

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204242Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 204242

SUPPL #

HFD #

Trade Name Zubsolv

Generic Name buprenorphine and naloxone sublingual tablets

Applicant Name Orexo AB

Approval Date, If Known July 3, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(2)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA# 020733 Suboxone (buprenorphine and naloxone) sublingual tablets

NDA# 022410 Suboxone (buprenorphine and naloxone) sublingual film

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:

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

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: Matthew Sullivan
Title: Chief, Project Management Staff (Acting), Division of Anesthesia, Analgesia, and Addiction Products
Date: July 3, 2013

Name of Office/Division Director signing form: Bob A. Rappaport
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/

MATTHEW W SULLIVAN
07/03/2013

BOB A RAPPAPORT
07/03/2013

Buprenorphine/Naloxone Sublingual Tablet (OX219)

MODULE 1

1.3.3 Debarment Certification

1.3.3 DEBARMENT CERTIFICATION

Orexo AB certifies that it did not and will not use in any capacity the services of any persons debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Signature:  _____

Date: June 12, 2012

Anders Pettersson, M.D. Ph.D.

Senior Vice President, Clinical Research and Development

Orexo AB

Signature:  _____

Date: July 24, 2012

Damaris DeGraft-Johnson, RPh, MSc. Med. Chem.

President

DJA Global Pharmaceuticals, Inc.

Confidential

Page 1 of 1

Orexo AB

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204242 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Zubsolv Established/Proper Name: buprenorphine and naloxone Dosage Form: sublingual tablet		Applicant: Orexo AB Agent for Applicant (if applicable): DJA Pharmaceuticals
RPM: Matthew Sullivan, MS		Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>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)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Suboxone SL Tablets – NDA 020733</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>Different ratio of buprenorphine naloxone</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 7/3/2013</p> <p>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.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>July 6, 2013</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

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (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).

<p>❖ 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 _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 5</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input checked="" type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

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

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
<p>❖ Copy of this Action Package Checklist⁴</p>	<p>7/8/2013</p>
Officer/Employee List	
<p>❖ 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>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
Action Letters	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) Approval – 7/3/2013</p>
Labeling	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<p>7/3/2013</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>9/6/2012</p>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	7/3/2013
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	9/6/2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ 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 	7/3/2013
<ul style="list-style-type: none"> ❖ 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>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	12/10/2012 12/7/2012;7/1/2013
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 11/16/2012 <input checked="" type="checkbox"/> DMEPA 6/17/2013 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 6/7/2013 <input checked="" type="checkbox"/> ODPD (DDMAC) 6/6/2013; 6/11/2013 <input checked="" type="checkbox"/> SEALD 6/28/2013 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	RPM filing – 11/16/2012
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2) 5/29/2013
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) 7/3/2013
<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 5/22/2013 If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	9/6/2012 10/29/2012 11/16/2012 12/14/2012 1/31/2013 4/17/2013 4/26/2013 5/22/2013 5/31/2013 6/6/2013 6/10/2013 6/19/2013 7/2/2013
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• 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
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 7/16/2012
• EOP2 meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	PIND – 3/4/2011
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
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 7/3/2013
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 6/12/2013
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None 2
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	
• Clinical review(s) <i>(indicate date for each review)</i>	11/6/2012; 5/24/2013
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None

⁶ Filing reviews should be filed with the discipline reviews.

❖ 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>)	Addressed in clinical review – 5/24/2013
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None 6/10/2013
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> Not applicable 5/13/2013
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	6/21/2013 7/3/2013 <input type="checkbox"/> None 6/27/2013
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/5/2013
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None 5/31/2013
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/2/2012; 5/31/2013; 6/10/2013; 6/27/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 11/15/2012; 11/19/2012; 3/5/2013; 6/6/2013; 6/29/2013
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input checked="" 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>		6/6/2013
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>		Date completed: 6/25/2013 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

MATTHEW W SULLIVAN
07/08/2013

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, July 02, 2013 10:39 AM
To: Damaris DeGraft-Johnson (ddj@djaglobalpharma.com)
Cc: Tyrah L. Miles (tlm@djaglobalpharma.com)
Subject: Additional PI comments/ NDA 204242

Damaris –

These are fairly straight forward PI comments. I would have made them myself, but since you still have the version with the menthol change included, you ought to make these and then send the new version back to us. (Tracked-changes included, please.)

1. The second and third statements under the Dosage and Administration header in Highlights do not reference the FPI. Include (2.1) after the second statement and (2.2) after the third statement. We recommend using bullets for each statement under the Dosage and Administration header in HL. The statement under the Adverse Reactions header in Highlights does not reference the FPI. Include (6) at the end of the statement.
2. The HL Limitation Statement is not on the line immediately beneath the HL heading. There is a space between the two. Delete the space.
3. The Initial U.S. Approval in HL is not placed immediately beneath the product title. There is a space between the two. Delete the space.
4. Subsection heading 5.9 in the TOC reads as “Neonatal” but subsection heading 5.9 in the FPI reads as “Neonatal Abstinence Syndrome. The TOC subsection heading should be changed.
5. In section 5.4 and 16, the cross reference to 17.2 should reference the section, not subsection heading (i.e., change to “[see Patient Counseling Information (17.2)]” instead of “[see Disposal of Unused ZUBSOLV Sublingual Tablets (17.2)]”). In section 8.1, the first paragraph, the cross-reference “[see Animal Data]” does not reference a section or subsection heading. Change reference to include the correct section heading followed by the numerical identifier in italics. In section 8.1, the fourth paragraph, the cross-reference “[See Warnings and Precautions]” does not include the numerical identifier and the entire contents are not in italics. Include the numerical identifier and italicize the entire contents.
6. Correct section heading 6.1 to read as “Clinical Trials Experience” instead of “Adverse Events in Clinical Trials-ZUBSOLV.”
7. Correct section heading 6.2 to read as “Postmarketing Experience” instead of “Adverse Events-Post-marketing Experience with buprenorphine/naloxone Sublingual Tablets.” Additionally, include the required text:

The following adverse reactions have been identified during post-approval use of buprenorphine and naloxone sublingual tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Thanks,
Matt

Matthew W. Sullivan, M.S.
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/s/

MATTHEW W SULLIVAN
07/02/2013

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, June 19, 2013 4:09 PM
To: Damaris DeGraft-Johnson (ddj@djaglobalpharma.com)
Cc: Tyrah L. Miles (tlm@djaglobalpharma.com)
Subject: Zubsolv PI + MG revisions
Attachments: Zubsolv labeling to Sponsor June19.doc; ZUBSOLV MG to Sponsor June 19.doc

Damaris –

As mentioned earlier, attached are our revisions to your PI and MG.

Thanks,
Matt

Matthew W. Sullivan, M.S.
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20 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following
this page

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/s/

MATTHEW W SULLIVAN
06/19/2013

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Monday, June 10, 2013 4:50 PM
To: Damaris DeGraft-Johnson (ddj@djaglobalpharma.com)
Cc: Tyrah L. Miles (tlm@djaglobalpharma.com)
Subject: Zubsolv REMS NDA 204242
Attachments: prescriber-letter-word.doc; prescriber-brochure-word.doc; pharmacist-letter-word.doc; pharmacist-brochure-word.doc; checklist-word.doc; rems-word.doc

Hi –

Here is our response to your email from Friday afternoon 6/7/2013. Please let us know if you have any questions.

- A. Provide confirmation that the BPMG has been contacted regarding inclusion in the BTOD REMS.

- B. The REMS document must be identical to BTOD REMS with the same goals, REMS elements, and appended materials. The appended materials include the Medication Guide, Dear Prescriber Letter, Dear Pharmacist Letter, Appropriate Use Checklist, Prescriber Brochure “Office -Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers”, Pharmacist Brochure “Office -Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists”, and BTOD REMS website. The appended materials should be amended with relevant product specific information to OX219. Attached are word versions of the appended materials for your revisions (Medication Guide not included as this will be specific to OX219).

- C. The term “Waiver Granted Shared REMS” should be revised to “Shared REMS” in all the materials.

- D. The REMS document for OX219 should also include a Timetable for Submission of Assessments, which is a requirement for NDA holders. The text to be included in the Timetable for Submission of Assessments is as follows:

“REMS assessments will be submitted to the FDA at each year, on August 30th. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. The NDA holder(s) will submit each assessment so that it will be received by the FDA on or before the due date.”

- E. REMS Supporting Document must be included with the REMS submission. The REMS Supporting Document must include the agreed upon assessment plan for the BTOD REMS. The assessment plan is as follows:

“The REMS assessment plan should include, but is not limited, to the following:

1. An evaluation of patients’ awareness and understanding of the serious risks associated with buprenorphine-containing products.
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
4. An evaluation of prescribers’ awareness and understanding of the serious risks associated with buprenorphine-containing products
5. An evaluation of pharmacists’ awareness and understanding of the serious risks associated with buprenorphine-containing products
6. An analysis to evaluate utilization patterns of buprenorphine-containing products including frequency of office visits, amount dispensed in prescriptions to new patients, and other indicators of adherence to practices important to safe use.
7. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose and addiction and any intervention taken resulting from signals of abuse, misuse, overdose and addiction. Surveillance will include, among other sources, reports of pediatric exposures
8. Monitoring and evaluation of the implementation of the ETASU
9. An assessment of the extent to which the REMS is meeting its goals. Specific measures that will be proposed to increase awareness if surveys of patients, prescribers, and pharmacists indicate that awareness is not adequate.”

Thanks,
Matt

Matthew W. Sullivan, M.S.
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/s/

MATTHEW W SULLIVAN
06/10/2013

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Thursday, May 30, 2013 4:16 PM
To: Damaris DeGraft-Johnson (ddj@djaglobalpharma.com)
Subject: Additional CMC information requests for NDA 204242.

Damaris –

Some additional CMC requests.
Matt

1. Use only one set of Specifications for the related substances in the drug product that are in accordance with ICH Q3B and consistent with the specifications set for the same impurities identified in the drug substances. The specification of (b) (4) listed adjacent to each of the related substance in the tables in section P. 5.1 is not in accordance with ICH Q3B.
2. The specification for the total related peaks for buprenorphine and the specification for total related peaks for naloxone in Section P.5.1. are too wide and are not supported by the batch analysis data. Tighten the specification for the total related peaks for buprenorphine and the specification for total related peaks for naloxone.
3. Release testing of the drug product should include testing for (b) (4) and tablet hardness.
4. The USP methods used must include the corresponding method number in the Specification tables in Section P.5.1
5. The method for Naloxone Assay is not specific since (b) (4) with Naloxone. Refine the Assay Method for Naloxone to be Specific for the Naloxone without (b) (4) of any other substances including (b) (4)
6. The related impurity Assay for Naloxone is not considered validated since the Accuracy range is too large for Naloxone. Refine the Assay for Naloxone to be accurate within a range of (b) (4) RSD.
7. Include the following time points in the post approval stability protocol 3, 6, 9 and 18 months per ICH Q1A(R2).
8. Stability testing should include testing for Hardness, (b) (4) and friability.
9. Provide Stability data for stress testing studies of the drug product that includes Photostability testing according to ICH Q1B.
10. Since all the degradants are known, characterized, and the analytical methods are in place, separate specifications for each degradant should be proposed.

Thanks,
Matt

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/s/

MATTHEW W SULLIVAN
05/31/2013

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, May 22, 2013 11:17 AM
To: 'Damaris DeGraft-Johnson'
Subject: CMC Information Request / NDA 204242

Hi Damaris –

Can you get back to us within a week on these issues?

Thanks
matt

1. Batch analysis tables in section 3.2. S.4.4 Buprenorphine HCl do not reflect the specifications for related substances consistent with the specifications listed in Section 3.2. S. 4.1. A consistent set of specifications must be used for all testing of API and should be set in accordance with those specifications set by the API manufacturer as listed in section 3.2.S.4.1. Update all batch analysis tables in Section 3.2.S.4.4. accordingly.
2. Particle Size Distribution specifications for Buprenorphine HCl are part of the release testing profile of the API and are not for information only. Update Batch Analysis Tables in section 3.2.S.4.4 Buprenorphine HCl with the 3-point particle size distribution specifications to be consistent with section 3.2.S.4.1 Buprenorphine HCl and other batch analysis tables in section 3.2.S.4.4. Buprenorphine HCl.
3. The data as listed for testing of related substances for batches RC000736, RC000998, RC000999 and RC001001 in Table 5 of Section 3.2.S.4.4 Buprenorphine HCl is not acceptable. Include the actual data for related substance testing for these batches.
4. Stability Specifications listed for related substances in tables 10-18 of Section 3.2.S.7.3 Buprenorphine HCl are not consistent with those listed for Tables 1-9 in the same Section. The tighter specifications in tables 1-9 are consistent with the release specifications. Update all stability data tables in Section 3.2.S.7.3 Buprenorphine HCl to reflect the tighter specifications for related substances.
5. Specifications for related substances in batches analysis Tables 2, 3 and 5, Naloxone HCl, do not match the Specifications for related substances A, B, C, and F listed in the Specifications Table in Section 3.2.S.4.1 Naloxone HCl and in Table 4 Batch Analysis Naloxone HCl Section 3.2.S.4.4. One consistent set of Specifications must be used for testing of Naloxone HCl at release and must be consistent with those specifications justified in Section 3.2.S.4.1
6. (b) (4) for Naloxone HCl drug substance is identified as the genotoxic impurity (b) (4) which is monitored separately at (b) (4). Yet Tables 2, 3 and 5 in Section 3.2. S.4.4 Naloxone HCl, have two different specifications for “(b) (4)” and for (b) (4). The results for both are also vastly different, and if the values reported for (b) (4) are correct and the impurity is controlled at (b) (4), as a genotoxic impurity, then all

the batches are considered as out of specification. Clarify or justify the data reported for this impurity in Tables 2,3 and 5.

7. The data as listed for related substances in Table 4 of Section 3.2.S.4.4. Batch Analysis Naloxone HCl is not acceptable. Include the actual data for related substance testing for these batches.
8. The related substances specifications for the drug product in Section 3.2.P.5.1 are not in accordance with ICH Q3B and are not consistent with the specifications for the related substances for each of the drug substances. Update the drug product specifications for all related substances to be consistent with those specifications for the same related substances in Section 3.2.S.4.1 Buprenorphine and Naloxone, respectively and in accordance with ICH Q3B.
9. Batch analysis tables for the drug products (Tables 2-16) do not have one consistent set of specifications for the related substances set as limits across all the batches tested. One set of specifications must be used that are consistent with the specification in section 3.2. P.5.1.
10. Regarding related substance data for shown in Tables 2-12 in Section 3.2.P.5.4, provide the actual data. Related substance data as listed in these tables is not acceptable.

Thanks,
Matt

Matthew W. Sullivan, M.S.
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MATTHEW W SULLIVAN
05/22/2013

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, April 17, 2013 9:28 AM
To: Damaris DeGraft-Johnson (ddj@djglobalpharma.com)
Cc: Aaron R. Truesdale
Subject: N204242 Information Request

Damaris –

The background package for the meeting request includes a pharmaceutical Failure Mode and Effects Analysis (RxFMEA), which was utilized to identify process gaps and outcome deficiencies of the existing REMS for buprenorphine/naloxone. While the analysis identifies individual gaps and respective hazard scores, a description of the parameters used to calculate the hazard scores was not provided. Therefore, the Agency requests the following information be provided by April 19, 2013 in order to continue our review of the analysis:

- a description of the hazard scoring methodology that was used to calculate hazard scores and their associated risks as provided in this RxFMEA analysis,
- the rating scales provided to respondents/committee for determining the probability and severity of a failure mode/gap, and
- a complete decision tree (including the use of a threshold level and rationale for that threshold level, if used) regarding the determination of whether or not a particular failure mode/gap warranted further action.

Thanks,
Matt

Matthew W. Sullivan, M.S.
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Division of Anesthesia, Analgesia,
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/s/

MATTHEW W SULLIVAN
04/17/2013

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Thursday, January 31, 2013 10:33 AM
To: 'Damaris DeGraft-Johnson'
Subject: Information Request N204242
Attachments: ACOGCommitteeOpinion2012Opioidaddictionpregnancy.pdf

Damaris –

Can you work on this information request for us?

As opioid dependence has become a significant public health issue, this also affects pregnant women and their newborns. Use of buprenorphine during pregnancy has become more common (see ACOG Committee Opinion), therefore as new products enter the market, labeling should inform what data/information is available about use in these subpopulations.

Therefore, we would like you to review the relevant published data on buprenorphine and lactation, with an eye toward updating the Nursing Mothers section of labeling.

We would like to see a proposed annotated label showing any changes that you feel are appropriate.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
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/s/

MATTHEW W SULLIVAN
01/31/2013

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, December 14, 2012 12:17 PM
To: 'Damaris DeGraft-Johnson'
Subject: NDA 204242

Damaris –

A couple of comments from the Biopharmaceutics review group:

1. Provided information/data showing a relationship between dissolution and disintegration. Note that regardless of the agency's future decision on your strategy of disintegration test in lieu of dissolution for your product, future SUPAC changes under post-approval supplements should be supported with dissolution profile and f2 data.
2. Provide solubility data of the drug buprenorphine hydrochloride as per the ICH Q6A, Decision tree # 7.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
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/s/

MATTHEW W SULLIVAN
12/14/2012



IND 110637
NDA 204242

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Orexo AB
c/o DJA Global Pharmaceuticals, Inc.
115 Commons Court
Chadds Ford, PA 19317

ATTENTION: Damaris DeGraft-Johnson, R.Ph., M.Sc., Med. Chem.
President

Dear Ms. DeGraft-Johnson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act, and your New Drug Application (NDA) dated September 5, 2012, received September 6, 2012 submitted under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Buprenorphine and Naloxone Sublingual Tablets, 1.4 mg/0.36 mg and 5.7 mg/1.4 mg.

We also refer to:

- your June 12, 2012 correspondence, received June 13, 2012, requesting review of your proposed proprietary name, Zubsolv under the IND; and
- your correspondence dated November 27, 2012, received November 28, 2012, requesting review of your proposed proprietary name, Zubsolv, under the NDA.

We have completed our review of the proposed proprietary name and have concluded that it is acceptable. The proposed proprietary name, Zubsolv, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. Additionally, if any of the proposed product characteristics as stated in your November 27, 2012 submission are altered prior to approval of the marketing application; the proprietary name should be resubmitted for review.

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NDA 204242
Page 2

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Mark Liberatore, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2221. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Matthew Sullivan at 301-796-1245.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
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/

CAROL A HOLQUIST
12/10/2012



NDA 204242

FILING COMMUNICATION

Orexo AB
c/o DJA Global Pharmaceuticals, Inc.
115 Commons Court
Chadds Ford, PA 19317

Attention: Damaris DeGraft-Johnson, RPh, MSc. Med. Chem.
President, DJA Global Pharmaceuticals, Inc.

Dear Ms. DeGraft-Johnson:

Please refer to your New Drug Application (NDA) dated September 5, 2012, received September 6, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for OX219 (buprenorphine and naloxone) sublingual tablets.

We also refer to your amendments dated October 18, and November 5, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 6, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 17, 2013.

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

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

SARA E STRADLEY on behalf of BOB A RAPPAPORT
11/16/2012

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Monday, October 29, 2012 12:30 PM
To: 'Damaris DeGraft-Johnson'
Subject: NDA 204242

Damaris –

Our Clinical Pharmacology team has identified the following two issues with respect to NDA 204242:

1. For Study OX219-003, provide the dataset with all PK raw data for your calculation of PK parameters and the final dataset of PK parameters that you used for your bioequivalence analysis, as well as the SAS codes.
2. For Study OX219-004, provide the dataset with all PK raw data for your calculation of PK parameters and the final dataset of PK parameters that you used for your dose proportionality analysis, as well as the SAS codes.

Our 60-day filing review timeline is quickly drawing to a close, so we'd like to hear your thoughts on the timeline for a response to these items.

Thanks,
Matt

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

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/s/

MATTHEW W SULLIVAN
10/29/2012



NDA 204242

NDA ACKNOWLEDGMENT

Orexo AB
c/o DJA Global Pharmaceuticals, Inc.
115 Commons Court
Chadds Ford, PA 19317

Attention: Damaris DeGraft-Johnson, RPh, MSc. Med. Chem.
President, DJA Global Pharmaceuticals, Inc.

Dear Ms. DeGraft-Johnson:

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

Name of Drug Product: OX219 (buprenorphine and naloxone) sublingual tablets

Date of Application: September 5, 2012

Date of Receipt: September 6, 2012

Our Reference Number: NDA 204242

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 5, 2012, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

MATTHEW W SULLIVAN
09/06/2012



IND 110637

MEETING MINUTES

Orexo AB
c/o DJA Global Pharmaceuticals, Inc.
115 Commons Court
Chadds Ford, PA 19317

Attention: Damaris DeGraft-Johnson, RPh, MSc.
President

Dear Ms. DeGraft-Johnson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OX219 (buprenorphine and naloxone) sublingual tablets.

We also refer to the meeting between representatives of your firm and the FDA on July 17, 2012. The purpose of the meeting was to discuss your upcoming NDA submission for OXE219.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: July 17, 2012, 1:30PM EDT
Meeting Location: White Oak 22, Room 1313
Application Number: IND 110637
Product Name: OX219 (buprenorphine and naloxone)
Indication: Maintenance treatment of opioid dependence
Sponsor/Applicant Name: Orexo AB

FDA Attendees	Title
Bob A. Rappaport, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, MD	Deputy Director, DAAAP
Celia Winchell, MD	Clinical Team Leader, DAAAP
Pam Horn, MD	Medical Officer, DAAAP
Ramesh Raghavachari, PhD	CMC Lead, DNDQA III, ONDQA
Danae Christodoulou, PhD	CMC Lead, DNDQA III, ONDQA
Julia Pinto, PhD	Chemistry Reviewer, ONDQA
Dan Mellon, PhD	Pharmacology / Toxicology Supervisor, DAAAP
Yun Xu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Ying Fan, PhD	Clinical Pharmacology Reviewer, OCP
Dionne Price, PhD	Statistics Team Leader, Office of Biostatistics (OB)
David Petullo, MS	Statistics Reviewer, OB
Katherine Won, PharmD	Regulatory Health Project Manager, DAAAP
Stephen Sun, MD	Medical Officer, Controlled Substance Staff (CSS)
Matthew Sullivan, MS	Regulatory Health Project Manager, DAAAP
Jessica Eisner, MD	Medical Officer, DAAAP
Douglas Warfield	Office of Business Informatics
Lauren Oliva	Pharmacy Student, CSS
Sponsor Attendees	Title
Åsa Holmgren, M.Sc.Pharm.	Senior Vice President Regulatory Affairs, Orexo AB
Anders Pettersson, M.D. Ph.D.	Senior Vice President Clinical R&D, Orexo AB
David Westberg, M.Sc. Chem. Engineering	Senior Project Leader, Orexo AB
Thomas Lundqvist, M. Sc. Pharm.	Executive Vice President, Head of Pharmaceutical R&D, Orexo AB
Anna-Karin Utberg, M Sc Chem	CMC Project Leader, analytical chemist, Orexo AB
Damaris DeGraft-Johnson, RPh, M.Sc., Med. Chem	Regulatory Consultant, US Agent, President DJA Global Pharmaceuticals, Inc.

Dennis DeCola, B.S. Biology,	Senior Regulatory Consultant DJA Global Pharmaceuticals Inc.
William Fiske, Ph.D.	Pharmacokinetic Consultant

BACKGROUND

DJA Global Pharmaceuticals, Inc., on behalf of Orexo, submitted a request for a Pre-NDA meeting. This request was granted, and the meeting was scheduled for July 17, 2012. A Meeting Package was provided on June 4, 2012. The Division provided preliminary responses on July 16, 2012.

Orexo plans to submit a 505(b)(2) application relying upon Suboxone tablets, NDA 020733. The Sponsor previously met with the Division on February 3, 2011, to discuss this application.

The questions from the June 4, 2012, meeting package are shown below in italic font, and the Division's July 16, 2012, preliminary responses are shown in bold font. Discussion from the meeting appears in normal font.

Subsequent to receiving the July 16, 2012, preliminary comments, the Sponsor informed the Division that they only wished to discuss responses to Question 6, and Attachment 1 (pages 17, 18 and 23). (Discussion related to the attachment appears at the end of the document.)

DISCUSSION

Question 1.a. In the pre-IND meeting held between Orexo AB and FDA on Feb 3, 2011, FDA requested that Orexo should demonstrate equivalent buprenorphine exposure to Suboxone® 8/2 (questions 1 and 8).

Orexo concludes that study OX219-003 demonstrates equivalent buprenorphine exposure according to standard equivalence criteria and that the study results are sufficient and appropriate to establish the bridge to Suboxone® tablets as a basis for this 505(b)(2) NDA.

Does the FDA agree?

Division Response:

Based on the preliminary data of equivalent buprenorphine exposure between (b) (4) mg of your product and 8/2 mg Suboxone tablet, it appears that the results are sufficient and appropriate for NDA filing for the (b) (4) mg strength. The adequacy of the data to establish a bridge to the referenced product, however, will be determined during the course of the NDA review.

As noted in our March 4, 2011, meeting minutes, you will need to submit a biowaiver request for your proposed lower strength of 1.4/0.36 mg, and supportive data for the dissolution profile comparison in three media using an appropriate in vitro dissolution method. Justify the adequacy of the dissolution method to be used. You may submit the justification in a dissolution method development report for review before you conduct the dissolution profile comparison studies.

Discussion:

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

Question 1.b. In the pre-IND meeting held between Orexo AB and FDA on February 3, 2011, FDA stated that a lower naloxone exposure would be acceptable (questions 1 and 14), and that lower norbuprenorphine exposure as compared to Suboxone® would not lead to a requirement for efficacy studies (question 13).

Orexo concludes that OX219-003 results are in agreement with FDA's requirements for naloxone and norbuprenorphine as expressed at the pre-IND meeting.

Does the FDA agree with Orexo's conclusion?

Division Response:

Yes. Lower naloxone exposure and lower norbuprenorphine exposure as compared to Suboxone are acceptable from a clinical pharmacology and clinical efficacy perspective.

Discussion:

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

Question 2.a. In the pre-IND meeting held between Orexo AB and FDA on February 3, 2011, FDA requested that Orexo should assess dose proportionality of OX219 over the dose range 1.4/0.36 to 11.4/2 mg (corresponding to Suboxone 2/0.5 to 16/4 mg) (question 16 and question 8). Orexo concludes that the study results regarding linearity and dose proportionality over the dose range are sufficient and appropriate to support the NDA.

Does the FDA agree?

Division Response:

Based on the preliminary data you submitted, the systemic exposure of buprenorphine and unconjugated naloxone in terms of Cmax and AUC increased in

a linear fashion with dose in the dose range tested (from 1.4/0.36 mg through 11.4/2.8 mg), but in a less than dose proportional fashion.

We agree the study results regarding linearity and dose proportionality over the dose range are sufficient and appropriate to support filing of the NDA. The adequacy of the data to support your conclusion, however, will be determined during the course of the NDA review.

Discussion:

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

Question 2.a. Based on agreement reached with FDA during the February 3, 2011 pre-IND meeting, regarding the required clinical program for this NDA, Orexo concludes that results from the PK studies OX219-003 and OX219-004 provide a complete clinical data package for this 505(b)(2) NDA.

Does the FDA agree with this conclusion?

Division Response:

Your approach seems appropriate from a clinical pharmacology perspective. However, we remind you that an additional biowaiver request for the lower strength should be included in the NDA. (See our response to Question 1.a.)

The final to-be-marketed formulation should be used in the studies in support of your product approval. Otherwise, you must provide adequate bridging information or justification that the study results can apply to your final to-be-marketed product.

Additionally, as mentioned in response to Question 11 in the March 4, 2011, meeting minutes, provide data on the time it takes for the product to completely dissolve in the mouth when administered.

Discussion:

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

Question 3. Local tolerability data from the OX219 clinical study program indicates that there were no abnormalities detected in local tolerability assessments performed after 298 exposures in 156 subjects with OX219 formulations. Orexo concludes that the local tolerability data provided will be sufficient and appropriate to support the NDA.

Does the FDA agree with Orexo's conclusion?

Division Response:

Yes, the exposure and assessments for local tolerability appear to be sufficient, pending a more detailed review during the NDA cycle.

Discussion:

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

Question 4. The in vitro extraction studies with OX219 demonstrated that both components (buprenorphine and naloxone) were co-extracted and that buprenorphine was not preferentially extracted, with the average amount of naloxone extracted being (b) (4). The systematic review of the scientific literature demonstrated that parenteral doses of (b) (4) mg of naloxone consistently precipitate withdrawal in individuals physically dependent on full μ -agonists.

Thus, Orexo concludes that in vitro extraction data and available literature support that the amount of naloxone released from the OX219 low strength under conditions of misuse is sufficient to precipitate an aversive reaction in individuals dependent on full μ -agonists.

Does the FDA agree with Orexo's conclusion?

Division Response:

We cannot agree or disagree that you have sufficiently demonstrated that the dose of naloxone in your product is likely to produce an aversive reaction under conditions of misuse until we have reviewed the submitted data and literature during the NDA cycle. However, your approach to providing the necessary data and supportive literature appears acceptable.

Additional Controlled Substance Staff (CSS) Comment:

The abuse profile of the buprenorphine component, a DEA Schedule III substance, will likely be unchanged in this formulation based upon the presented pharmacokinetics profile from Study OX219-003 and OX219-004, due to its similarity to the referenced product. However, review of these studies will be necessary to support this conclusion.

Discussion:

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

Question 5.a. As there are several sublingual buprenorphine products approved on the US market, Orexo proposes that the label for OX219 will indicate that any such buprenorphine product should be used for induction therapy. The draft labeling provided reflects this conclusion.

Does FDA agree with this proposal?

Division Response:

Yes, the statement “OX219 sublingual tablets should be used in patients who have been initially inducted using buprenorphine sublingual tablets” is acceptable.

Discussion:

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

Question 5.b. Section 2.6 Switching between OX219 sublingual Tablets and other buprenorphine/naloxone combination products. A proposed text for this section is provided in Attachment III.

Does the FDA agree with this approach?

Division Response:

Yes, we generally agree that including this type of information in the product label will be useful to prescribers and we will have further labeling comments as necessary during the NDA review.

Discussion:

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

Question 5.c. Orexo plans to summarize relevant PK results from OX219 dose proportionality study OX219-004 that provide pharmacokinetic results for the OX219 to be marketed tablet strengths; 1.4 mg/0.36 mg and 5.7 mg/1.4 mg.

Does FDA agree with this plan?

Division Response:

Your plan is reasonable. The final content in the label will be determined during the review of NDA submission.

Discussion:

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

Question 6. In recognition of the known risks associated with opioid products including buprenorphine, Orexo plans to develop a REMS for OX219 closely aligned with the REMS that has been approved for Suboxone® tablets and film. Orexo is providing an outline of the features of the proposed REMS for OX219 in Attachment IV of this background package. Orexo would like to discuss the proposed features and obtain FDA's current view on risk management expectations for buprenorphine/naloxone products. This would ensure timely completion and acceptance of the REMS for OX219 NDA.

Does the FDA agree with Orexo's plan?

Division Response:

It is premature to discuss the proposed features of the REMS in detail. However, we can make some general recommendations regarding how to proceed. Ideally, your company will join the other Sponsors in the buprenorphine single shared system REMS. You should submit a REMS that looks like the approved REMS for Suboxone and Subutex (as available on our website: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientandProviders/ucm111350.htm>). We will notify you of any additional safety issues identified during the review cycle that need to be addressed in the REMS. Additionally you should contact the primary point-of-contact for the buprenorphine REMS industry group and inform them that you want to join the group.

Additional comment:

There is a safety signal indicating that buprenorphine may cause QT interval prolongation at therapeutic concentrations. Therefore, you will be required to conduct a tQT study to support the safety of your product. This study, however, may be completed as a Postmarketing Requirement (PMR). You should include such a request in your NDA.

Discussion:

The Sponsor stated that they had little familiarity with REMS programs, and asked the Division to provide some thoughts on how the proposed single shared system might work. The Division responded that the Buprenorphine Industry Group was still discussing the REMS system, so changes may still occur, but, in general, the system is designed to minimize the burden on the health care system by eliminating the need for duplicative REMS programs while ensuring that the benefits of the drug outweigh the risks. Additionally, it is expected that all member companies would share the cost of implementing and operating the system.

The Division stated that they would provide the point of contact to the Sponsor once the group provides that information to the Agency. The Sponsor also noted that they were willing to initiate discussions with the Buprenorphine Industry Group prior to submission of their NDA.

The Sponsor asked the Division which buprenorphine products would be included in the single shared system, to which the Division responded that only those products indicated for the treatment of opioid dependence that present the same types of safety concerns as the current sublingual products (e.g., diversion, abuse, accidental pediatric exposure) would be included.

Question 7. Does the Agency agree that the requirement for pediatric safety and efficacy studies can be waived for all children under 17 years of age?

Division Response:

Birth to 5 weeks:

We do not agree with your contention that treatment of NAS is a separate indication from treatment of opioid dependence. We also do not agree that you are likely to obtain a waiver based on a lack of feasibility of enrolling a sufficient number of subjects or lack of an accepted outcome measure. However, a waiver request based on your argument that naloxone has no therapeutic value in neonates experiencing abstinence syndrome is reasonable since your product is a combination of buprenorphine and naloxone.

5 weeks to 12 years:

A waiver request appears reasonable for this age group, although you should include adequate supportive data with your request in the NDA submission.

12 years to 16 years:

To support your request for a waiver, we recommend that you submit an assessment of the pediatric use of pharmacotherapy for opioid dependence in this population. This should include a report of pediatric use data for currently marketed buprenorphine/naloxone products, which could include prevalence data, literature review, expert interviews, and review of insurance databases. Additionally, include an assessment of the prevalence of opioid dependence in this age group, including all illicit and prescription opioids, and the proportion of these cases that are treatment-seeking.

The Division, after consultation with the Pediatric Review Committee (PeRC), will make the final determination of the adequacy of your waiver requests during the NDA review cycle.

Discussion:

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

Question 8. Would the FDA agree to review a proposed study protocol during the initial NDA review using the Special Protocol Assessment Procedure under sections 505(b)(4)(B) and (C) of the Modernization Act?

It is Orexo's understanding that if the agency accepts review of this protocol during review of the initial NDA, this has no impact on approval and PDUFA timeline for the initial NDA. Is this correct?

Division Response:

You may submit a study protocol to support an induction indication to IND 110637 at any time and may request a Special Protocol Assessment (SPA) irrespective of the timing of an NDA review cycle. Your request will be evaluated and granted or denied based on the criteria outlined in the Guidance for Industry: *Special Protocol Assessment*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080571.pdf>. However, because there is not a well-established approach to the type of study you propose, an agreement under the SPA mechanism is unlikely.

You are correct that our agreement to conduct a SPA review and any regulatory decision on the SPA under the IND while an NDA cycle is ongoing will not impact the regulatory decision or PDUFA timeline for the NDA. However, if you conduct a new study that you did not submit as part of the NDA application and there is new safety data available at the time of the 120-day safety update of the NDA cycle, you would be required to submit this data to the NDA in the 120-day safety update. Any safety data submitted at the 120-day safety update becomes part of the NDA application, is subject to review during the NDA cycle, and could affect the regulatory decision on the NDA.

Discussion:

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

Question 9. Because no new animal pharmacology, pharmacokinetics or toxicology studies have been conducted for OX219, Orexo AB does not plan to provide any tabulated summaries for sections 2.6.3 pharmacology tabulated summary, 2.6.5 pharmacokinetic tabulated summaries and 2.6.7 toxicology tabulated summary in the NDA application.

Does FDA agree with Orexo's plan for these sections?

Division Response:

Yes, we agree that tabulated summaries are not needed if there are no new data.

Discussion:

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

Question 10. Orexo AB plans to provide in module 1.14.1.2 an annotated draft OX219 label that indicates which sections of the OX219 label have been taken directly from the Suboxone® tablet label (RLD). Sections of the OX219 label that contain any new information will be annotated referencing the location of the summary and technical sections of the NDA that support any new labeling information. In addition, the most current (currently December 2011) Suboxone® tablet RLD and film labels will be provided in section 1.14.3.3.

Does FDA agree with this approach?

Division Response:

Your plan for annotating the draft label is generally acceptable. Because the Suboxone tablet label was recently converted to PLR format and approved, the information in this label should be sufficient to guide you in writing your label and for submission to section 1.14.3.3. You should not reference the Suboxone film label unless you intend to rely upon the Agency's previous finding of safety for the Suboxone Film NDA (and provided appropriate patent certification) as part of your 505(b)(2) application.

Discussion:

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

Question 11. Orexo AB plans to comply with 21 CFR part 314.50(f)(2) and only provide completed individual case report forms for volunteers who died during the clinical study, experienced a serious adverse event (SAE) or withdrew from the clinical study due to an adverse event (AE). No other completed case report forms will be provided.

Does the Agency agree with this plan?

Division Response:

Yes, that is acceptable.

Discussion:

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

Question 12. Orexo AB plans to submit Adverse Event Listings (by subject), Frequency of Adverse Events by Body System, by Intensity and Relationship, and Local Tolerability Assessments. Additionally, Orexo plans to provide listings of Laboratory and Safety Measurements by Subject.

Does FDA agree with Orexo's plan or does FDA require additional case report form tabulations in order to conduct a proper review?

Division Response:
Your proposal appears acceptable.

Discussion:

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

Question 13. The OX219 clinical study program will consist of pharmacokinetic studies in healthy volunteers. Orexo AB plans to submit safety narratives only for subjects who experience an SAE during the clinical study.

Does the Agency agree?

Division Response:
No. Provide narratives for discontinuations due to adverse events in addition to SAEs.

Discussion:

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

Question 14. Orexo AB proposes to provide the New Drug Application (NDA) in Electronic Common Technical Document (eCTD) format.

Does the Agency agree with Orexo's plan?

Division Response:
Yes, it appears acceptable.

Discussion:

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

Question 15. For all studies and the Integrated Summary of Safety (ISS) (see Table 8 for the list), Orexo plans to submit data tabulation datasets using SDTM, version 3.1.2. This will be augmented with analysis datasets using ADaM version 2.1.

Does the Agency agree with Orexo's plan with regards to raw and analysis dataset formatting and that all four OX219 studies are to be included in the ISS?

Division Response:
Yes, this appears acceptable.

Discussion:

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

Question 16. Orexo plans to provide MedDRA coded adverse events and clinical study reports in the eCTD format. Studies OX219-001 and OX219-002 were reported using MedDRA version 13.1 and 14 respectively. Orexo proposes to present study reports using the existing MedDRA codings, but will re-code at the ISS level to match the MedDRA versions used in studies OX219-003 and OX219-004 (Version 15.0 or higher).

Does the Agency agree with Orexo's plan?

Division Response:
In sections of the application where safety data from individual studies are reported, use the MedDRA version that was used in the study. In sections of the application where data are pooled from more than one study and not all studies used the same MedDRA version, re-code the data to the most recent MedDRA version used in any of the pooled studies.

Discussion:

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

Question 17. As discussed and outlined in the February 3rd, 2011 FDA pre-IND Meeting minutes, this 505(b)(2) NDA will rely on Suboxone® tablet as the RLD to support the efficacy of OX219 administered by sublingual route. No further efficacy studies are planned for this NDA. Therefore, Orexo proposes that an Integrated Summary of Efficacy (ISE) is not warranted.

Orexo proposes that an Integrated Summary of Safety (ISS) be prepared across studies OX219-001, 002, 003 and 004.

Does the agency agree with Orexo's plan?

Division Response:

You do not need to submit an ISE. In the ISS, pool the data in two ways: all four studies and studies 003 and 004 together (the studies that used the to-be-marketed formulation).

Discussion:

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

Question 18. Published data on reference compounds and data from OX219 clinical study program to support the 505(b)(2) application

Given that buprenorphine in combination with naloxone are well-known active substances in the maintenance treatment of opioid dependency, Orexo AB proposes that the documentation from the approved NDA for the Suboxone® tablet RLD and a literature search starting from 2002, combined with data from the OX219 clinical study program, will support submission of a 505(b)(2) application for the maintenance treatment of opioid dependence. Please see Attachment V for the literature search parameters. In addition to the literature search, Orexo plans to evaluate and provide in the NDA, the FDA MedWatch for adverse events for the Suboxone® tablet since its introduction in 2002.

Does the agency agree with the overall plan and literature search parameters?

Division Response:

Yes, they appear acceptable. Your evaluation of the results of the literature search and FDA MedWatch reports should include a summary and discussion.

Discussion:

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

Question 19. Does FDA agree with Orexo's plan and that the proposed nonclinical label text is acceptable and addresses the point made in the pre-IND meeting?

Division Response:

The proposal to substitute your dose in the nonclinical sections of the label which use AUC comparisons is acceptable. However, substituting your dose in sections which use comparisons based on mg/m² is scientifically inaccurate. Additional language will be necessary to put the exposure margins in context. We would consider something like:

OX219 has been shown to have greater bioavailability compared to other buprenorphine and naloxone-containing sublingual products. The exposure margins are based on doses that yield equivalent systemic exposures and are therefore comparable.

Final determination of the language in the product label will be determined during the NDA review.

Discussion:

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

Question 20. OX219 sublingual tablets will be white. The high strength is a round, flat-faced, bevel-edged tablet 7 mm in diameter, debossed on one side. The low strength is an arc triangle (base 7.4 mm, height 7.1 mm) flat faced, bevel-edged tablet, debossed on one side. Illustration of the pictures of OX219 sublingual tablets are provided in Attachment VIII for reference.

Does the FDA agree that this improved tablet differentiation is acceptable?

Division Response:

From the CMC standpoint, the differentiation between a circular and triangular shaped tablet appears to be acceptable. However, provide tablet samples at the time of NDA submission.

Discussion:

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

Question 21.a. The material used is tested for child-resistant effectiveness and fulfills the requirement for peelable style F=8. A statement from the test laboratory is attached. Orexo believes that the test performed supports the child-resistant effectiveness of the proposed blister card design and no further tests are required.

Does the FDA agree?

Division Response:

From the CMC standpoint, your approach seems acceptable.

Question 21.b. It's Orexo understanding that 21 CFR 201 does not require an individual code for each blister cavity. Thus Orexo does not plan to provide individual codes on the final design of the blister.

Does the FDA agree with this understanding?

Division Response:

From the CMC standpoint, your approach seems acceptable.

Discussion:

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

Question 22. Available primary, commercial and supportive stability data anticipated to be available at time of NDA filing are presented in Attachment X, Tables III-1 & III-2.

Updated stability data to be submitted during NDA review will be in compliance with GRMP timelines/PDUFA dates as directed in Division's email correspondence on October 28th, 2011.

Updated stability data from above-mentioned primary, commercial and supportive batches a minimum of three (3) months stability data for one (1) batch each of the high (5.7/1.4 mg) and low (1.4/0.36 mg) strengths, generated under referenced ICH conditions; manufactured at the second commercial site, AAIPharma Services, US, and at commercial scale; using the intended final commercial product (FCP); in the final commercial package material and made using drug substances made from the planned commercial manufacturers

Does the FDA agree that this data package is sufficient for the NDA filing?

Does the FDA agree that this proposed stability data and plan addresses the FDA's request and feedback in above-referenced FDA communications?

Division Response:

As recommended in ICH Q1A-E Guidances, we expect that the NDA is complete on submission to support a proposed shelf life, based upon the data provided (a minimum or 12 months of the primary stability batches made at the proposed commercial site). You should provide as much stability data as possible (including supportive stability data) in the NDA submission. Expiry dating will be assigned based on the amount of real time stability data provided. Should additional stability data be provided during the course of the NDA we will review the updates as resources and time permits.

Discussion:

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

**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. Failure to submit adequate impurity qualification or justification for the safety of new excipient use 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.**

Controlled Substance Staff Comments

- 1. You should compile abuse-related adverse events from the clinical studies into an abuse potential assessment as part of the submission in the New Drug Application according to the Guidance for Industry: *Assessment of Abuse Potential of Drugs* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>**
- 2. You should also continue pharmacovigilance activities during the clinical evaluation specifically related to misuse, abuse, addiction, diversion, and overdose, including those that might result in study drop-outs, and highlight the findings in the NDA submission.**

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

Pediatric Plan

You must submit a pediatric plan with the NDA submission regarding studies in pediatric patients to be conducted to fulfill the requirements of the Pediatric Research Equity Act (PREA). The plan must include the studies to be conducted; a timeline for the studies that states for each study, the date of final protocol submission, date of study start, date of study completion, and date of final study report to be submitted to the Agency; requests for waivers and deferrals with justifications; and, where possible, protocol synopses of the proposed studies.

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/LawsActs/andRules/ucm084159.htm> for fictitious examples of labeling in the new format (e.g., Indicon 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/LawsActs/andRules/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/LawsActs/andRules/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.

General Study Data Comments

Clinical trials research study designs should define the protocol for data collection. 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. The Agency prefers implementation of analyses datasets to tabulations datasets traceability. In addition, the Agency prefers each study submitted to be complete and evaluated on its own merits. The Agency also prefers studies be maintained independently in the SEND datasets, SDTM datasets, and that analyses (ADaM) datasets provide traceability to the study's SDTM, including analyses that combine multiple studies (e.g. Safety and/or Efficacy analyses) (See [SEND](#), [SDTM](#) and [ADaM](#) as referenced in [Study Data Specifications](#)).

Dataset Comments

1. Provide an integrated safety (adverse event) dataset for all studies.

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, date of birth, and race
- e. Duration of event (or start and stop dates)
- f. Outcome of event (e.g., ongoing, resolved, led to discontinuation)
- g. 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).

- h. Marker for serious adverse events**
 - i. 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. 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.**
 - 5. 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.**
 - 6. 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.**
 - 7. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include ATC code/decode.**
 - 8. 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.**
 - 9. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.**

- 10. 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.**
- 11. 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.)**
- 12. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.**
- 13. For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.**
- 14. With reference to the table on the following page, note that the HLG T and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLG T 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 (AES EQ)	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		

Discussion:

With respect to the Controlled Substance Staff (CSS) comments in Appendix 1, the Sponsor noted that they have not conducted either clinical or non-clinical studies and, therefore, felt that many of the comments did not apply. CSS responded that the comments were included as standard comments, but that they would apply to any future clinical studies that the Sponsor may conduct. The Sponsor stated their understanding.

The Sponsor also noted that since they have not conducted non-clinical studies, they would not be submitting data in SEND format, as requested in the General Study Data Comments section of Appendix 1. The Division stated that this was acceptable.

Action Items:

1. The Division will provide the Sponsor with the Buprenorphine Industry Group point of contact when it becomes available.
2. The Sponsor will engage in a discussion with the Buprenorphine Industry Group about joining a future buprenorphine single shared system.
3. The Sponsor intends to submit their NDA prior to the end of November 2012, and will keep the Division updated as to the specific timing of the submission.

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
08/07/2012



IND 110637

**MEETING REQUEST -
Written Responses**

Orexo AB
c/o DJA Global Pharmaceuticals, Inc
115 Commons Court
Chadds Ford, PA 19317

Attention: Damaris DeGraft-Johnson, RPh, MSc
President

Dear Ms. DeGraft-Johnson:

Please refer to your Investigational New Drug Application (IND) submitted April 11, 2011, received April 12, 2011, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OX219 (buprenorphine and naloxone) sublingual tablets.

We also refer to our June 15, 2011, communication notifying you that we would provide a written response to the questions in your June 1, 2011, meeting request within 90 days after receiving your background materials. The background materials were received on June 21, 2011.

Our responses to your questions are enclosed. If you have additional questions, you must submit a new meeting request.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE

BACKGROUND

On June 1, 2011, the Sponsor submitted a meeting request to discuss Chemistry, Manufacturing, and Controls (CMC), and Non-Clinical questions. The Division informed the Sponsor that it would provide written responses within 90 days of receipt of the background package.

The questions from the June 20, 2011, background package are shown below in italics and the responses are shown in normal text.

CMC Questions

Question 1 Buprenorphine HCl and naloxone HCl, (b) (4) will be tested according to the current USP monographs by the supplier. An exception is related substances where the methods from the European Pharmacopeia (Ph. Eur.) are considered better than the USP in terms of selectivity for buprenorphine HCl and selectivity and sensitivity for naloxone HCl, (b) (4) (USP method is based on TLC). Consequently, and based on the FDA's policy outlined in MAPP 5310.72, the Ph. Eur. methods and limits have been selected for testing of related substances. The drug substances are (b) (4).

All analytical methods based on the USP and Ph. Eur. are considered validated and Orexo proposes that no further validation is required. Method validation or qualification information will be provided only on alternate or non-compendial methods.

After receipt of each API lot with Certificate of Analysis (CoA) from the supplier, Orexo will re-test identification, assay, related substances and residual solvents and release the drug substances in accordance with Orexo's specifications prior to use in the manufacture of drug product. The Orexo analytical testing is performed by (b) (4) under the supervision of Orexo.

Does the FDA agree with this approach to testing and release?

FDA Response:

Your approach appears to be acceptable. Your data will be evaluated during the NDA review. Provide complete bridging of the quality and manufacturing data of the drug substances between the different manufacturing sites.

Question 2 The final specifications for the drug substances are under development and will be provided as amendments to the IND and in the NDA as the development program progresses. Current proposed specifications including test parameters to be used for development batches are provided in Attachment II. Full description of the relevant analytical tests, procedures and acceptance criteria will be provided in the NDA.

Proposed specifications with justification will be based on the pharmacopoeia standards defined in the USP/Ph. Eur. monographs of the drug substances, USP general chapters and ICH guideline Q6A (Specifications), together with batch experience for batches used during development and anticipated manufacturing experience.

Comparative analytical data for batches used during development, including data from the suppliers and Orexo, will be provided in the NDA. For the purpose of this background package, currently available data for four (4) batches of buprenorphine HCl and one (1) batch of naloxone HCl, (b) (4) showing results from (b) (4) and Orexo (b) (4) are provided in Attachment III.

Orexo believes this approach and data package will be sufficient to support the development program and future NDA.

Does the FDA agree with this approach to setting specifications for the drug substance?

FDA Response:

From a chemistry, manufacturing and controls perspective, your approach appears to be acceptable.

However, from a pharmacology/toxicology perspective, any impurity that exceeds ICH Q3A(R2) thresholds for qualification must be adequately qualified for safety with appropriate nonclinical studies. Adequate qualification must include:

1. 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.
2. Repeat dose toxicology of appropriate duration to support the proposed indication (90-days for a chronic indication).

Question 3 The final specifications for the drug product are under development. In general, the attributes will be in accordance with the general USP and Ph. Eur. monographs for tablets and oromucosal preparations as well as the ICH guideline Q6A (Specifications). Current proposed drug product specifications are provided in Attachment IV.

For the NDA, the final specification with justification will be based on pharmacopoeia standards together with batch analytical data for batches used in stability, clinical studies, as well as current and anticipated manufacturing experience. Batch analysis of the drug product will be obtained using in-house methods and the USP in accordance with product specification.

Batch analytical data for batches used in stability, clinical and other development studies will be provided in the NDA.

Orexo believes this approach and data package satisfies the NDA requirements.

Does the FDA agree with this approach to setting specifications for the drug product?

FDA Response:

From a chemistry, manufacturing and controls perspective, your approach appears to be acceptable. Your data will be evaluated during the NDA review.

However, from a pharmacology/toxicology perspective, any impurity/degradant that exceeds ICH Q3B(R2) thresholds for qualification must be adequately qualified for safety with appropriate nonclinical studies. Adequate qualification must include:

1. 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.
2. Repeat dose toxicology of appropriate duration to support the proposed indication (90-days for a chronic indication).

Question 4 (b) (4) *the API-supplier that Orexo has selected for buprenorphine HCl for the OX219 project, is currently performing a Technology Transfer of the buprenorphine HCl process from their (b) (4) to their (b) (4).*

The API supplier confirms that the API is synthesized using the same route of synthesis, and will provide data on other critical quality attributes to demonstrate equivalence between material made at both sites. The manufacture of buprenorphine HCl at (b) (4) will be a similar scale using equipment with the same operating principles and controls as used at (b) (4). As would be expected, there will be some differences in equipment configuration / materials of construction. The (b) (4) step will be performed using the same type of equipment. Details of the manufacturing processes, including scale, to be used at both (b) (4), will also be provided via the US Type II DMF. API from both sites will be released against the same specification, including particle size, using the same validated analytical method.

Orexo plans to provide comparative data demonstrating equivalence between buprenorphine HCl manufactured at (b) (4) and to be used in the pivotal BA/BE study to material from the commercial (b) (4) by characterizing the physical, chemical and process related properties of the buprenorphine HCl from both sites.

Does the FDA agree that this data package meets the NDA requirements to support this API manufacturing site change?

FDA Response:

Your approach appears to be acceptable. Your data will be evaluated during the NDA review.

Question 5 The material (FCP) to be used for the pivotal BA/BE clinical study is planned to be manufactured at commercial scale of (b) (4) at Orexo, Sweden. This (b) (4)

The final commercial product (FCP) and manufacturing process will be investigated using QbD (Quality by Design) experimental design approach to ascertain a robust manufacturing process. The plan is to use equivalent (same design and operating principles) equipment and the same quality of APIs and excipients at the (b) (4) site for commercial production and to perform the (b) (4). Detailed comparison between the manufacturing processes to be used at Orexo and the (b) (4) will be provided in the NDA. A flow chart of the current manufacturing process used for production of CTM for clinical study OX219-002 is provided in Attachment V.

The drug product from both Orexo and (b) (4) sites is planned to be released against the same specifications using the same validated analytical methods in accordance with ICH Q2(R1).

Comparative batch analytical data for batches made at both Orexo and (b) (4) will be provided in the NDA to demonstrate in vitro equivalence between these two sites.

Orexo proposes that this data package and plan for addressing the buprenorphine HCl API, and drug product site changes, as well as maintaining the same source of naloxone HCl, (b) (4) provides the required link between the APIs and drug product used in clinical development (including material to be used for the pivotal BA/BE study) and the final commercial product/sites. Hence, Orexo proposes that no BE study is required for these manufacturing site changes.

Does the FDA agree with this conclusion?

FDA Response:

Your approach appears to be acceptable. Your data will be evaluated during the NDA review.

Question 6 In accordance with the FDA February, 3, 2011 pre-IND meeting minutes (see Attachment I, Division Response page 14) Orexo understands that it would be possible to waive the requirement for in vivo BA/BE data for the OX219 lower strength [corresponding to the 2 mg (buprenorphine)/0.5 mg (naloxone)]

Suboxone® tablet] assuming that the formulations are proportionally similar and provided that the in vitro dissolution profiles are also similar.

In addition, it's also important to note that the OX219 lower strength tablet will be used in the planned PK-dose proportionality study (OX219-004).

The current formulation for the higher strength tablet has a diameter of 7 mm and a weight of 110 mg, which Orexo considers to be a suitable size for a sublingual product. The lower strength tablet will contain (b) (4) of the active ingredients. For patient convenience, Orexo finds it unsuitable to reduce the tablet size of the low strength tablet (b) (4) that of the high strength tablet. Instead, (b) (4)

(b) (4)

The lower strength tablet is based on the (b) (4). The total weight of the dosage form remains within $\pm 10\%$ of the total weight of the strength to be used in the planned pivotal BA/BE study (i.e. the higher strength). The same inactive ingredients are used in both strengths and the changes in the inactive ingredients are within the limits defined by SUPAC-IR guidance⁴ up to and including Level II. The compositions of the current high and low dosage strength formulations are presented in Attachment VI.

The dosage strengths to be used in the pivotal BA/BE (OX219-003) and PK-dose proportionality (OX219-004) studies, and the final commercial product (FCP) will be determined after obtaining the results of clinical study OX219-002.

Tests performed on the current formulations show that in vitro dissolution and disintegration properties are similar for the high and low dosage strengths. Available comparative in vitro dissolution and disintegration data are provided in Attachment VI. The final commercial products are expected to show similar dissolution and disintegration characteristics.

Based on above points, Orexo proposes that the lower strength tablet qualifies for a biowaiver.

Does the FDA agree?

FDA Response:

We agree that the formulation for the proposed lower strength meets the definition of proportionally similar. In your NDA submission, include the biowaiver request and the

OX219 sublingual tablets will be white and Orexo plans to differentiate tablet strengths using different shapes. The planned shapes are round for the high strength and arc triangle for the low strength, see Attachment VII. Tablet packaging will be differentiated by color.

Orexo proposes that this differentiation is appropriate for the commercial product.

Does the FDA agree?

FDA Response:

Embossing/debossing is a requirement in accordance with 21 CFR 206. Differentiation by shape alone will not suffice. You should consider utilizing higher contrasting tablet shape pairs (e.g., round & rectangle) that can also further enhance strength differentiation.

Additionally, if the proposed OX219 tablet should not be cut or split, then symbols resembling a scored line on a tablet should be avoided as your choice of code imprint.

Question 8 The primary package for the drug product is planned to be aluminum/aluminum Child Resistant Control (CRC) blisters. Orexo plans to differentiate tablet strengths using packages that will be differentiated by color.

Full description of the packaging material will be provided in the NDA.

Orexo believes this approach and data package is sufficient for the NDA.

Does the FDA agree?

FDA Response:

The proposed blister packaging must have complete labeling information in accordance with 21 CFR 201.

Question 9 At the time of NDA filing, Orexo plans to provide nine (9) months primary stability data [ICH Q1A(R2)] from three (3) batches of both tablet strengths. These drug product batches will be manufactured at commercial scale, (b) (4) tablets, using buprenorphine HCl manufactured at (b) (4), Switzerland, and naloxone from the final commercial manufacturer (see Table 1). Updated stability data from these studies will be provided as needed during the NDA review period. Primary and supportive stability studies are listed in Attachment VIII

Six batches (three batches of each strength) for primary stability study will be produced at Orexo using buprenorphine HCl from (b) (4),

(b) (4) and naloxone HCl, (b) (4) from the final commercial manufacturer (see Table 1 and Attachment VIII). One of the high dose batches will also be used as CTM for pivotal BA/BE study.

The primary packaging material for the primary stability study will be aluminum/aluminum blisters. The package for the primary stability study is planned to be the same or, in terms of stability, equivalent to the primary packaging material to be used at the (b) (4) for commercial use.

Orexo proposes that, since none of the drug substances are new chemical entities, this stability package provides the required primary stability data, and is sufficient to support the initial NDA filing. Orexo also believes that no additional data from the (b) (4) for buprenorphine HCl and drug product (b) (4) site is required at the time of NDA filing.

Does the FDA agree?

FDA Response:

Your expiry dating period for the drug product will be granted based on the real time and supporting stability data you provide in your proposed submission. We recommend you provide a minimum of 3 months of stability data from the proposed commercial manufacturing site.

Non-Clinical Questions

Question 10 As directed in the FDA Feb 3, 2011 pre-IND meeting minutes (see Attachment I, page 10, comment #2) regarding addressing maximum daily exposure for each excipient in the OX219 formulation, Orexo consulted all referenced FDA Guidance documents and relevant literature. The following provides the assessment of this evaluation:

With the exception of sucralose, all excipients used in OX219 are within the FDA maximum potency for inactive ingredients and have been approved for other sublingual and/or orally disintegrating formulations widely used in other pharmaceutical products, see Attachment IX.

For sucralose (sweetener), the high strength OX219 tablet will contain (b) (4) in the OX219 formulation to reduce the bitter taste of the tablet. Current maximum dose of sucralose for an orally disintegrating tablet is 5.75 mg for approved products. The maximum anticipated dose for the OX219 tablet will be 3 (three) tablets per day giving a total daily dose of (b) (4) mg sucralose.

The Joint Food and Agriculture Organization and WHO Expert Committee on Food Additives (JECFA) decided in 1990 that the Acceptable Daily Intake (ADI) of sucralose is 0-15 mg/kg (see Attachment X), and after further investigations, the Scientific Committee on Food (SCF) in EU agreed later (2000) with this

decision (see Attachment XI). Thus, a daily total dose of (b) (4) sucralose is within the ADI with good margin.

Furthermore, the local tolerance of sucralose in OX219 formulation is being monitored by visual inspection of the sublingual area in the protocol for the current IND clinical study OX219-002. This protocol states “Visual inspection of the sublingual area will be performed by a nurse or a physician to assess local tolerability prior to and at 1, 8, and 24 hours after IMP (investigational medicinal product) dosing.” [see section 6.12 (Local Tolerability Assessments) in OX219-002 study protocol submitted May 19, 2011 as Amendment SN0001 to original IND 110637].

To the best of Orexo’s knowledge, there exists no specific study addressing the local tolerance of sucralose in animals. However, in the “Opinion of the Scientific Committee on Food on sucralose” issued by the Scientific Committee on Food in EU (see Attachment X), it is stated that “there is a clear NOEL of 3000 mg/kg bw/day for any effects on lymphoid organs and immune system”. Thus, at doses higher than the limit dose of 2 g/kg, no immunological responses have been observed regarding cells, tissues and function of the immune system. A safety margin of more than 23,000 times can be calculated (based on a maximum dose of (b) (4) sucralose per day and a patient body weight of 70 kg) concerning an immunologic response (irritating effect). Orexo’s conclusion is that it is highly unlikely that the additional amount (b) (4) of sucralose, compared to other approved sublingual products, will trigger an immunological response after administration of OX219.

It’s important to note that this FDA guidance applies to novel excipients, whereas all the OX219 excipients including sucralose are well-known. However, for completeness, and also to take a conservative approach, Orexo evaluated this FDA guidance, and concluded there is no relevant direct application of this to excipients in OX219.

Based on above points, Orexo considers that a maximum daily dose of (b) (4) sucralose is acceptable, and will not cause local irritation. Therefore, the amount (b) (4) per tablet in the OX219 formulation is appropriate and no further preclinical studies are warranted.

Does the FDA agree?

FDA Response:

Based on the information provided in the meeting package, your justification for the safety of the systemic dose of sucralose appears reasonable and no further nonclinical studies should be needed. Lack of evidence for immunotoxicity does not necessarily translate into lack of local tissue irritation potential; however, we recognize that this can be assessed in the clinical setting. Ultimately, final determination of the acceptability of your justification for the safety of this excipient will be made upon review of the NDA submission.

Question 11 Organic impurities that are process related and/or degradation products will be tested in the drug substances. (b) (4) the API manufacturer has optimized the processes for synthesis of both naloxone HCl, (b) (4) and buprenorphine HCl to meet the impurity specification limits in the Ph. Eur. monographs. Therefore, the impurity limits are not necessarily in accordance with ICH Q3A(R2) limits, and it is proposed that the limits for individual and total impurities be set according to the limits in the Ph. Eur. monographs. Orexo believes this is acceptable based on the FDA's policy outlined in MAPP 5310.78.

Does the FDA agree with this conclusion?

FDA Response:

It is not clear what you mean by the phrase "organic impurities that are process related and/or degradation products" and why you are separating this chemical class of compounds in your overall safety qualification program. Impurities and degradation products are regulated as per ICH Q3A(R2) and Q3B(R2), respectively. Impurities derived from the container closure must be evaluated for safety as leachables and extractables. Extraneous contaminants that should not occur in new drug products must be addressed as good manufacturing practices (GMP) issues.

From a pharmacology/toxicology perspective, any impurity that exceeds ICH Q3A(R2) or ICH Q3B(R2) thresholds for qualification must be adequately qualified for safety with appropriate nonclinical studies (See response to Questions 2 and 3 above). Reference to specifications in various pharmacopeial monographs does not provide any information regarding the basis of a safety determination used to set the specifications and is, therefore, not adequate to support the safety of the impurity.

Question 12 The potential genotoxic impurity in naloxone HCl, (b) (4) (b) (4), is expected to be a process related impurity, but not likely a degradation product, and will, therefore, only be tested in drug substance. For the NDA and commercial product, (b) (4) will be limited to (b) (4) ppm, which is in line with the API manufacturer's specification limit for this impurity, and less than 1.5 µg/day at an anticipated dose that will not exceed three (3) high strength tablets per day.

Based on current knowledge, other potential structural alert impurities in buprenorphine HCl or naloxone HCl, (b) (4) have not been detected (see Type II DMFs (b) (4) and (b) (4)). If structural alert impurities other than (b) (4) are found, Orexo will follow the recommendation for the Threshold of Toxicological Concern (TTC) according to the EMA guideline EMEA/CHMP/QWP/251344/2006 as well as FDA's draft guideline "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches" (2008) to avoid safety concerns due to impurities.

Thus, since impurities are not expected to belong to the Cohort of Concern, the maximum daily intake for other impurities with associated genotoxic potential will be 1.5 µg/day or less.

Does the FDA agree with this approach?

FDA Response:

Yes, we agree with your approach.

Question 13 The impurity, (b) (4), will be tested using a validated HPLC-MS method in accordance with ICH Q2(R1). A copy of the method and validation report is included in (b) (4) amendment submitted April 6, 2011), and is also provided in Attachment XII. The levels of quantification (LOQ) and the levels of detection (LOD) will be summarized in the NDA.

Orexo believes this method and validation is appropriate for this impurity for the NDA.

Does the FDA agree?

FDA Response:

Based on the information provided in this package your approach appears to be acceptable.

Question 14 The limits for residual solvents will be in accordance with USP <467> and the ICH guideline for residual solvents Q3C(R4).

Batch analysis data for drug substance batches used in clinical, stability, and other development studies will be provided in the NDA. For the purpose of this background package currently available data are provided in Attachment III.

Orexo proposes that the above outline for testing and qualifying impurities in the drug substances (3.4.1.1, 3.4.1.2, 3.4.1.3) satisfies FDA requirements for the development program and NDA and that no additional non-clinical studies are needed.

Does the FDA agree with this conclusion?

FDA Response:

From a chemistry, manufacturing and controls perspective, the limits of residual solvents should be based on batch test data.

From a nonclinical pharmacology toxicology perspective, if the levels of residual solvents are below the thresholds set by ICH Q3C(R4) no nonclinical studies will be needed.

Question 15 Only organic impurities that are degradation products will be tested in the drug product. For the drug product, Orexo has developed a method for this combination product. Limits for identification and qualification will be set in accordance with the ICH guideline Q3B(R2).

Batch analysis data for drug product batches used in clinical, stability and other development studies will be provided in the NDA.

Orexo believes this approach and data package meets the requirement for the development program and the NDA. Orexo believes no additional non-clinical studies are warranted.

Does the FDA agree?

FDA Response:

From a chemistry, manufacturing and controls perspective, your approach is acceptable. Your data will be evaluated during the NDA review.

From a nonclinical pharmacology toxicology perspective, if the impurities in your drug product are below ICH Q3B(R2) thresholds for qualification and do not contain structural alerts for mutagenicity, no additional nonclinical studies will be needed.

As noted in our response to Question 11, it is not clear why you have specifically requested feedback only on “organic impurities that are degradation products” in the drug product. Any organic or inorganic impurity that is not related to the drug product that is present in the drug product would be deemed a contaminant. The identification and source of any contaminant along with a safety justification must be provided.

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
10/04/2011



IND 110637

MEETING PRELIMINARY COMMENTS

Orexo AB
c/o DJA Global Pharmaceuticals, Inc.
115 Commons Court
Chadds Ford, PA 19317

Attention: Damaris DeGraft-Johnson, RPh, MSc.
President

Dear Ms. DeGraft-Johnson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OX219 (buprenorphine and naloxone) sublingual tablets.

We also refer to your March 22, 2012, correspondence, received March 22, 2012, requesting a Pre-NDA meeting to discuss development plans for OXE219 in support of your upcoming NDA.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: July 17, 2012, 1:30PM EDT
Meeting Location: White Oak 22, Room 1313
Application Number: IND 110637
Product Name: OX219 (buprenorphine and naloxone)
Indication: Maintenance treatment of opioid dependence
Sponsor/Applicant Name: Orexo AB

FDA Attendees	Title
Bob A. Rappaport, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, MD	Deputy Director, DAAAP
Celia Winchell, MD	Clinical Team Leader, DAAAP
Pam Horn, MD	Medical Officer, DAAAP
Prasad Peri, PhD	Branch Chief, Division III Branch VIII, Office of New Drug Quality Assessment (ONDQA)
Ramesh Raghavachari, PhD	CMC Lead, DNDQA III, ONDQA
Danae Christodoulou, PhD	CMC Lead, DNDQA III, ONDQA
Julia Pinto, PhD	Chemistry Reviewer, ONDQA
Dan Mellon, PhD	Pharmacology / Toxicology Supervisor, DAAAP
Elizabeth Bolan, PhD	Pharmacology / Toxicology Reviewer, DAAAP
Yun Xu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Ying Fan, PhD	Clinical Pharmacology Reviewer, OCP
Dionne Price, PhD	Statistics Team Leader, Office of Biostatistics (OB)
David Petullo, MS	Statistics Reviewer, OB
Angelica Dorantes, PhD	Biopharmaceutics Team Leader, ONDQA
John Duan, PhD	Biopharmaceutics Reviewer, ONDQA
Stephen Sun, MD	Medical Officer, Controlled Substance Staff (CSS)
Matthew Sullivan, MS	Regulatory Health Project Manager, DAAAP
Sponsor Attendees	Title
Åsa Holmgren, M.Sc.Pharm.	Senior Vice President Regulatory Affairs, Orexo AB
Anders Pettersson, M.D. Ph.D.	Senior Vice President Clinical R&D, Orexo AB
David Westberg, M.Sc. Chem. Engineering	Senior Project Leader, Orexo AB
Thomas Lundqvist, M. Sc. Pharm.	Executive Vice President, Head of Pharmaceutical R&D, Orexo AB
Anna-Karin Utberg, M Sc Chem	CMC Project Leader, analytical chemist, Orexo AB
Damaris DeGraft-Johnson, RPh, M.Sc., Med. Chem	Regulatory Consultant, US Agent, President DJA Global Pharmaceuticals, Inc.

Dennis DeCola, B.S. Biology,	Senior Regulatory Consultant DJA Global Pharmaceuticals Inc.
(b) (4)	

INTRODUCTION

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 17, 2012. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

BACKGROUND

DJA Global Pharmaceuticals, Inc., on behalf of Orexo, submitted a request for a Pre-NDA meeting. This request was granted, and the meeting was scheduled for July 17, 2012. A Meeting Package was provided on June 4, 2012.

Orexo plans to submit a 505(b)(2) application relying upon Suboxone tablets, NDA 020733. The Sponsor previously met with the Division on February 3, 2011, to discuss this application.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests 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.				

DISCUSSION:

Question 1.a. In the pre-IND meeting held between Orexo AB and FDA on Feb 3, 2011, FDA requested that Orexo should demonstrate equivalent buprenorphine exposure to Suboxone® 8/2 (questions 1 and 8).

Orexo concludes that study OX219-003 demonstrates equivalent buprenorphine exposure according to standard equivalence criteria and that the study results are sufficient and appropriate to establish the bridge to Suboxone® tablets as a basis for this 505(b)(2) NDA.

Does the FDA agree?

Division Response:

Based on the preliminary data of equivalent buprenorphine exposure between (b) (4) mg of your product and 8/2 mg Suboxone tablet, it appears that the results are sufficient and appropriate for NDA filing for the (b) (4) mg strength. The adequacy of the data to establish a bridge to the referenced product, however, will be determined during the course of the NDA review.

As noted in our March 4, 2011, meeting minutes, you will need to submit a biowaiver request for your proposed lower strength of 1.4/0.36 mg, and supportive data for the dissolution profile comparison in three media using an appropriate in vitro dissolution method. Justify the adequacy of the dissolution method to be used. You may submit the justification in a dissolution method development report for review before you conduct the dissolution profile comparison studies.

Question 1.b. In the pre-IND meeting held between Orexo AB and FDA on February 3, 2011, FDA stated that a lower naloxone exposure would be acceptable (questions 1 and 14), and that lower norbuprenorphine exposure as compared to Suboxone® would not lead to a requirement for efficacy studies (question 13).

Orexo concludes that OX219-003 results are in agreement with FDA's requirements for naloxone and norbuprenorphine as expressed at the pre-IND meeting.

Does the FDA agree with Orexo's conclusion?

Division Response:

Yes. Lower naloxone exposure and lower norbuprenorphine exposure as compared to Suboxone are acceptable from a clinical pharmacology and clinical efficacy perspective.

Question 2.a. In the pre-IND meeting held between Orexo AB and FDA on February 3, 2011, FDA requested that Orexo should assess dose proportionality of OX219 over the dose range 1.4/0.36 to 11.4/2 mg (corresponding to Suboxone 2/0.5 to 16/4 mg) (question 16 and question 8). Orexo concludes that the study results regarding linearity and dose proportionality over the dose range are sufficient and appropriate to support the NDA.

Does the FDA agree?

Division Response:

Based on the preliminary data you submitted, the systemic exposure of buprenorphine and unconjugated naloxone in terms of C_{max} and AUC increased in a linear fashion with dose in the dose range tested (from 1.4/0.36 mg through 11.4/2.8 mg), but in a less than dose proportional fashion.

We agree the study results regarding linearity and dose proportionality over the dose range are sufficient and appropriate to support filing of the NDA. The adequacy of the data to support your conclusion, however, will be determined during the course of the NDA review.

Question 2.a. Based on agreement reached with FDA during the February 3, 2011 pre-IND meeting, regarding the required clinical program for this NDA, Orexo concludes that results from the PK studies OX219-003 and OX219-004 provide a complete clinical data package for this 505(b)(2) NDA.

Does the FDA agree with this conclusion?

Division Response:

Your approach seems appropriate from a clinical pharmacology perspective. However, we remind you that an additional biowaiver request for the lower strength should be included in the NDA. (See our response to Question 1.a.)

The final to-be-marketed formulation should be used in the studies in support of your product approval. Otherwise, you must provide adequate bridging information or justification that the study results can apply to your final to-be-marketed product.

Additionally, as mentioned in response to Question 11 in the March 4, 2011, meeting minutes, provide data on the time it takes for the product to completely dissolve in the mouth when administered.

Question 3. Local tolerability data from the OX219 clinical study program indicates that there were no abnormalities detected in local tolerability assessments performed after 298 exposures in 156 subjects with OX219 formulations. Orexo concludes that the local tolerability data provided will be sufficient and appropriate to support the NDA.

Does the FDA agree with Orexo's conclusion?

Division Response:

Yes, the exposure and assessments for local tolerability appear to be sufficient, pending a more detailed review during the NDA cycle.

Question 4. The in vitro extraction studies with OX219 demonstrated that both components (buprenorphine and naloxone) were co-extracted and that buprenorphine was not preferentially extracted, with the average amount of naloxone extracted being (b) (4) mg. The systematic review of the scientific literature demonstrated that parenteral doses of (b) (4) mg of naloxone consistently precipitate withdrawal in individuals physically dependent on full μ -agonists.

Thus, Orexo concludes that in vitro extraction data and available literature support that the amount of naloxone released from the OX219 low strength under conditions of misuse is sufficient to precipitate an aversive reaction in individuals dependent on full μ -agonists.

Does the FDA agree with Orexo's conclusion?

Division Response:

We cannot agree or disagree that you have sufficiently demonstrated that the dose of naloxone in your product is likely to produce an aversive reaction under conditions of misuse until we have reviewed the submitted data and literature during the NDA cycle. However, your approach to providing the necessary data and supportive literature appears acceptable.

Additional Controlled Substance Staff (CSS) Comment:

The abuse profile of the buprenorphine component, a DEA Schedule III substance, will likely be unchanged in this formulation based upon the presented pharmacokinetics profile from Study OX219-003 and OX219-004, due to its similarity to the referenced product. However, review of these studies will be necessary to support this conclusion.

Question 5.a. As there are several sublingual buprenorphine products approved on the US market, Orexo proposes that the label for OX219 will indicate that any such buprenorphine product should be used for induction therapy. The draft labeling provided reflects this conclusion.

Does FDA agree with this proposal?

Division Response:

Yes, the statement “OX219 sublingual tablets should be used in patients who have been initially inducted using buprenorphine sublingual tablets” is acceptable.

Question 5.b. Section 2.6 Switching between OX219 sublingual Tablets and other buprenorphine/naloxone combination products. A proposed text for this section is provided in Attachment III.

Does the FDA agree with this approach?

Division Response:

Yes, we generally agree that including this type of information in the product label will be useful to prescribers and we will have further labeling comments as necessary during the NDA review.

Question 5.c. Orexo plans to summarize relevant PK results from OX219 dose proportionality study OX219-004 that provide pharmacokinetic results for the OX219 to be marketed tablet strengths; 1.4 mg/0.36 mg and 5.7 mg/1.4 mg.

Does FDA agree with this plan?

Division Response:

Your plan is reasonable. The final content in the label will be determined during the review of NDA submission.

Question 6. In recognition of the known risks associated with opioid products including buprenorphine, Orexo plans to develop a REMS for OX219 closely aligned with the REMS that has been approved for Suboxone® tablets and film. Orexo is providing an outline of the features of the proposed REMS for OX219 in Attachment IV of this background package. Orexo would like to discuss the proposed features and obtain FDA's current view on risk management expectations for buprenorphine/naloxone products. This would ensure timely completion and acceptance of the REMS for OX219 NDA.

Does the FDA agree with Orexo's plan?

Division Response:

It is premature to discuss the proposed features of the REMS in detail. However, we can make some general recommendations regarding how to proceed. Ideally, your company will join the other Sponsors in the buprenorphine single shared system REMS. You should submit a REMS that looks like the approved REMS for Suboxone and Subutex (as available on our website: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>). We will notify you of any additional safety issues identified during the review cycle that need to be addressed in the REMS. Additionally you should contact the primary point-of-contact for the buprenorphine REMS industry group and inform them that you want to join the group.

Additional comment:

There is a safety signal indicating that buprenorphine may cause QT interval prolongation at therapeutic concentrations. Therefore, you will be required to conduct a tQT study to support the safety of your product. This study, however, may be completed as a Postmarketing Requirement (PMR). You should include such a request in your NDA.

Question 7. Does the Agency agree that the requirement for pediatric safety and efficacy studies can be waived for all children under 17 years of age?

Division Response:

Birth to 5 weeks:

We do not agree with your contention that treatment of NAS is a separate indication from treatment of opioid dependence. We also do not agree that you are likely to obtain a waiver based on a lack of feasibility of enrolling a sufficient number of subjects or lack of an accepted outcome measure. However, a waiver request based on your argument that naloxone has no therapeutic value in neonates experiencing abstinence syndrome is reasonable since your product is a combination of buprenorphine and naloxone.

5 weeks to 12 years:

A waiver request appears reasonable for this age group, although you should include adequate supportive data with your request in the NDA submission.

12 years to 16 years:

To support your request for a waiver, we recommend that you submit an assessment of the pediatric use of pharmacotherapy for opioid dependence in this population. This should include a report of pediatric use data for currently marketed buprenorphine/naloxone products, which could include prevalence data, literature review, expert interviews, and review of insurance databases. Additionally, include an assessment of the prevalence of opioid dependence in this age group, including all illicit and prescription opioids, and the proportion of these cases that are treatment-seeking.

The Division, after consultation with the Pediatric Review Committee (PeRC), will make the final determination of the adequacy of your waiver requests during the NDA review cycle.

Question 8. Would the FDA agree to review a proposed study protocol during the initial NDA review using the Special Protocol Assessment Procedure under sections 505(b)(4)(B) and (C) of the Modernization Act?

It is Orexo's understanding that if the agency accepts review of this protocol during review of the initial NDA, this has no impact on approval and PDUFA timeline for the initial NDA. Is this correct?

Division Response:

You may submit a study protocol to support an induction indication to IND 110637 at any time and may request a Special Protocol Assessment (SPA) irrespective of the timing of an NDA review cycle. Your request will be evaluated and granted or denied based on the criteria outlined in the Guidance for Industry: *Special Protocol Assessment* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080571.pdf>. However, because there is not a well-established approach to the type of study you propose, an agreement under the SPA mechanism is unlikely.

You are correct that our agreement to conduct a SPA review and any regulatory decision on the SPA under the IND while an NDA cycle is ongoing will not impact the regulatory decision or PDUFA timeline for the NDA. However, if you conduct a new study that you did not submit as part of the NDA application and there is new safety data available at the time of the 120-day safety update of the NDA cycle, you would be required to submit this data to the NDA in the 120-day safety update. Any safety data submitted at the 120-day safety update becomes part of the NDA application, is subject to review during the NDA cycle, and could affect the regulatory decision on the NDA.

Question 9. Because no new animal pharmacology, pharmacokinetics or toxicology studies have been conducted for OX219, Orexo AB does not plan to provide any tabulated summaries for sections 2.6.3 pharmacology tabulated summary, 2.6.5 pharmacokinetic tabulated summaries and 2.6.7 toxicology tabulated summary in the NDA application.

Does FDA agree with Orexo's plan for these sections?

Division Response:

Yes, we agree that tabulated summaries are not needed if there are no new data.

Question 10. Orexo AB plans to provide in module 1.14.1.2 an annotated draft OX219 label that indicates which sections of the OX219 label have been taken directly from the Suboxone® tablet label (RLD). Sections of the OX219 label that contain any new information will be annotated referencing the location of the summary and technical sections of the NDA that support any new labeling information. In addition, the most current (currently December 2011) Suboxone® tablet RLD and film labels will be provided in section 1.14.3.3.

Does FDA agree with this approach?

Division Response:

Your plan for annotating the draft label is generally acceptable. Because the Suboxone tablet label was recently converted to PLR format and approved, the information in this label should be sufficient to guide you in writing your label and for submission to section 1.14.3.3. You should not reference the Suboxone film label unless you intend to rely upon the Agency's previous finding of safety for the Suboxone Film NDA (and provided appropriate patent certification) as part of your 505(b)(2) application.

Question 11. Orexo AB plans to comply with 21 CFR part 314.50(f)(2) and only provide completed individual case report forms for volunteers who died during the clinical study, experienced a serious adverse event (SAE) or withdrew from the clinical study due to an adverse event (AE). No other completed case report forms will be provided.

Does the Agency agree with this plan?

Division Response:

Yes, that is acceptable.

Question 12. Orexo AB plans to submit Adverse Event Listings (by subject), Frequency of Adverse Events by Body System, by Intensity and Relationship, and Local Tolerability Assessments. Additionally, Orexo plans to provide listings of Laboratory and Safety Measurements by Subject.

Does FDA agree with Orexo's plan or does FDA require additional case report form tabulations in order to conduct a proper review?

Division Response:
Your proposal appears acceptable.

Question 13. The OX219 clinical study program will consist of pharmacokinetic studies in healthy volunteers. Orexo AB plans to submit safety narratives only for subjects who experience an SAE during the clinical study.

Does the Agency agree?

Division Response:
No. Provide narratives for discontinuations due to adverse events in addition to SAEs.

Question 14. Orexo AB proposes to provide the New Drug Application (NDA) in Electronic Common Technical Document (eCTD) format.

Does the Agency agree with Orexo's plan?

Division Response:
Yes, it appears acceptable.

Question 15. For all studies and the Integrated Summary of Safety (ISS) (see Table 8 for the list), Orexo plans to submit data tabulation datasets using SDTM, version 3.1.2. This will be augmented with analysis datasets using ADaM version 2.1.

Does the Agency agree with Orexo's plan with regards to raw and analysis dataset formatting and that all four OX219 studies are to be included in the ISS?

Division Response:
Yes, this appears acceptable.

Question 16. Orexo plans to provide MedDRA coded adverse events and clinical study reports in the eCTD format. Studies OX219-001 and OX219-002 were reported using MedDRA version 13.1 and 14 respectively. Orexo proposes to present study reports using the existing MedDRA codings, but will re-code at the ISS level to match the MedDRA versions used in studies OX219-003 and OX219-004 (Version 15.0 or higher).

Does the Agency agree with Orexo's plan?

Division Response:

In sections of the application where safety data from individual studies are reported, use the MedDRA version that was used in the study. In sections of the application where data are pooled from more than one study and not all studies used the same MedDRA version, re-code the data to the most recent MedDRA version used in any of the pooled studies.

Question 17. As discussed and outlined in the February 3rd, 2011 FDA pre-IND Meeting minutes, this 505(b)(2) NDA will rely on Suboxone® tablet as the RLD to support the efficacy of OX219 administered by sublingual route. No further efficacy studies are planned for this NDA. Therefore, Orexo proposes that an Integrated Summary of Efficacy (ISE) is not warranted.

Orexo proposes that an Integrated Summary of Safety (ISS) be prepared across studies OX219-001, 002, 003 and 004.

Does the agency agree with Orexo's plan?

Division Response:

You do not need to submit an ISE. In the ISS, pool the data in two ways: all four studies and studies 003 and 004 together (the studies that used the to-be-marketed formulation).

Question 18. Published data on reference compounds and data from OX219 clinical study program to support the 505(b)(2) application

Given that buprenorphine in combination with naloxone are well-known active substances in the maintenance treatment of opioid dependency, Orexo AB proposes that the documentation from the approved NDA for the Suboxone® tablet RLD and a literature search starting from 2002, combined with data from the OX219 clinical study program, will support submission of a 505(b)(2) application for the maintenance treatment of opioid dependence. Please see Attachment V for the literature search parameters. In addition to the literature search, Orexo plans to evaluate and provide in the NDA, the FDA MedWatch for adverse events for the Suboxone® tablet since its introduction in 2002.

Does the agency agree with the overall plan and literature search parameters?

Division Response:

Yes, they appear acceptable. Your evaluation of the results of the literature search and FDA MedWatch reports should include a summary and discussion.

Question 19. Does FDA agree with Orexo's plan and that the proposed nonclinical label text is acceptable and addresses the point made in the pre-IND meeting?

Division Response:

The proposal to substitute your dose in the nonclinical sections of the label which use AUC comparisons is acceptable. However, [REDACTED] (b) (4) [REDACTED]. Additional language will be necessary to put the exposure margins in context. We would consider something like:

OX219 has been shown to have greater bioavailability compared to other buprenorphine and naloxone-containing sublingual products. The exposure margins are based on doses that yield equivalent systemic exposures and are therefore comparable.

Final determination of the language in the product label will be determined during the NDA review.

Question 20. OX219 sublingual tablets will be white. The high strength is a round, flat-faced, bevel-edged tablet 7 mm in diameter, debossed on one side. The low strength is an arc triangle (base 7.4 mm, height 7.1 mm) flat faced, bevel-edged tablet, debossed on one side. Illustration of the pictures of OX219 sublingual tablets are provided in Attachment VIII for reference.

Does the FDA agree that this improved tablet differentiation is acceptable?

Division Response:

From the CMC standpoint, the differentiation between a circular and triangular shaped tablet appears to be acceptable. However, provide tablet samples at the time of NDA submission.

Question 21.a. The material used is tested for child-resistant effectiveness and fulfills the requirement for peelable style F=8. A statement from the test laboratory is attached. Orexo believes that the test performed supports the child-resistant effectiveness of the proposed blister card design and no further tests are required.

Does the FDA agree?

Division Response:

From the CMC standpoint, your approach seems acceptable.

Question 21.b. It's Orexo understanding that 21 CFR 201 does not require an individual code for each blister cavity. Thus Orexo does not plan to provide individual codes on the final design of the blister.

Does the FDA agree with this understanding?

Division Response:

From the CMC standpoint, your approach seems acceptable.

Question 22. Available primary, commercial and supportive stability data anticipated to be available at time of NDA filing are presented in Attachment X, Tables III-1 & III-2.

Updated stability data to be submitted during NDA review will be in compliance with GRMP timelines/PDUFA dates as directed in Division's email correspondence on October 28th, 2011.

Updated stability data from above-mentioned primary, commercial and supportive batches a minimum of three (3) months stability data for one (1) batch each of the high (5.7/1.4 mg) and low (1.4/0.36 mg) strengths, generated under referenced ICH conditions; manufactured at the second commercial site, AAIPharma Services, US, and at commercial scale; using the intended final commercial product (FCP); in the final commercial package material and made using drug substances made from the planned commercial manufacturers

Does the FDA agree that this data package is sufficient for the NDA filing?

Does the FDA agree that this proposed stability data and plan addresses the FDA's request and feedback in above-referenced FDA communications?

Division Response:

As recommended in ICH Q1A-E Guidances, we expect that the NDA is complete on submission to support a proposed shelf life, based upon the data provided (a minimum of 12 months of the primary stability batches made at the proposed commercial site). You should provide as much stability data as possible (including supportive stability data) in the NDA submission. Expiry dating will be assigned based on the amount of real time stability data provided. Should additional stability data be provided during the course of the NDA we will review the updates as resources and time permits.

**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. Failure to submit adequate impurity qualification or justification for the safety of new excipient use 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.

Controlled Substance Staff Comments

1. You should compile abuse-related adverse events from the clinical studies into an abuse potential assessment as part of the submission in the New Drug Application according to the Guidance for Industry: *Assessment of Abuse Potential of Drugs*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>
2. You should also continue pharmacovigilance activities during the clinical evaluation specifically related to misuse, abuse, addiction, diversion, and overdose, including those that might result in study drop-outs, and highlight the findings in the NDA submission.

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

Pediatric Plan

You must submit a pediatric plan with the NDA submission regarding studies in pediatric patients to be conducted to fulfill the requirements of the Pediatric Research Equity Act (PREA). The plan must include the studies to be conducted; a timeline for the studies that states for each study, the date of final protocol submission, date of study start, date of study completion, and date of final study report to be submitted to the Agency; requests for waivers and deferrals with justifications; and, where possible, protocol synopses of the proposed studies.

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>

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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.

General Study Data Comments

Clinical trials research study designs should define the protocol for data collection. 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. The Agency prefers implementation of analyses datasets to tabulations datasets traceability. In addition, the Agency prefers each study submitted to be complete and evaluated on its own merits. The Agency also prefers studies be maintained independently in the SEND datasets, SDTM datasets, and that analyses (ADaM) datasets provide traceability to the study's SDTM, including analyses that combine multiple studies (e.g. Safety and/or Efficacy analyses) (See [SEND](#), [SDTM](#) and [ADaM](#) as referenced in [Study Data Specifications](#)).

Dataset Comments

1. Provide an integrated safety (adverse event) dataset for all studies.

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, date of birth, and race
- e. Duration of event (or start and stop dates)
- f. Outcome of event (e.g., ongoing, resolved, led to discontinuation)
- g. 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).
- h. Marker for serious adverse events
- i. 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. 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.
5. 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.
6. 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.
7. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include ATC code/decode.
8. 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.
9. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
10. 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.
11. 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.)
12. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.
 13. For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.
 14. With reference to the table on the following page, note that the HLG and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLG 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
07/16/2012



PIND 110637

MEETING MINUTES

Orexo AB
c/o DJA Global Pharmaceuticals, Inc
115 Commons Court
Chadds Ford, PA 19317

Attention: Damaris DeGraft-Johnson, RPh, MSc
President

Dear Ms. DeGraft-Johnson:

Please refer to your Pre-Investigational New Drug Application (PIND) submitted November 19, 2010, received November 23, 2010, for OXY219 (buprenorphine and naloxone) sublingual tablets.

We also refer to the meeting between representatives of your firm and the FDA on February 3, 2011. The purpose of the meeting was to discuss the development plan for OXY219.

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, M.S.
Senior 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: February 3, 2011

TIME: 2:30 pm to 3:30 pm

LOCATION: FDA White Oak Campus
Silver Spring, MD

APPLICATION: PIND 110637

PRODUCT: OXY219 (buprenorphine and naloxone) sublingual tablets

INDICATIONS: Maintenance treatment of opioid dependence

SPONSOR: Orexo AB

TYPE OF MEETING: Type B

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

MEETING RECORDER: Matthew Sullivan, M.S., Senior Regulatory Project Manager, DAAP

FDA Attendees	Title
Bob A. Rappaport, M.D.	Division Director, Division of Anesthesia and Analgesia Products (DAAP)
Rigoberto Roca, M.D.	Deputy Division Director, DAAP
Celia Winchell, M.D.	Clinical Team Leader, DAAP
Pamela Horn, M.D.	Clinical Reviewer, DAAP
Suresh Doddapaneni, Ph.D.	Clinical Pharmacology Team Leader, DAAP
Sheetal Agarwal, Ph.D.	Clinical Pharmacology Reviewer, DAAP
Dan Mellon, Ph.D.	Pharmacology / Toxicology Supervisor, DAAP
Ramesh Raghavachari, Ph.D.	CMC Lead ONDQA
Lori Love, MD, Ph.D.	Team Leader, Controlled Substance Staff (CSS)
Stephen Sun, M.D.	Clinical Reviewer, CSS
Angelica Dorantes, Ph.D.	Biopharmaceutics Team Leader, ONDQA
Matthew Sullivan, MS	Regulatory Project Manager, DAAP

Orexo AB Attendees	Title
Asa Holmgren, M.Sc. Pharm	Senior Vice President Regulatory Affairs, Orexo
Anders Pettersson, M.D., Ph.D.	Senior Vice President Clinical R&D, Orexo
Martin Jönsson, M.Sc. Pharm	Clinical Trial Manager, Orexo
David Westberg, M.Sc. Chem. Engineering	Project Leader, Orexo
Damaris DeGraft-Johnson, RPh, M.Sc., Med. Chem.	Regulatory Consultant, US Agent, President DJA Global Pharmaceuticals, Inc.
Dennis DeCola B.S. Biology	Senior Regulatory Consultant, DJA Global Pharmaceuticals, Inc.

(b) (4)

Meeting Objective(s): To discuss questions related to the development plans for OXY219.

Opening Discussion: Following introductions, the discussion focused on the Sponsor's questions that were included in the December 16, 2010, meeting package. Written comments were sent to the Sponsor on February 2, 2011. The Sponsor provided written responses on February 2, 2011, which are included below the applicable question.

REGULATORY QUESTIONS

Question 1. Application route: Proposed strategy and basis for 505(b)(2)

Orexo plans to bridge safety and efficacy data to the RLD Suboxone by comparative pharmacokinetic studies demonstrating equivalent exposure of buprenorphine. Results from the initial PK study indicate that OX219 has increased bioavailability of buprenorphine and naloxone as compared to the RLD. This would preclude demonstration of bioequivalence as per definition 21 CFR 320(e). Orexo proposes that the 505(b)(2) application route is appropriate for this product based on the following:

- *FDA's findings of safety and efficacy for Suboxone, the approved RLD*
- *Provision of Orexo AB's OX219 data from PK/bioavailability studies that bridge OX219 to the Suboxone RLD with respect to safety and efficacy profiles.*

Does the FDA agree?

Division Response:

We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of

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

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

You must provide comparative bioavailability data for your product demonstrating equivalent exposure to buprenorphine and equivalent or less exposure to naloxone when used as intended.

Discussion:

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

Question 2. Both the Suboxone tablet 8/2mg (NDA N020733) and the Suboxone film 8/2mg (NDA N022410) are listed as RLDs in the Orange Book. Both RLDs share the sublingual route of administration with OX219. Orexo performed the initial PK study comparing OX219 to Suboxone tablet (see Attachment 1), prior to the approval of the film. Although OX219 is the same dosage form as the Suboxone tablet, currently available information indicates that OX219 may have more similar in-vivo characteristics to the Suboxone film than to Suboxone tablet. These in-vivo characteristics include shorter dissolve time and increased bioavailability for OX219 [comparing OX219 initial PK data, (Attachment 1), to relevant data available on www.suboxone.com (Attachment 2)].

Moreover, considering that the film has a more recent approval, Orexo proposes that the film is the most suitable RLD for establishing the appropriate labeling concerning safety and efficacy of sublingual OX219.

Does the FDA agree?

Division Response:

No. The most appropriate reference product would be Suboxone (NDA 020732), because the findings of safety and efficacy for the buprenorphine/naloxone

combination for this indication were made in the context of that application. You may still use the Suboxone film label as a guide even if you do not use the Suboxone film as your reference.

Orexo February 2, 2011, response:

Orexo would like to clarify that if the Suboxone tablet RLD is withdrawn for reasons other than safety or efficacy (for example abuse, misuse or diversion) this would not affect the review of our NDA other than the potential for the additional step by the Agency. Under these circumstances it is our interpretation that the FDA suggested Suboxone RLD (tablet) will remain the same.

With respect to the additional review step can FDA clarify the process and comment on the impact on the NDA review i.e. does it extend the review time?

Discussion:

The Sponsor sought to clarify whether, if the referenced product was withdrawn for reasons other than safety or efficacy (for example abuse, misuse or diversion, as stated by the Sponsor of the referenced product), the NDA review timeline would be affected. The Division responded that if a determination has not been made prior to the time of NDA submission, it would be made as part of the review process and would not extend the review timeline. The Division further noted that every withdrawal is evaluated on a case-by-case basis and that, if an NDA is withdrawn due to misuse or abuse, the withdrawal *could be* considered to have been due to a safety issue. The Sponsor expressed concern that if one formulation of buprenorphine was found to be safer than another for the same indication that this could lead to a withdrawal for reasons of safety of the inferior product. The Division stated that they have made no such determination, but if we were to make such a determination, the product could be considered withdrawn due to a safety reason.

Question 3. In the event that Suboxone tablet is the sole RLD selected by the FDA for OX 219, Orexo has concerns that because Reckitt-Benckiser Pharmaceutical Company has the more recently approved Suboxone sublingual film (NDA N022410), it is conceivable that at some point in time the NDA (N020733) for Suboxone tablet may be withdrawn for reasons other than safety or effectiveness or discontinued from the US market. It is Orexo's understanding that in the event Reckitt-Benckiser withdraws their Suboxone tablet for reasons other than safety or effectiveness the review and approval process for OX219 would not be affected.

Does the FDA agree?

Division Response:

In the event of a withdrawal of the NDA of the drug relied upon for approval, the Agency will make a final determination as to whether it was withdrawn for reasons of safety or effectiveness as part of your product's NDA review. Withdrawal of the NDA would add this additional step to the review process but would not prevent your NDA submission from being reviewed.

Discussion:

See discussion after Question 2.

Question 4. Orexo has noted that the Suboxone film has exclusivity for a new dosage form until August 30, 2013 as listed in the Orange Book. Orexo believes that this would not preclude filing and FDA assessment of an OX219 505(b)(2) NDA prior to this date.

Does the FDA agree?

Division Response:

If you select the Suboxone tablet (NDA 020732) as your sole referenced product as we suggest in our response to Question 2, then the unexpired exclusivity on Suboxone film (NDA 022410) would have no bearing on your ability to submit, and possibly receive approval for, a 505(b)(2) application.

If, on the other hand, you were to reference the Suboxone film (NDA 022410), then any unexpired exclusivity would prevent approval (but not submission or filing) of your 505(b)(2) application.

Discussion:

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

Question 5. The Suboxone tablet Orphan Drug Exclusivity expired Oct 8, 2009. However, the Orphan Drug Designation was extended to Suboxone film as indicated in the NDA approval letter dated August 30, 2010. It is Orexo's understanding that the expired Orphan Drug Exclusivity also applies to Suboxone film. Therefore Orexo does not foresee any Orphan Drug Exclusivity issues related to either the tablet or the film.

Does the FDA agree with this interpretation?

Division Response:

Yes. The Orphan Drug Exclusivity is available only for the first product approved with the active moiety and the Orphan Drug Exclusivity for Suboxone for the treatment of opioid dependence has expired.

Discussion:

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

Question 6. Orexo intends to use the more recently approved Suboxone film as the basis for development of the OX219 label. Orexo believes that this approach will provide the most current safety, efficacy data and relevant information as well as directions for use including REMS. Also, Orexo

suggests that the Suboxone film label better reflects current knowledge and use information for maintenance of opioid dependence.

Does the FDA agree?

Division Response:

We agree that the Suboxone film label reflects our most current thinking about the combination of buprenorphine and naloxone for the treatment of opioid dependence.

Discussion:

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

Question 7. Orexo expects to develop a label text similar to Suboxone film providing pharmacokinetic properties documented for OX219 and appropriately adjusted dose recommendations. Orexo also plans to describe any relevant differentiating properties for OX219 (b) (4)

Does the FDA agree that this approach to labeling is acceptable?

Division Response:

No. Your claims appear to be promotional in tone and we do not recommend including such claims in the product labeling. You may include relevant properties of your drug product in the appropriate section of the labeling provided they are not presented as comparative.

If the claims are truthful, not misleading and have been appropriately validated by the Agency, the claims could potentially be presented in promotional labeling, advertising or carton and container labels. Such claims would need to be fully evaluated by the Division of Drug Marketing, Advertising and Communications. Additionally, the Division of Medication Error Prevention and Analysis would need to examine carton and container labels. Because these claims potentially denote a benefit to the drug characteristic described, use on carton labeling may require presentation of the indication and risk information on the carton and dissemination with Prescriber Information. Some of the claims may also require validation by the CMC review team.

Discussion:

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

Question 8. In order to address potential switching practices in the Medical Community, Orexo plans to include information on corresponding doses under the appropriate sections of the label that compares OX219 therapeutic dosing requirements versus Suboxone. For instance, the

recommended target dose for OX219 will likely be in the order of (b) (4) mg buprenorphine/naloxone per day as a single daily dose. This would correspond to 16/4 mg Suboxone.

Does the FDA agree with this approach?

Division Response:

Yes, we agree with the proposed approach,

(b) (4)

Orexo February 2, 2011, response:

Orexo would like to clarify that (b) (4) we plan to demonstrate that OX219 5/1.25mg dose is equivalent to Suboxone 8/2mg. Further, we understand that it would be required to demonstrate equivalent exposure for the low dose strength or obtain a BA/BE waiver for the lower dose. We also plan to study dose proportionality using multiple OX219 tablets covering the therapeutic dose range (Reference question 16 below). Orexo would like to discuss FDA's preliminary response in light of these clarifications.

Discussion:

The Sponsor stated that they plan to demonstrate that the OX219 5/1.25 mg dose is equivalent to Suboxone 8/2 mg. The Division responded that efficacy for the referenced product was demonstrated between 12 and 16 mg of buprenorphine, with 16 mg being the labeled dose, so demonstration of bioequivalence at the 16 mg Suboxone equivalent dose would be desirable.

After some discussion, the Division noted that it would include whether bioequivalence should be demonstrated at 16 mg or 8 mg Suboxone equivalent dose in the post meeting minutes. The Division also stated that because they will evaluate the BA/BE of the two proposed dosing strengths, they do not need to submit a request for a biowaiver, as the development program alone would suffice.

With respect to dose-proportionality, the Sponsor proposed Suboxone equivalent doses of 4, 8, and 16 mg in the dose-proportionality study. The Division responded that Suboxone equivalent doses of 2, 8, 12, and 16 mg should be included and this will be clarified in the post meeting minutes. The Sponsor proposed that to allow inclusion of 4 doses, a 4-treatment, 3-period, and incomplete block study design may be appropriate since blood sampling may otherwise require excess blood volumes to be drawn from the study subjects. The Agency responded that the Sponsor can propose this approach with appropriate justification.

Post-meeting note:

With respect to your bioequivalence proposal, we agree with your proposal to demonstrate that the OX219 5/1.25 mg dose is equivalent to the Suboxone 8/2 mg dose. With respect to dose-proportionality, we agree with your proposal to evaluate four OX219 doses corresponding to Suboxone equivalent doses of 2, 8, 12, and 16 mg respectively.

Question 9. The initial PK results indicate improved bioavailability of buprenorphine and naloxone for OX219, with lower doses of the active ingredients required as compared to currently approved Suboxone products. This therefore reduces the total buprenorphine dose for the patient and the overall amount that could be diverted and misused in the United States market.

(b) (4)

Does the FDA agree with this conclusion and proposal?

Division Response:

No. Conclusions and claims regarding the potential for misuse or diversion to be included in the label must be substantiated by convincing data. The doses of buprenorphine that you are proposing to study are within the range of doses that are misused and diverted and we do not anticipate a distinct public health advantage for your product based on increased bioavailability alone.

Discussion:

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

Question 10. The results of the initial PK study show no signs of sublingual irritation in human subjects indicating that there is no tendency for OX219 to induce local tolerability concerns.

These results are in accordance with clinical results for the Suboxone tablet (4) (with the same molar ratio of buprenorphine and naloxone as OX219) where no sublingual adverse side effects have been observed clinically. Mouth inspection will be included in the remaining PK studies for OX219. The active compounds can also be bridged from Suboxone and supported by local tolerability data acquired from the OX219 human pharmacokinetics studies.

In addition, all of the excipients found in OX219 meet USP standards and based on the above, Orexo believes that the risk for OX219 to cause harmful local effects will be sufficiently studied in the proposed human study program.

With regards to tolerability for OX219, the Orexo tablet technology has proven to be well tolerated in other sublingual products Edluar (US approved NDA,

21-997) and Abstral (US approval pending NDA 22-510). The tolerability data acquired for the active ingredients and excipients (USP) have previously been approved for other sublingual and/or orally disintegrating formulations.

Based on the above information and reliance on FDA's finding of safety as embodied in the label for the RLD, Orexo believes this should be a sufficient safety data package to support a 505(b)(2) application for maintenance treatment of opioid dependence and that no additional non-clinical studies are warranted.

Does the FDA agree with this approach and conclusion?

Division Response:

Assuming your exposure levels for buprenorphine and naloxone are comparable to the referenced product(s), based on the information presented in the meeting package, no additional nonclinical toxicology studies for buprenorphine, naloxone or the combination appear necessary to support a 505(b)(2) application that relies upon the Agency's previous finding of safety for Suboxone. However, the following general pre-NDA comments are provided which may require further studies to support your ultimate NDA application.

- 1. 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.**
- 2. Although there does not appear to be novel excipients in your drug product formulation, your IND and NDA should include detailed discussion of why the maximum daily exposure to each excipient does not present any safety concerns. This can be accomplished via reference to the Inactive Ingredient's Guide and literature, if needed. We refer you to our May, 2005, Guidance for Industry document *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients* which is available on the CDER web page at the following <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.**
- 3. Any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as described in ICHQ3A(R2) and ICHQ3B(R2) guidances at the time of NDA submission.**

Adequate qualification would include:

- a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies; e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**
 - b. Repeat dose toxicology of appropriate duration to support the proposed indication.**
- 4. Phenanthrene-derivative opioid drug product, including naloxone, may contain impurities containing an α,β -unsaturated ketone moiety, which is a structural alert for mutagenicity. Therefore, the specification for these impurities in the drug substance must be reduced to NMT 1.5 mcg/day or adequate safety qualification must be provided. We recommend that you consult with your DMF holder to determine the levels of these impurities in the drug substance you are obtaining and if needed, to decrease the limit of these impurities. Should qualification data be necessary 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.**
- 5. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICHQ3A and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold must be adequately justified for safety from a toxicological perspective.**
- 6. Failure to submit adequate impurity qualification, justification for the safety of new excipient use, or an extractable leachable safety assessment, may result in a Refusal-to-File or other adverse action.**

Orexo February 2, 2011, response:

(With respect to bullet number 1)

Our understanding of FDA’s response is that if OX219 has the same buprenorphine and naloxone exposure levels in humans as the Suboxone RLD, no further non clinical studies are required.

Discussion:

The Division stated that, due to increased bioavailability of OX219, the total daily dose may be lower than the referenced drug product yet provide comparable exposure levels. Most of the nonclinical data in the referenced drug product labeling includes exposure margins that are based on body surface extrapolations. Exposure margins are necessary to put the nonclinical findings into clinical perspective. Adjusting the body surface area exposure margins based on total daily dose alone would imply a greater safety margin, which would be inaccurate and misleading if the actual exposure with the product is comparable to the referenced drug product.

The Division also noted that product labeling will need to take this into consideration and the Sponsor will need to either propose adequate language that is scientifically accurate, clinically meaningful, and not misleading or provide actual exposure data to revise the safety margins. The latter may require animal toxicokinetic studies that mimic the dosing regimen employed in the studies cited in the referenced product labeling.

Question 11. An initial PK study has been performed comparing OX219 6/1.5mg and Suboxone tablet 8/2 mg. The protocol and results of this study can be found in Attachment 1. In this study OX219 showed an approximately 20% increased buprenorphine and naloxone exposure as compared to the Suboxone tablet, based on geometric mean ratios for AUC_{0-48h} and C_{max} even with the lower doses of 6/1.5 mg buprenorphine and naloxone used. In the current development plans for OX219, Orexo intends to further reduce the dose of buprenorphine and naloxone (while maintaining the 4:1 buprenorphine/naloxone ratio) to provide equivalent exposure of buprenorphine as compared to Suboxone. Current data indicate that the appropriate OX219 dose equivalent to Suboxone 8/2mg may be in the order of 5/1.25 mg. Orexo also intends to develop a low dose strength (e.g. 1.25/0.31mg) corresponding to Suboxone 2/0.5 mg.

In order to meet the requirements of a 505(b)(2) application, Orexo believes that it is appropriate to only bridge the higher strength of OX219 (e.g. 5/1.25 mg) to the RLD Suboxone 8/2 mg by demonstrating equivalent buprenorphine exposure in-vivo.

Orexo proposes the following study program as the clinical basis for the NDA:

- 1 A second PK study to compare optimized formulations of OX219 tablet to the FDA selected Suboxone 8/2 mg RLD in order to determine the final dose.*
- 2 One pivotal, fasting, single dose, two treatment, two-period crossover, comparative bioavailability study, comparing OX219 Final Commercial Product (FCP) and dose to the FDA selected Suboxone 8/2 mg RLD.*
- 3 One fasting, single dose, crossover dose proportionality study, comparing different doses of OX219 over a suitable dose range (e.g. 2.5/0.625 mg, 5/1.25 mg and 10/2.5 mg).*

It is Orexo's view that studies 2 and 3 together will provide sufficient data for bridging safety and efficacy to Suboxone over the relevant dose range.

Does the FDA agree that the proposed approach and study program is sufficient to support the NDA?

Division Response:

We have the following comments with respect to your clinical development program:

- 1. Design your pivotal BA/BE study(s) to be capable of demonstrating equivalent exposure for both buprenorphine and naloxone with respect to C_{max} and AUC between OX219 and Suboxone. Although equivalent exposure should be demonstrated for buprenorphine; lower naloxone levels when the product is used as intended; i.e, sublingually, may be acceptable as the naloxone in the formulation is expected to play a role only when the product is used by other routes.**
- 2. Evaluate the time it takes for the product to completely dissolve when administered in humans.**
- 3. Since you are only developing your product for maintenance treatment of opioid dependence, address how you will discuss induction treatment in the label.**
- 4. Provide data demonstrating that your product releases sufficient naloxone under conditions of misuse to precipitate withdrawal in persons dependent on full agonist opioids.**
- 5. See our responses to Questions 13 through 20 for additional details.**

Discussion:

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

Question 12. In accordance with FDA's reply to the Reckitt-Benckiser citizens petition, docket number FDA-2009-P-0325-0001, Orexo believes that in-vivo equivalence studies on the low strength could be waived, assuming that the formulations of the two strengths of OX219 are proportionally similar and/or will meet FDA's requirements for waiver of BE. The FDA draft guidance document (5) on Buprenorphine Hydrochloride; Naloxone Hydrochloride indicates that a waiver of in-vivo testing will be granted for the 2/0.5mg strength based on (i) acceptable BE study on the 8/2mg strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Does the FDA agree with this interpretation and conclusion?

Division Response:

We note that you are referring to the Office of Generic Drugs (OGD) draft Guidance document *Buprenorphine Hydrochloride; Naloxone Hydrochloride for sublingual oral tablets*.

We agree with your interpretation of the draft guidance regarding the information needed to support a waiver request for the CFR's requirement to provide in vivo BA/BE data for the lower(s) strength of your product (i.e., 1) data from an acceptable BE study on the highest strength, 2) data showing that the formulations are compositionally proportional, and 3) in vitro dissolution comparison profile data (individual, mean, SD, plots) and similarity f2 values for all the strengths using the same dissolution testing conditions and 12 units/test). In addition, you will need to provide the results from your PK-dose proportionality study showing that the formulations are dose-proportional.

Please note that we will consider your BA/BE waiver request during the NDA review.

Discussion:

See discussion after Question 8.

Question 13. The initial PK study indicates a norbuprenorphine/buprenorphine metabolic ratio that is lower for OX219 than for Suboxone tablet after single dose administration. Orexo believes that this in-vivo observation is inherently related to the OX219 formulation technology providing increased sublingual bioavailability of buprenorphine. This lower norbuprenorphine exposure is expected, since an increased bioavailability of sublingual buprenorphine absorption and a lower buprenorphine dose will result in less buprenorphine being swallowed. Therefore less buprenorphine will undergo first pass metabolism in the liver and/or gut thus less norpbuprenorphine will be produced.

In the FDA's Clinical Pharmacology and Biopharmaceuticals Summary Basis of Approval document for Suboxone it is stated that norbuprenorphine is an inactive metabolite.

Relevant literature searches comparing norbuprenorphine and buprenorphine effects determined the following:

- 1. In-vitro, norbuprenorphine displays an affinity to the μ -opioid receptor similar to buprenorphine but a lower potency, as indicated by a 20 times higher EC50 value in an [³⁵S]GTP γ S binding assay (1).*
- 2. Based on direct measurement from brain tissue norbuprenorphine shows a much lower distribution to the brain than buprenorphine after intravenous administration to rats (2). More norbuprenorphine than buprenorphine was required to achieve the same degree of analgesic*

effect in an acetic acid tail writhing test in mice (1). In a rat tail flick test the analgesic effect of norbuprenorphine was estimated to be approximately 1/50 of buprenorphine (2).

Although no specific studies regarding the clinical significance for norbuprenorphine have been performed, post mortem data support that norbuprenorphine has low penetration into the Central Nervous System (7, 8). Patients with renal insufficiency, receiving infusions with high doses of buprenorphine, were found to accumulate norbuprenorphine without signs of additional opioid adverse effects (9). Moreover, drug interaction studies in buprenorphine-treated opioid dependent patients did not reveal any changes in clinical response despite lower steady state norbuprenorphine levels (10, 11).

Given the FDA's position that norbuprenorphine is an inactive metabolite and further support from the above literature, Orexo concludes that norbuprenorphine does not contribute significantly to the central effects of buprenorphine. Therefore a lower reduction of norbuprenorphine exposure to the degree relevant for OX219 (estimated to be approximately 35% lower for a dose of 5/1.25 mg of OX219) should be acceptable without requirements for additional efficacy studies.

Does the FDA agree?

Division Response:

In the most recently approved label of Suboxone film (NDA 022410), it is mentioned that “norbuprenorphine has been found to bind opioid receptors in-vitro; however, it has not been studied clinically for opioid-like activity.” Therefore, we do not agree with your interpretation that our position is that norbuprenorphine is an inactive metabolite.

You should apply the same BE principles (90% confidence intervals) for norbuprenorphine analysis. You don't have to demonstrate BE between OX219 and Suboxone with respect to norbuprenorphine. At this time, we do not anticipate that lower norbuprenorphine exposure as compared to Suboxone, seen in your pilot study with OX219, will lead to any requirement for efficacy studies related to this issue.

Discussion:

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

Question 14. Naloxone is included in OX219 and Suboxone to deter intravenous abuse and serves no therapeutic purpose when taken as directed. Naloxone bioavailability is low when administered sublingually and previous comparisons between Suboxone and Subutex (buprenorphine only) indicate that addition of naloxone has no significant impact on efficacy.

FDA's Draft guidance document (5) on Buprenorphine Hydrochloride; Naloxone Hydrochloride indicates that buprenorphine, norbuprenorphine, and "naloxone (total and unconjugated)" in plasma should be measured. Under the section beneath this, the guidance indicates that "Bioequivalence based on (90% CI) buprenorphine and naloxone", without any indication as to whether this includes unconjugated naloxone or total naloxone (or both).

Data from Orexo's initial PK study indicates that there was a significant intra-subject variability in naloxone (unconjugated) exposure after administration of both OX219 and Suboxone tablet (Attachment 1); total naloxone was not analyzed in this study.

For unconjugated naloxone, Orexo plans to calculate the geometric mean ratios and 90% CIs for AUC and C_{max}. Considering the role of naloxone, the low levels of systemic exposure and the high intra-subject variability, Orexo proposes that a widening of the acceptable GMR 90% CI limits for AUC and C_{max} to 70-143% would be appropriate for this analyte in order to conduct a comparative bioavailability study with a reasonable sample size.

Orexo plans to submit total naloxone results as supportive data only and does not expect the 90% confidence intervals to fall within any prespecified limits due to wide intra-subject variability with this analyte.

Does the FDA agree?

Division Response:

In our experience, BE can be demonstrated with unconjugated as well as total naloxone with Suboxone (8/2 mg) tablets. You should conduct BE analysis for unconjugated and total naloxone using the standard 80 to 125% limits. However, lower naloxone exposure, when the product is used as intended, i.e., sublingually, would be acceptable because the naloxone in the formulation is expected to play a role only when the product is not used as intended. Also see our response to Questions 1 and 17.

Discussion:

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

Question 15. Buprenorphine pharmacokinetics is characterized by a rapid distribution phase followed by a slow terminal elimination phase with low, slowly decreasing, plasma concentrations (mean $t_{1/2}$ of approximately 33 hours) (3). For the metabolite norbuprenorphine a mean $t_{1/2}$ of approx 42 hours has been described (3). The FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations, March 2003 (Revision 1) (12) recommends blood sampling for at least three terminal half-lives under normal conditions. For long half-life drugs however, the sampling time could be reduced to

72 hours if the drug demonstrates low intra-subject variability in distribution and clearance. As indicated by a relatively small intra-subject variability in buprenorphine AUC in the initial PK-study (26%), this appears to be valid for sublingual buprenorphine. Due to the biphasic pharmacokinetics of buprenorphine, plasma concentrations at 72 hours are normally <5% of C_{max} and AUC_{0-72h} normally represent >80% of the extrapolated AUC. Orexo also proposes that it is very unlikely that potential differences in sublingual formulations would lead to differences of the PK curve beyond 72 hours after administration, since the absorption phase should be completed.

Orexo suggests that 72 hours sampling time is appropriate for the pivotal study and that AUC_{0-72h} is used as exposure measurement in lieu of AUC_{0-t} and AUC_{0-∞} for buprenorphine and norbuprenorphine.

Does the FDA agree?

Division Response:

A sampling time up to 72 hours is reasonable; however, it is standard practice to employ both AUC_{0-t} and AUC_{0-∞} for BE analysis and we recommend that you use both of these measures.

In addition to buprenorphine and norbuprenorphine, measure naloxone levels in your pivotal study and conduct BE analysis on each of the three moieties.

Discussion:

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

Question 16. The pharmacokinetic studies are planned to be performed in healthy volunteers under naltrexone blockade. Experience from the initial PK study and previous experience (6) shows that the naltrexone block does not completely block buprenorphine effects and that many subjects are troubled by opioid side effects (including nausea and vomiting as the most pronounced effects). Previous studies have demonstrated that naltrexone block works sufficiently well in healthy volunteers up to at least 16 mg although side effects were recorded and naltrexone dose had to be increased in several cases.

According to the Suboxone film label, the therapeutic dose is normally between 4 and 24 mg buprenorphine, which would correspond to approximately 2.5 to 15 mg buprenorphine for the OX219 formulation. Orexo suggests that the highest dose for the dose proportionality study is limited to a dose corresponding to Suboxone 16 mg (e.g. 10 mg OX219 buprenorphine), which has been confirmed as safe and reasonably tolerable in healthy volunteers under naltrexone block. Orexo contends that extrapolation of results from a dose proportionality study conducted on three doses between 2.5 and 10 mg buprenorphine to cover the

complete dose range up to 15 mg should be acceptable for OX219.

Does the FDA agree?

Division Response:

Since OX219 is a new formulation and differs significantly from the reference product in terms of nominal doses of buprenorphine and naloxone, you should assess dose proportionality using multiples of your product to cover the entire therapeutic range of Suboxone tablets as labeled, i.e. 2 to 24 mg. The study should assess buprenorphine, norbuprenorphine and naloxone plasma levels.

The lowest strength of your product should be tested in this study such that buprenorphine and naloxone plasma levels from the lowest strength are available for review.

Regarding the doses to be studied, we recommend that you include doses that will reflect the most commonly used therapeutic doses (e.g., 16 mg of Suboxone compared with 2 of the 5.25 mg OX219 tablets) and scenarios where multiples of 3 or more units of OX219 may need to be used (e.g., 12 mg of Suboxone compared with 1 of 5.25 mg and 2 of 1.25 mg OX219 tablets).

We acknowledge your comment that, in your experience and in the literature, subjects experience opioid-related side effects from buprenorphine, including nausea and vomiting. We note that naltrexone can also cause nausea and vomiting in some patients. Despite the potential for these adverse reactions, the pharmacokinetics of buprenorphine have been studied in normal subjects in doses up to 32 mg, and your study should assess dose proportionality to cover the entire therapeutic range you are proposing. The timing of naltrexone dosing in the OX219-001 protocol appears to be appropriate. However, you may wish to consider starting subjects at a dose of naltrexone higher than 50 mg when they are to receive buprenorphine doses in the upper part of the dosing range. In the study by McAleer, et al. (2003) provided in the meeting package, the dose of naltrexone used in conjunction with higher doses of buprenorphine was 100 mg or 150 mg. Additionally, the informed consent document and informed consent process should clearly outline the risk of opioid-related side effects, including their severity.

Orexo February 2, 2011, response:

Orexo would like to clarify that we are only planning to have two dosage strengths of OX219 (1.25/0.31mg and 5/1.25mg) that correspond to the two dosage strengths of Suboxone (2/0.5 mg and 8/2mg). Orexo would like to clarify that our proposed dose proportionality study will be conducted over the range of OX219 that corresponds to the Suboxone dose range. The dose proportionality study will not compare OX219 to Suboxone. Based on the preliminary response to this question Orexo proposes that the dose proportionality OX219 study will be performed using the doses in the table below which covers the labeled therapeutic dose range;

Discussion:

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

Question 17. Since Orexo intends to develop a formulation which delivers equivalent exposure as compared to the RLD, Orexo believes that safety and efficacy can be completely bridged from the RLD by pharmacokinetic studies and that no additional efficacy or clinical safety studies are warranted.

Does the FDA agree?

Division Response:

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

Because you are proposing an indication for maintenance treatment, higher exposure to naloxone will not result in a requirement for additional efficacy data. However, if you were to seek an indication for induction, higher exposure to naloxone would result in this additional requirement. Although naloxone does have some sublingual bioavailability, it is expected to be of minimal consequence in patients stabilized on and dependent on buprenorphine, because it does not compete well with buprenorphine at the mu receptor.

The purpose of including naloxone in the formulation is to make the product less attractive for diversion by precipitating withdrawal in persons dependent on full opioids when the product is misused parenterally. There may be a nominal minimum dose of naloxone which is capable of producing this effect. In order to meet regulatory requirements, a combination product must demonstrate that each component contributes to the product's safety or effectiveness. In the case of your proposed product, you must provide data demonstrating that your product releases sufficient naloxone under conditions of misuse to precipitate withdrawal in persons dependent on full agonist opioids.

If exposure for buprenorphine or naloxone is higher than the referenced product when used as intended (C_{max} and AUC values), then additional safety data will be required. Because this is not a novel dosage form or route of administration and

you do not appear to be employing novel excipients, safety data in addition to the data collected in the planned studies will not be required.

Orexo February 2, 2011, response:

Under the assumption that the exposure to Naloxone from OX219 is not higher than that from Suboxone please clarify what would be required for an induction indication.

Regarding provision of data demonstrating OX219 releases sufficient naloxone under conditions of misuse, the literature appears to support that a dose of 0.31mg naloxone from the lowest strength of OX219 will be sufficient to precipitate withdrawal in persons dependent on full opioid agonists.

Discussion:

The Division stated that since Suboxone has not been studied as initial (“induction”) treatment, the Sponsor would need to conduct a study to assess treatment success after a number of weeks of treatment to support labeling for induction as well as maintenance. The Division stated that the design of such a study could randomize patients to either buprenorphine or the buprenorphine/ naloxone combination, and measure the percentage of patients who are successfully titrated and stabilized onto treatment (e.g., reach a stable dose and complete one or two weeks of treatment). The Sponsor inquired if one or two studies would be necessary. The Division responded that internal discussion would be necessary, and that a post-meeting note addressing the issue would be included in the meeting minutes. The Division also stated that the study or studies should be appropriately powered to detect efficacy based upon an appropriate expected treatment effect size.

Post-meeting Note:

You may be able to meet the requirements for substantial evidence of effectiveness for approval of your product for use in initial treatment with one adequate and well-controlled trial if other convincing data is available that supports this use.

The Sponsor sought clarification as to what would be required to demonstrate that the level of naloxone in OX219 would precipitate withdrawal in those dependent on full agonist opioids. The Division stated that a behavioral pharmacology study may be necessary, although it is possible that literature exists which would address the issue as well. The Division further explained that once the Sponsor determines how much naloxone is released, relevant literature should be reviewed to determine if that level has been consistently shown to precipitate withdrawal in those dependent on full agonist opioids. If the literature does not support it, then a study would be necessary. The Division stated that one possible design for such a behavioral pharmacology study would be a blinded, placebo-controlled study. The Division referred the Sponsor to studies that have been conducted by Dr. John Mendelson in San Francisco and at the Behavioral Pharmacology Research Unit at Johns Hopkins University School of Medicine in designing a study.

Question 18. Pharmacokinetic data from the initial PK study indicates that OX219 and Suboxone sublingual tablet have similar rate of absorption (i.e. similar t_{max}). Provided that this finding is confirmed in the pivotal bioavailability

study Orexo proposes that it is unlikely that OX219 should have a higher abuse liability than Suboxone and that abuse liability studies are not warranted.

Does the FDA agree?

Division Response:

No. Provide data demonstrating that your product releases sufficient naloxone under conditions of misuse to precipitate withdrawal in persons dependent on full agonist opioids. Note that maintaining a 4:1 ratio of buprenorphine:naloxone alone is not sufficient to ensure that the product will perform as intended under conditions of misuse (i.e., that it will precipitate withdrawal in persons dependent on full agonists). It is also essential that an adequate naloxone dose be maintained in your product to ensure that the naloxone component performs as intended. You may need to demonstrate this in studies of the lowest doses of the product under conditions of misuse.

Discussion:

See discussion after Question 17.

Question 19. In order to support the OX 219 505(b)(2) NDA application for the maintenance treatment of opioid dependence, literature searches will be performed in their entirety to provide additional documentation. The literature searches will be performed using two separate databases:

- *Medline – this database is managed by the National Library of Medicine and contains citations from 1950 to the present.*
- *Toxnet – this resource is a cluster of databases covering toxicology, hazardous chemicals, environmental health and related areas and is managed by the National Library of Medicine. Toxnet contains citations from 1965 to the present.*

Searches in these databases, using the basic search terms (examples of which are described below), will be performed and the date of the search and number of citations recovered will be presented. All abstracts will be reviewed for new, relevant findings in the areas of clinical efficacy, clinical safety, pharmacokinetics and toxicology. In addition, within each of these areas, specific search terms will be used to find information on specific topics within the basic citations.

Examples of search terms to be used are as follows:

Subutex, Suboxone, buprenorphine hydrochloride, naloxone hydrochloride

The general approach will be to include literature citations with relevant information in support of the NDA. Literature will be summarized and presented, and the citations themselves will be submitted hypertext-linked to the descriptive text. Details such as study design, dose and duration of

treatment, endpoints evaluated, statistical analyses, adverse events (serious and non-serious), discontinuations, and deaths will be included. Publications will be in a text, not graphic, format in order to facilitate searching and readability.

Does the FDA agree with this proposal?

Division Response:

We have no specific comments about your proposal because it is unclear what aspects of the application the literature review will be intended to support.

Discussion:

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

Question 20. In the approval letter for Suboxone film, FDA waived pediatric requirements since this indication is considered orphan. Hence, Orexo believes that pediatric requirements should also be waived for OX219.

Does the FDA agree?

Division Response:

No. The granting of orphan designation is performed by the Office of Orphan Products. Subutex received orphan drug designation on June 15, 1994, and Suboxone received orphan drug designation on October 27, 1994, prior to the 2000 Drug Addiction Treatment Act and the institution of office-based opioid-dependence treatment with buprenorphine products.

If you do not receive orphan designation by the time of NDA submission, you will be obliged to fulfill the pediatric requirements under the Pediatric Research Equity Act (PREA). Specifically, you must provide a pediatric development plan with a request for a waiver and/or deferral of studies in the appropriate pediatric populations, justification for waiving and/or deferring the assessments, and evidence that the deferred pediatric studies are being conducted or will be conducted with due diligence. We refer you to the Guidance for Industry *How to Comply with the Pediatric Research Equity Act* (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf>).

Under PREA, you may be required to conduct PK, safety, or efficacy studies for your proposed indication in patients less than 17 years old. Please note that pediatric participants in clinical studies must be symptomatic or at risk for the condition(s) treated by the product to be consistent with 21 CFR 50.53 and the related ethical framework for research in children.

Orexo February 2, 2011, response:

If Orexo needs to fulfill the pediatric requirements under PREA what is FDA's current thinking on the appropriate age group for this indication?

Discussion:

The Division stated that the appropriate age groups for study would be neonates (neonatal abstinence syndrome) and adolescents (opioid dependence). The Sponsor expressed concern about the appropriateness of the dosage form and the feasibility of the route of administration in the neonatal population. The Division clarified that under PREA, if the formulation of the product is not suitable for the pediatric age group in question, the Sponsor is required to develop a formulation that is suitable. The Division further stated that a deferral for these studies until after NDA approval should be requested, which seems appropriate, although the Pediatric Equity Research Committee (PERC) must concur with the review Division's recommendation. A waiver should be requested for the intermediate age groups.

Action Items:

1. The Sponsor will work to develop exposure margins for inclusion in product labeling that is scientifically accurate, clinically meaningful, and not misleading. Alternately, revised safety margins supported by actual exposure data may be necessary.
2. If labeling for use of the product as initial ("induction") treatment is sought, the Sponsor will study induction and assess patient completion after a number of weeks.
3. The Sponsor will provide information to demonstrate that the amount of naloxone released from their low-dose product under conditions of misuse is sufficient to precipitate an aversive reaction in individuals dependent on full agonists, either from convincing evidence from literature, or from clinical pharmacology study/studies to be conducted by or for the Sponsor.

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/s/

MATTHEW W SULLIVAN
03/04/2011