However, during the review cycle, the team may request additional information based on review of the CSR. Though we do not anticipate significant review issues to arise with this study, if you are not able to provide additional information requested during the review cycle, the review team could conclude that the lack of information is an application deficiency.

Discussion:

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

Question 10(i) Included in the NDA submission will be two Phase 2 studies, study BUP-201 (a double-blind, double-dummy, placebo- and active-controlled evaluation of the efficacy, safety, and tolerability of BEMA buprenorphine in the treatment of pain associated with third molar extraction), and study EN3409-204 (an evaluation of the tolerability of switching subjects on chronic ATC opioid therapy to BEMA buprenorphine). Study BUP-201 is a single-dose, exploratory efficacy study in an acute dental pain setting following dental extraction, and study EN3409-204 is evaluating a 50% equianalgesic dose of buprenorphine over a 24-hour period with the objective to characterize the risk of buprenorphine induced withdrawal when converting subjects from full opioid agonist. Because of the nature of these studies (pain condition studied [BUP-201], limited dosing [BUP-201 and EN3409-204], and short duration of treatment [BUP-201 and EN3409-204]), Endo does not intend to pool data from these studies. Does the Agency agree with this proposal not to pool data from the referenced studies?

Division Response:

Yes, we concur.

Discussion:

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

Question 10(ii)

(b) (4)

[REDACTED] (b) (4)
Does the Agency concur (b) (4)
[REDACTED] ?

Division Response:
No, we do not concur. [REDACTED] (b) (4) **is**
a review issue.

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

Question 11(i) The Integrated Summary of Safety (ISS) will include data from all Phase 1, 2, and 3 studies. Phase 3 studies will include data from 4 completed studies and from 1 ongoing long-term safety study. Studies BUP-301 (a double-blind, placebo-controlled study in opioid-naïve and opioid-experienced subjects), and BUP-305 (an open-label, long-term safety study) evaluated buprenorphine HCl buccal films at doses of 60 µg to 240 µg administered twice daily. In addition, we have worked with BDSI to conduct studies EN3409-307 (a double-blind, placebo-controlled study in opioid-experienced subjects) at doses of 150 µg to 900 µg twice daily, EN3409-308 (a double-blind, placebo-controlled study in opioid-naïve subjects) at doses of 150 µg to 450 µg twice daily and EN3409-309 (an open-label, long-term safety study) at doses of 150 µg to 900 µg twice daily.

As described above, the studies conducted and expected to be included in the NDA have differences in the doses studied (60 µg to 240 µg twice daily vs 150 µg to 900 µg twice daily) and populations (BUP-301/BUP-305, opioid naïve and opioid experienced combined; EN3409-307, opioid experienced; EN3409-308, opioid naïve). [REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)
Does the Agency concur (b) (4)
[REDACTED] ?

Division Response:
No, we do not concur. Pool the data from different studies together for subjects that had the same dose level and prior opioid experience (opioid-experienced or opioid-naïve).

Discussion:

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

Question 11(ii) In the Integrated Summary of Efficacy (ISE), (b) (4)

(b) (4)

(b) (4) Does the Agency
concur (b) (4)?

Division Response:

No, we do not concur. Pool the data from different studies together for subjects that had the same dose level and prior opioid experience (opioid-experienced or opioid-naïve).

Discussion:

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

Question 12 Endo is planning to exclude site 1008 from the intent-to-treat (ITT) efficacy analysis in 2 clinical studies (EN3409-307 and EN3409-308). This was determined after the Sponsor fulfilled its obligation under US FDA Regulation 21 CFR 312.56(b) to report the closure of this site for significant violations on November 14, 2013. During the course of our normal review process, Endo and BDSI determined that data abnormalities existed at the site. Through the review of this data, a quality audit was performed at this site on October 16 and 17, 2013, which revealed several critical findings related to the integrity of the data from the 3 referenced clinical trials (EN3409-307, EN3409-308, and EN3409-309). During the aforementioned audit, a review of subject case records revealed similarities in photocopies of urine toxicology screens. Upon deeper investigation, several of the subject source records appeared to be identical photocopies of the same negative urine drug screen, replicated, and then used for multiple subjects. Between July 24, 2013 and August 6, 2013, it appears as if 3 different study coordinators at this site could have used the same negative urine sample or similar negative urine sample report template on 5 separate dates, involving 12 subjects (10 subjects in EN3409-308 and 2 subjects in EN3409-307). Based on these findings and prior to unblinding the study, Endo decided to not include the site in the ITT analysis for EN3409-308 and EN3409-307 for efficacy. Safety data and sensitivity analysis of the efficacy data were

performed inclusive of this site. Does the Agency concur with the exclusion of site 1008 from the ITT analysis?

Division Response:

On face, it appears that your rationale for exclusion of this site from the ITT analysis is appropriate, but this will be a review issue. As you have done in the background materials, include the results of the analyses with and without Site 1008.

Discussion:

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

Question 13 Phase 3 studies will include data from 4 completed studies and from 1 ongoing long-term safety study. Studies BUP-301 (a double-blind, placebo-controlled study in opioid-naïve and opioid-experienced subjects), and BUP-305 (an open-label, long-term safety study) evaluated buprenorphine HCl buccal films at doses of 60 µg to 240 µg administered twice daily. In addition, we have worked with BDSI to conduct studies EN3409-307 (a double-blind, placebo controlled study in opioid-experienced subjects) at doses of 150 µg to 900 µg twice daily, EN3409-308 (a double-blind, placebo-controlled study in opioid-naïve subjects) at doses of 150 µg to 450 µg twice daily and EN3409-309 (an open-label, long-term safety study) at doses of 150 µg to 900 µg twice daily (Table 35). At the time of NDA submission, long-term safety study EN3409-309 with doses up to 900 µg twice daily will be ongoing. An interim report based on data collected up to 6 months prior to submission will be included in the original submission. The report will include disposition of all subjects as well as drug exposure, serious adverse events (SAEs), AEs, AEs leading to discontinuation, and data summaries. Additional information on safety from this study will be presented in the 120-day safety update. Included in the NDA will be a safety database that contains over 2100 unique subjects from Phase 3 studies who have been exposed to buprenorphine HCl buccal film, of which more than 400 subjects will be treated for 24 weeks, and over 200 subjects treated for 48 weeks. The overall exposure numbers for the studies are estimated in Table 29, Table 30, and Table 31. Endo believes that the safety database, which exceeds the ICH E1 minimum, will provide adequate data for the evaluation of long-term safety of buprenorphine HCl buccal films. Does the Agency concur with Endo's plan as presented (submission of long-term safety data as presented above and that exposure data that will be provided at the time of NDA submission [Table 29, Table 30, and Table 31] and supplemented at the planned 120-day safety update) is adequate to evaluate the long-term safety for the NDA?

Division Response:

Yes, it appears acceptable.

Discussion:

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

Question 14 Based on the differences in electrocardiogram (ECG) data collection processes in studies BUP-301/BUP-305 versus studies EN3409-307/EN3409-308/EN3409-309, Endo believes that the data from studies BUP-150, EN3409-307, EN3409-308, and EN3409-309 provide adequate information to assess the electrophysiological cardiac safety of buprenorphine HCl buccal films. Does the Agency concur that data from the referenced studies adequately assess the electrophysical cardiac safety of buprenorphine HCl buccal films?

Division Response:

No, your data are not adequate to assess the electrophysical cardiac safety of buprenorphine hydrochloride films because the naltrexone used in the BUP-150 study is now known to interfere with the effect of buprenorphine on cardiac repolarization and renders the data uninterpretable. Data from EN3409-307, EN3409-308, and EN3409-309 can be supportive but they are not able to detect a modest effect on cardiac repolarization.

In the absence of a repeat study without naltrexone blockade, we have safety information about the effect of buprenorphine on cardiac repolarization that can be applied to the risk-benefit assessment of your product. The results of a study submitted to FDA indicate that (b) (4)

However, as the study is proprietary in nature, we will not be able to share the data with you.

(b) (4)
This safety information will be conveyed in product labeling.

Therefore, while you are not required to repeat the thorough QT study with your product without naltrexone blockade, a repeat study is necessary if you wish to have data specific to your product that can be described in labeling to accompany the QT warnings.

ENDO July 14, 2014, written response:

Endo understands the risk/benefit information you have is proprietary. In order for labeling development is the Division willing to share high level information regarding suggested labeling with us at this time, or could the Division provide a timeline of when you would be able to do so?

Discussion:

The Division noted that [REDACTED] (b) (4) but that the data are proprietary and cannot be shared with Endo. If Endo were to generate appropriate cardiac electrophysiologic data on buprenorphine buccal film without the use of naltrexone, then it could be included in labeling. Alternatively, if Endo were to uncover the source of the proprietary data and acquire authorization to reference it, then it could also be included in labeling. However, absent either of these, it will be necessary to include some high-level precautionary statements in labeling to provide appropriate warnings to prescribers. The Sponsor was also informed that they could review other buprenorphine labels for examples of QT warnings.

The Sponsor asked if the specific mechanism of the cardiac effect had been identified. The Division stated that the mechanism was still unknown, as was the mechanism by which naltrexone blocked the effect.

Question 15 All Phase 1 and Phase 2 clinical studies except BUP-118, BUP-150 and EN3409-120 have data structures that are not in CDISC STDM/ADaM format as presented in Appendix C, however they will be provided as SAS transport files. Endo does not intend to convert any of this data into STDM/ADaM format. All the Phase 3 studies have data structures that are in CDISC STDM/ADaM format as presented in Appendix C. Does the Agency concur with the proposed study data specifications and data set format as presented in Appendix C?

Division Response:
Yes, the proposal is acceptable.

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

Regulatory

Question 16 Does the Agency concur with the proposed plan to request a waiver for studies in 0- to 6-year-old subjects and a deferral of 7- to 16-year-old subjects?

Division Response:
Yes, your proposal appears to be reasonable. Note that you will need to provide current data to support your contention that studies are impossible or highly impracticable in the birth through 6 year old age group when you submit your plan. We reserve further comment on the acceptability of a waiver for this age group pending review of your NDA submission and consultation with the Pediatric Review Committee (PeRC).

Additional information regarding the requirements of the Pediatric Research Equity Act is provided below in the PREA REQUIREMENTS section.

Discussion:

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

Post-Meeting Note:

Internal Agency discussions about the appropriate age cutoff for granting a waiver from conducting pediatric studies for extended-release/long-acting opioids are ongoing. Data submitted in the iPSP to support the contention that studies are impossible or highly impracticable in the (b) (4) age group must include recent pediatric opioid use data (i.e., 2009 and later), including usage data for both immediate-release and extended-release oral opioids in both the inpatient and outpatient settings.

Question 17 Does the Agency concur that buprenorphine HCl buccal film will be subject to the Extended-Release and Long-Acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) program?

Division Response:

Yes, your product will be subject to the ER/LA Opioid Analgesics REMS program.

Discussion:

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

Question 18 Endo notes other buprenorphine products delivering the same amount of drug in different formulation/delivery systems are currently Schedule III drugs. Based on prior precedent of currently approved products with the same amount of active moiety, Endo believes the weight of evidence supports buprenorphine HCl buccal film as a Schedule III drug. Does the Agency concur that Buprenorphine HCl Buccal Film will be considered a Schedule III drug?

Division Response:

Yes, we agree. As other buprenorphine base and salt products, your product is categorized as a Schedule III drug under the Controlled Substances Act (CSA) (21 CFR § 1308.13(e)(2)). However, you are still required to submit an abuse potential assessment of your product. For a new drug application (NDA) submitted for a drug that has a potential for abuse, the Sponsor submits as part of their NDA submission an abuse potential assessment of the product. This includes cases in which a product contains a drug that is already scheduled.

We request that the abuse potential assessment include comprehensive descriptions of all pertinent preclinical, pharmacological, chemistry, biochemical, human laboratory, clinical studies and drug formulation data. A determination of abuse potential and the need if applicable for any scheduling related information will be made following review of the NDA. We are available to review abuse potential protocols prior to the commencement of studies. More information may be required at the time of your NDA submission, see (e.g., page 5) the draft guidance

for industry *Assessment of Abuse Potential of Drugs*, available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

Discussion:

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

Action Items:

1. The Sponsor will utilize the ICH Q3C (b) (4) calculation method for residual solvents and will ensure that the details of the calculation are clearly presented in the NDA submission.
2. The Division will respond in a Post-Meeting Note to the dissolution-related items under Question 2.
3. The Sponsor may wish to repeat their tQT study or investigate other sources of data that may provide evidence of the effects of buprenorphine on cardiac repolarization. Otherwise, labeling will reflect the safety information concerning the potential for QT prolongation without specifically including or referencing proprietary data that the Sponsor does not own or have right of reference to.

ADDITIONAL COMMENTS

PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. 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. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\)](#) and [\(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

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.				

505(b)(2) REGULATORY PATHWAY

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, in part, 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, in part, 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, in part, 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 relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. 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 in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing 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>
<i>4.</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 Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

STUDY DATA SPECIFICATIONS

The Agency prefers Sponsor to submit datasets based on the *Study Data Specifications* (currently 2.0).

The *PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017* guidance provides specific requirements for electronic submissions and standardization of electronic drug application data. Sponsor should design and implement data standardization in all research protocols to be included in regulatory submissions, as required based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. Sponsor should use the Clinical Data Interchange Standards Consortium (CDISC) Technical Road Map to design end-to-end harmonized data standardization, including the Clinical Data Acquisition Standards Harmonization (*CDASH*) standard for design and implementation of data collection instruments.

The Agency's methodology and submission structure supports research study design, as indicated in the *Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* and the *Study Data Specifications*. The Agency's methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits. Sponsor should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See *SEND*, *SDTM* and *ADaM* as referenced in *Study Data Specifications*). Study analyses datasets should be traceable to the tabulations datasets.

In addition, please reference the *CDER Common Data Standards Issues Document* for further information on data standardization in submissions.

The agency also offers a process for submitting sample standardized datasets for validation. Please refer to *Submit a Sample eCTD or Standardized Data Sample*.

Additional Links:

Electronic Regulatory Submissions and Review Helpful Links
Electronic Common Technical Document (eCTD)
Study Data Standards Resources

Attachment 1: Additional Comments for Pre-NDA Stage of Drug Development

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. Include at least 12 months of real time data and 6 months of accelerated data in the NDA. Alternatively, submit an appropriate amount of satisfactory stability data to cover the proposed expiry dating.
3. 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.

4. 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.
5. 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.

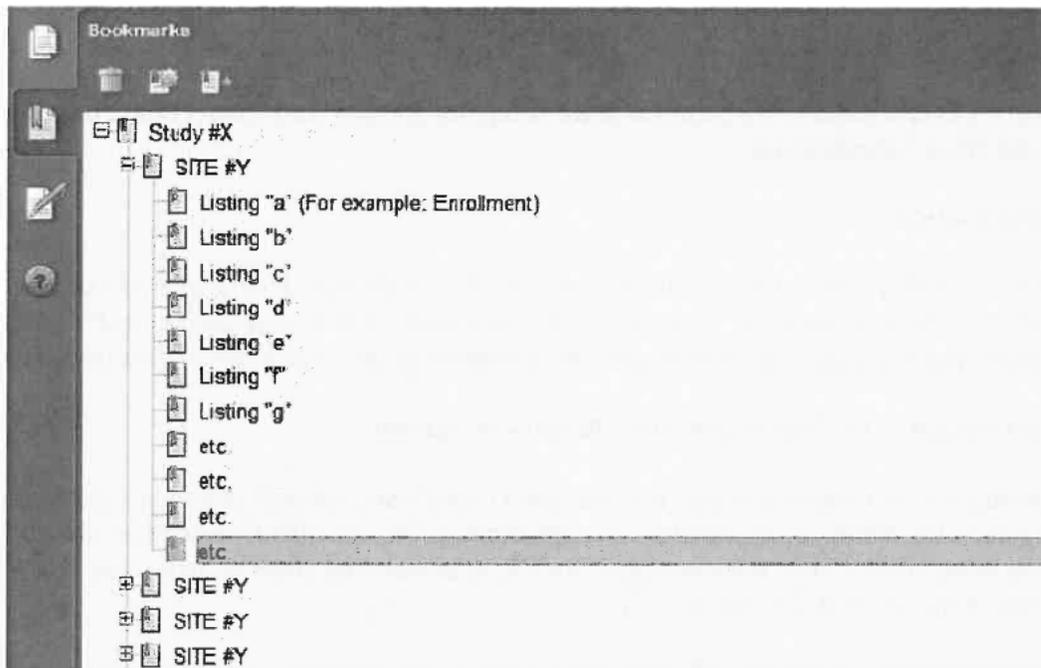
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Subpart 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

- 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
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
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
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 parties. 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

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
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
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

Reference ID: 3605556

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	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
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	FINLISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

INITIAL	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>)

IND 072428
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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 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 (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
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		

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/s/

MATTHEW W SULLIVAN
08/06/2014



IND 072428

MEETING MINUTES

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

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

Dear Dr. Wright:

Please refer to your Investigational New Drug Application (IND) submitted December 15, 2005, received December 16, 2005, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BEMA buprenorphine.

We also refer to the September 14, 2010, meeting between representatives of your firm and the FDA. The purpose of the meeting was to discuss your Phase 3 development plans.

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
Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

SPONSOR MEETING MINUTES

MEETING DATE: September 14, 2010

TIME: 12:00 pm to 1:00 pm

LOCATION: FDA White Oak Campus
Silver Spring, MD

APPLICATION: IND 072428

PRODUCT: BEMA buprenorphine

INDICATIONS: (b) (4) severe pain in patients (b) (4)

SPONSOR: BioDelivery Sciences International, Inc (BDSI)

TYPE OF MEETING: Type B, End-of-Phase 2

MEETING CHAIR: Sharon Hertz, MD, Deputy Director, Division of Anesthesia and Analgesia Products (DAAP)

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

FDA Attendees	Title
Sharon Hertz, MD	Deputy Director, Division of Anesthesia and Analgesia Products (DAAP)
Pamela Horn, MD	Clinical Reviewer, DAAP
Julia Pinto, PhD	CMC Reviewer, Office of New Drugs Quality Assessment (ONDQA)
Alan Schroeder, PhD	CMC Lead (Acting), ONDQA
Gary Bond, PhD	Pharmacology / Toxicology Reviewer, DAAP
Adam Wasserman, PhD	Pharmacology / Toxicology Supervisor, DAAP
David Lee, PhD	Clinical Pharmacology Reviewer, DAAP
Dionne Price, PhD	Statistical Team Leader, DAAP
John Gong, PhD	Pharmacologist, Controlled Substance Staff
Matthew Sullivan, MS	Regulatory Project Manager, DAAP
Sponsor Attendees	Title
David Wright, PhD, RAC	Vice President, Regulatory Affairs (BDSI Delegation Head)
Renee Boerner, PhD	Director, CMC Regulatory Compliance
Gary Goodson	Director, Formulation Development
Niraj Vasisht, PhD	Senior Vice President, Product Development
Susan Kerls	Associate Director, Clinical and Regulatory Science
Andrew Finn, PharmD	Executive Vice President, Product Development
(b) (4)	Medical Consultant and Investigator
(b) (4)	Statistical Consultant
Mark Sirgo, PharmD	President and Chief Executive Officer

Background:

The Division's responses to the questions from the July 30, 2010, meeting package were sent to the Sponsor on September 10, 2010.

Presented below are the Division's comments and responses to questions in the background meeting package. The Sponsor's questions are listed in italics, with Agency responses and comments in bold. Discussion that took place at the meeting is captured in normal text following the question to which it pertains.

After introductions, the conversation focused on the Division's September 10, 2010, preliminary meeting responses.

Quality (Chemistry, Manufacturing and Controls)

Question 1 Does the Agency have any comments on the proposed buprenorphine hydrochloride drug substance release specifications for the proposed NDA submission?

Division Response:

The related substances should be controlled per ICH guidelines.

Discussion:

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

Question 2 Does the Agency have any concerns regarding buprenorphine hydrochloride drug substance produced by either of the proposed suppliers?

Division Response:

The drug substance from both suppliers should be comparable, using the same manufacturing process, controls and similar equipment. Furthermore, the facility should be supported by comparable batch analysis and stability data.

An alphabetical list of all manufacturing and testing facilities and their complete addresses should be attached to the FDA Form 356h, along with a statement about their cGMP status. For all sites, provide a contact name, address, telephone, and fax number, and the site CFN number. Clearly specify the responsibilities of each facility (e.g., manufacturer, packager, release tester, stability tester), 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. Ensure that all of the facilities are ready for inspection by the day the application is submitted, and include a statement confirming this in the NDA cover letter.

Discussion:

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

Question 3 Does the Agency have any concerns with any of the proposed BEMA Buprenorphine drug product manufacturers?

Division Response:
See our response to Question 2.

Discussion:

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

Question 4 Does the Agency have any concerns with using BEMA Buprenorphine drug product from more than one manufacturer within a single clinical study or across clinical studies?

Division Response:
The drug product from all manufacturers should be supported by comparable batch analysis data, dissolution data, and stability data. Furthermore, only one manufacturing site should be listed as the primary site.

Discussion:

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

Question 5 Does the Agency have any concerns with the proposed plan to supply the anticipated range of necessary BEMA Buprenorphine drug product film strengths using two or three mucoadhesive formulations differing only in buprenorphine concentration and film size?

Division Response:
The drug product formulation, differing only in buprenorphine concentration, should be comparable and supported by comparative batch analysis, dissolution and stability data as well as controlled by the same set of specifications. Additionally, the stability batch data provided in the NDA should be of the batch used in the clinical studies.

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 drug product release and stability specifications for the proposed NDA submission?

Division Response:
All specifications should be justified and supported by batch analysis data as well as ICH guidelines. Further, we note that in the current data, the Assay and Content Uniformity results are on the low end of the currently proposed specifications.

Discussion:

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

Question 7 Does the Agency agree that the BEMA Buprenorphine registration batch plan is acceptable for the proposed NDA submission?

Division Response:

Three batches manufactured from a site designated as a primary site in addition to three other primary NDA stability batches manufactured at each of the additional sites should be submitted. These batches should be supported by comparable batch analysis, dissolution, and stability data.

Discussion:

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

Question 8 Does the Agency agree that the registration batches do not necessarily need to have the ink film strength identification number printed on the films?

Division Response:

Additional information is needed in order to evaluate the safety of omitting the ink identification number printed on the films.

Discussion:

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

Question 9 Does the Agency agree that it is acceptable to include (b) (4) month BEMA Buprenorphine drug product stability data in the original NDA and provide (b) (4) month data with the 120-day safety update?

Division Response:

It is expected that at least 12-months of real time data and 6-months of accelerated data will be included in the NDA at the time of submission. Stability data submitted during the NDA will be reviewed as resources permit and depending on when they are submitted. It is possible that stability data that comes in too late for review will result in a shorter expiry than desired.

Additional Chemistry, Manufacturing and Controls comments:

Provide with your NDA submission:

- 1. 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. Summary stability data on a parameter-by-parameter basis (instead of only on a batch-to-batch basis), and 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.**

Discussion:

The Sponsor sought clarification about whether they could submit 12 months of real-time and 6 months of accelerated data for the primary manufacturer, and 6 months of real-time with 6 months of accelerated for the secondary manufacture(s) at the time of submission. The Division commented that this plan is acceptable, as long as the data originates from more than one batch. The Sponsor noted their agreement, and also mentioned that they will provide a stability update at the time of the 120-day safety update.

The Division remarked that three proposed manufacturing sites at the time of NDA submission seemed like a lot. The Sponsor replied that they weren't sure that all three would eventually be submitted with the application, but that they wanted to plan for the possibility. Additionally, they noted that two of the sites are in the US, while one is in Europe.

Nonclinical

Question 10 Does the Agency concur that the design of the proposed 9-month buccal toxicity study meets the Agency's requirements for BEMA Buprenorphine in the proposed indication?

Division Response:

With regard to buprenorphine, if your drug product produces maximal exposures that are within those of the 505(b)(2) referenced drug(s), a 9-month study will not be necessary to support the safety of buprenorphine. Should levels be in excess of those in your referenced product(s), the following recommendations are made regarding the protocol:

- 1. Test multiple dose levels. Include doses which produce exposures equal to and greater than (e.g., multiples of) the maximum proposed human dose.**
- 2. Histologically evaluate all organs in addition to local buccal tissue as part of a complete GLP study.**

Additionally, adequate documentation will need to be provided that all patch components (e.g., excipients) in the drug product are used in approved chronic use products through the buccal, sublingual, or oral route at levels equal to or greater than in the proposed drug product. In the absence of sufficient safety support from literature or other sources, the 9-month buccal study will need to be conducted, the design of which, based on review of the summary description, is satisfactory with the following comments:

- 1. Conduct dosing similar to the 28-day buccal study (i.e., dosing to same buccal site) using a placebo BEMA patch.**

2. **Include recovery groups to evaluate reversibility of systemic or local toxicity.**
3. **Conduct a full histopathologic evaluation of all tissues including the site of administration to address systemic and local toxicity, respectively.**

Discussion:

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

Question 11 Does the Agency agree that the proposed 9-month buccal toxicity study can be conducted using BEMA Buprenorphine films without the ink film strength identification number printed on the films?

Division Response:

If a study of this type is necessary, the product tested should be as similar to the to-be-marketed formulation as possible, or if a placebo patch is tested then the ink identification should be included unless otherwise justified. In lieu of such testing, provide acceptable documentation (e.g., dedicated study or information in the public domain) to support the local and systemic safety of the ink utilized in the drug product.

Discussion:

The Sponsor stated that the ink used in the identification markings is included in the FDA's inactive ingredients guide, as well as being included in a Drug Master File (DMF). The Division replied that the Sponsor should provide sufficient detail to allow us to review the product and that it could be submitted prior to the NDA. The Division will make an effort to notify the Sponsor if data gaps are apparent. The Sponsor then asked if a 28-day buccal toxicity in the dog model would be adequate if the information on the ink were found not to be adequate. The Division responded that it was too early to comment.

Question 12 Does the Agency agree that no additional nonclinical studies are required to support a 505(b)(2) NDA for BEMA Buprenorphine in the proposed indication?

Division Response:

No additional nonclinical studies, other than those described above as necessary, should be required. However, a final assessment cannot be made until the NDA is reviewed.

Discussion:

The Sponsor stated that the 28-day dog study utilized a different formulation than the clinical product with the latter having (b) (4)

. The Division stated that the Sponsor

will need to justify the adequacy of this nonclinical formulation for supporting the final to-be-marketed clinical formulation.

Clinical

Question 13 Does the Agency agree that no additional clinical pharmacology studies are required to support a 505(b)(2) NDA for BEMA Buprenorphine in the proposed indication?

Division Response:

Although the types of proposed studies seem appropriate, you did not provide sufficient detail on the study designs. Therefore, we are unable to comment specifically on whether or not additional studies are necessary. On a general note, for a 505 (b)(2) NDA submission, you have to provide bioavailability information relative to the referenced drug(s).

In proposed Study 117, the bioavailability of your product relative to Buprenex will be assessed. However, in your proposed studies, we did not see an assessment of the bioavailability of your product relative to Subutex. In light of several formulation changes thus far in your development program, previously acquired relative bioavailability information may not be relevant. Either submit information to show that the previously acquired information is relevant or assess the bioavailability of your product relative to Subutex.

In Study 118, you are proposing to study the effect of liquids on the PK of buprenorphine. However, details of the actual liquids that will be studied have not been provided.

We recommend that you assess the PK of your product in patients with oral mucositis of grades 1, 2, and 3. Alternatively, you may first study patients with grade 3 oral mucositis, and if there is no change in the PK in this group, patients with lower grade mucositis need not be studied.

With respect to the TQT study, we are willing to provide feedback on the final protocol. In the TQT study, your proposal to administer BEMA buprenorphine with naltrexone will introduce a confounding factor and will result in a study that cannot be interpreted. Additionally, scientifically justify your choice of the suprathreshold dose of buprenorphine in the TQT study.

All Phase 3 clinical trials should use the to-be-marketed formulation. If the to-be-marketed formulation is not used in the Phase 3 trials, then the to-be-marketed and clinical trial formulation should be linked through appropriate BA/BE and/or in vitro dissolution data, as appropriate.

Discussion:

The Sponsor stated that they would add a Subutex arm to Study 117, as the Division has requested.

The Division emphasized that, before comments could be provided for Study 118, a protocol with a rationale supporting the PK testing strategy should be submitted. The Sponsor acknowledged this request, and noted that their goal is to identify if consumption of various liquids after medication administration significantly affected the PK.

The Sponsor stated that they planned to utilize the BEMA buprenorphine product without the ink identification during the Phase 3 studies, but that they would conduct an f2 dissolution assessment comparing both products prior to the NDA submission. The Division stated that a post-meeting note would be included in the minutes commenting on this proposal.

Post-Meeting Note:

The proposal to bridge the formulations with and without the ink identification by f2 dissolution assessment prior to the NDA submission is acceptable.

Question 14 Does the Agency have any comments related to the design or conduct of clinical study BUP-150?

Division Response:

As noted in response to Question 13, the administration of naltrexone introduces a confounding effect into the study. Naltrexone administration is not always necessary to make a thorough QT study adequately safe and we discourage the use of naltrexone.

When you submit your full protocol, it will be reviewed by the QT interdisciplinary review team.

Discussion:

With respect to the TQT study, the Sponsor stated that they would submit a justification supporting the administration of naltrexone concurrently with BEMA buprenorphine. The Division said that it would review such a protocol, but that use of naltrexone has not been allowed previously. The Sponsor stated that they were concerned that expected adverse effects of opioids, such as nausea and vomiting, could affect the ability to gather meaningful data on the QT interval and that administering naltrexone was a strategy to decrease the occurrence of these expected adverse effects. The Division suggested that the Sponsor could use a population that was tolerant to opioids.

Question 15 Does the Agency have any comments related to the design or conduct of clinical study BUP-301?

Division Response:

We have the following comments regarding clinical study BUP-301:

- 1. The open-label titration period should allow for decreases in dose in addition to increases in dose.**
- 2. The protocol design raises concern for inducing opioid withdrawal in patients during the open-label titration period. Include a plan for careful assessment of opioid withdrawal during the open-label titration period. Consider modifying the conversion procedures to mitigate the chance of opioid withdrawal.**
- 3. The protocol does not adequately assess opioid withdrawal symptoms during the double-blind treatment period. Include more frequent assessments of opioid withdrawal symptoms since opioid withdrawal may manifest as pain.**
- 4. To increase the safety of patients enrolled in this study, exclude patients with:**
 - a. Evidence of moderate to severe impaired liver function upon entry into the study**
 - b. QTc > 450 msec on ECG**
- 5. The primary endpoint should be defined as change from baseline to Week 12, rather than to “final visit.”**
- 6. The Intent-to-Treat (ITT) population should be defined as all randomized subjects who received study drug, without the proposed exclusion regarding postdose assessments.**
- 7. On the basis of our experience with similar drugs, the sample size you have proposed appears small. Provide scientific justification for the assumptions used to calculate the sample size.**
- 8. The imputation rules lack detail. Modify the protocol to provide more detail when certain rules will apply and clearly identify how you are defining “baseline.” Provide details on how use of rescue medication will be accounted for in the imputation plan. Include procedures to ensure discontinuations due to opioid withdrawal symptoms, lack of efficacy, or adverse events are not missed or misclassified as Withdrew Consent.**

Discussion:

The Division stated that, because buprenorphine is a partial-agonist, withdrawal may be induced if opioid-tolerant patients are not tapered from their original opioid prior to receiving buprenorphine. Symptoms of opioid withdrawal may introduce a confounding factor, as opioid withdrawal can manifest as pain. The Division recommended that a withdrawal assessment scale such as Clinical Opiate Withdrawal Scale (COWS) or Short Opiate Withdrawal Scale (SOWS) be included. Additionally, to minimize subject dropout, the Division encouraged the Sponsor to

taper subjects very slowly in order to minimize withdrawal symptoms and to use flexibility in dosing.

The Sponsor stated that they have added two visits to the protocol on Study Days 4 and 11 for assessment of opioid withdrawal symptoms. The Sponsor stated that they have also added a washout period prior to the open-label titration period.

Additionally, the Sponsor noted their agreement with items 4, 5, 6, and 7, of the Division's response.

With respect to item 8, the Division noted that imputing a single value for missing data is not in keeping with the National Academy of Sciences (NAS) recent recommendations (http://www.nap.edu/catalog.php?record_id=12955). The Division informed the Sponsor that they could propose a strategy that would address concerns outlined in the report or submit a rationale supporting the use of a single imputation strategy. However, The Division noted that it may be difficult to formulate such a rationale in light of the NAS report. The Division agreed to work with the Sponsor.

The Division also commented that the Sponsor could consider a continuous responder function, comparing treatment groups. Subjects should be treated for at least twelve weeks, as this is our surrogate for a chronic use indication.

Question 16 Does the Agency concur that one pivotal, randomized withdrawal study in subjects with chronic low back pain (BUP-301) meets the Agency's efficacy requirements to support a 505(b)(2) NDA for BEMA Buprenorphine in the proposed indication?

Division Response:

Yes. One positive adequate and well-controlled study should suffice to support efficacy for your proposed indication.

Discussion:

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

Question 17 Does the Agency have any comments related to the design or conduct of clinical study BUP-305?

Division Response:

Based on the brief description provided, Study BUP-305 may provide useful safety information.

Discussion:

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

Question 18 Does the Agency concur that the planned safety population and extent of exposure planned for the original NDA and 120-day Safety Update meets the Agency's safety requirements to support a 505(b)(2) NDA for BEMA Buprenorphine in the proposed indication?

Division Response:

Barring any unforeseen safety signals, the planned safety population and extent of exposure appears adequate.

Discussion:

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

Regulatory

Question 19 Does the Agency have any comments on the proposed indication?

Division Response:

The proposed indication is acceptable.

Discussion:

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

Question 20 Does the Agency have any comments on the draft proposed Target Product Profile?

Division Response:

For the non-clinical sections of the label, use existing labeled nonclinical safety data as part of the 505(b)(2) submission to determine BEMA buprenorphine product-specific dosing margins between nonclinical and maximum proposed human clinical dosing. Numerical dose levels are contained in reference NDA labels for buprenorphine but dose margins (nonclinical:clinical) must be converted relative to the proposed human dosing with BEMA buprenorphine. If possible, pharmacokinetic/toxicokinetic-based comparisons are preferred.

With regard to other sections of the label, given that most of the proposed text speculates on what the studies will show, it is premature to discuss labeling at this point.

Discussion:

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

Question 21 Does the Agency agree that, dependent on the actual results, clinical study (b) (4) could support the proposed labeling statement (b) (4) ?

Division Response:

No. There will be no (b) (4) claims (b) (4) in the label for your product. Buprenorphine is a DEA Schedule III moiety (b) (4)

Discussion:

The Sponsor sought clarification (b) (4)

The Division stated that we were unsure if this would be acceptable or not, but that they would try to include a Post-Meeting Note to that effect.

The Division advised the Sponsor to investigate the abuse liability of their products and that protocols with this objective can be submitted for review. Data on how people abuse currently marketed formulations of buprenorphine to obtain euphoric effects would inform the design of abuse liability studies for this product. The Sponsor could use this information to determine how susceptible to abuse BEMA buprenorphine may be.

Post-Meeting Note:

(b) (4)

Thus promotional materials for a drug product with such (b) (4) claims will be misleading and are in violation of the regulations.

Question 22 Does the Agency concur that, dependent on the actual results, clinical study [redacted] could support the proposed labeling statement [redacted] (b) (4)

Division Response:

No. Claims of [redacted] (b) (4) will not be included in the label. [redacted] (b) (4)

Discussion:

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

Question 23 Does the Agency agree that, dependent on the actual results, clinical study [redacted] could support the proposed labeling statement [redacted] (b) (4)

?

Division Response:

No. [redacted] (b) (4)

Discussion:

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

Question 24 Does the Agency concur that, dependent on the actual results, clinical study [redacted] could support the proposed labeling statement [redacted] (b) (4)

?

Division Response:

A consultation is pending to address this question. You will receive a separate communication when the consultation is complete.

Discussion:

There was no discussion beyond the Division's initial written response. However, responses to our consult requests have been received from the Study Endpoints and Labeling Development (SEALD) Team as well as the Division of Psychiatry Products. Their comments are reproduced below.

Post-Meeting Note:

You have not provided sufficient supporting evidence [redacted] (b) (4) to support labeling claims. [redacted] (b) (4)



Question 25 Does the Agency agree that, dependent on the actual results, clinical study (b) (4) could support the proposed labeling statement (b) (4)?

Division Response:

A consultation is pending to address this question. You will receive a separate communication when the consultation is complete.

Discussion:

There was no discussion beyond the Division's initial written response. However, responses to our consult requests have been received from the Study Endpoints and Labeling Development (SEALD) Team as well as the Division of Metabolic and Endocrine Products. Their comments are reproduced below.

Post-Meeting Note:

You have not provided sufficient supporting evidence (b) (4) support labeling claims of treatment benefit. (b) (4)



Question 26 Can the Agency share any thoughts on risk management for BEMA Buprenorphine in the proposed indication?

Division Response:

The requirements for long acting/extended release opioids are currently under review. At this time, we refer you to the REMS for Butrans (NDA 021306) to plan your REMS.

Discussion:

The Sponsor sought clarification as to whether the class-wide opioid REMS would apply to their product, to which the Division replied in the affirmative. The Division also noted that, if the NDA is submitted prior to the class-wide REMS being implemented, than the Sponsor is expected to submit a REMS which contains a Medication Guide and educational materials for prescribers.

Post-Meeting CSS Comment:

Buprenorphine is Schedule III under the Controlled Substances Act (CSA). During Phase 3 clinical studies, you must address abuse-related adverse events and provide information related to overdose, misuse, abuse, physical dependence/withdrawal syndrome, tolerance and diversion.

You must ensure that investigators are prospectively trained to recognize the adverse events and other behaviors that may indicate abuse. Additionally, you must maintain strict monitoring of drug accountability and compliance during clinical development.

For additional information, we refer you to our draft guidance *Assessment of Abuse Potential of Drugs*, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

General Discussion:

The Sponsor inquired as to what sort of (b) (4) claim(s) could be included in their labeling. The Division replied that if the BEMA product could demonstrate, through rigorous study, (b) (4) then some

description of this may be allowed in the labeling. The Division further elaborated that the product would need to be evaluated (b) (4)

The Division asked the Sponsor to ensure that they submit a justification in the NDA for the inclusion of (b) (4) in some clinical batches but not other batches. The Sponsor said that they would do so, and added that the (b) (4)

Action Items:

1. The Sponsor will submit a justification for the administration of naltrexone in their TQT study.
2. The Sponsor will include information supporting the safety of the ink identification that is to be used (e.g., DMF letter of authorization).
3. The Division will review and provide comments for Study 118 once the Sponsor finalizes and submits their protocol.

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
10/18/2010

Reference ID: 2851455

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