

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022410Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 22410

SUPPL #

HFD # 170

Trade Name Suboxone

Generic Name buprenorphine and naloxone

Applicant Name Reckitt Benckiser

Approval Date, If Known August 30, 2010

### **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)(1)

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?

The Sponsor didn't appear to overtly make a request for exclusivity. However, they noted that they have received an orphan designation.

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# 20732

Subutex (buprenorphine) sublingual tablets

NDA# 20733

Suboxone (buprenorphine and naloxone) sublingual tablets

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:

RB-US-07-001

12 week, open-label study in patients already stabilized on Suboxone; AEs and oral mucosal exams at clinic visits. Enrollment = 194 patients.

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

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

RB-US-07-001, the 12-week open label study, was necessary for approval and was conducted specifically to support this NDA submission.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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

Investigation #1  
IND # 75811            YES             ! NO   
! Explain:

Investigation #2  
IND #                    YES             ! NO   
! Explain:

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

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

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

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

YES  NO

If yes, explain:

---

Name of person completing form: Matt Sullivan  
Title: RPM  
Date: August 30, 2010

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

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22410	ORIG-1	RECKITT BENCKISER PHARMACEUTICA LS INC	SUBOXONE (BUPRENORPHINE/NALOXONE ) sublingual film

---

**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  
08/30/2010

RIGOBERTO A ROCA  
08/30/2010

**Debarment Certification**

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

Reckitt Benckiser Pharmaceuticals, Inc.  
by: Deborah C. Moffitt

Signature: 

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 022410 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Suboxone Established/Proper Name: buprenorphine and naloxone Dosage Form: sublingual film		Applicant: Reckitt Benckiser Agent for Applicant (if applicable):
RPM: Matt Sullivan		Division of Anesthesia and Analgesia Products
<p><b>NDA:</b> NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input 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><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>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.</b></p>
<p>❖ Actions</p> <ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is 8/30/10 (extended from 5/30/10)</li> </ul>		<p><input checked="" type="checkbox"/> AP    <input type="checkbox"/> TA    <input type="checkbox"/> CR</p>
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<p><input type="checkbox"/> None CR: 8/21/09</p>

<sup>1</sup> 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.

<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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics<sup>2</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</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 checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span></p> <p>Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR <span style="margin-left: 200px;">REMS: <input checked="" type="checkbox"/> MedGuide</span>  <input type="checkbox"/> Submitted in response to a PMC <span style="margin-left: 100px;"><input type="checkbox"/> Communication Plan</span>  <input type="checkbox"/> Submitted in response to a Pediatric Written Request <span style="margin-left: 100px;"><input checked="" type="checkbox"/> ETASU</span>  <span style="margin-left: 400px;"><input type="checkbox"/> REMS not required</span></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"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Press Office notified of action (by OEP)</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<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

<sup>2</sup> 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"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>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></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(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></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(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></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(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></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>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></li> </ul>	<input 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"> <li>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.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>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.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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></li> </ul>	<input 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>	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	--

**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	8/30/10
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) AP: 8/30/10 CR: 8/21/09
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	8/30/2010
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	11/24/2009
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 8/25/10

❖ 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"> <li>Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	6/16/2010
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	11/24/2009
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	
❖ Labels ( <b>full color</b> 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"> <li>Most-recent draft labeling</li> </ul>	4/29/2010
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	4/30/10, 2/19/10, 7/8/09 4/21/10, 2/18/10, 1/14/09
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 7/2/09 <input checked="" type="checkbox"/> DRISK 6/8/10, 8/6/09 <input checked="" type="checkbox"/> DDMAC 7/8/09 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	8/4/09
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment ( <i>indicate date</i> )	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____</li> <li>Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	(n/a: Orphan designated)  <input type="checkbox"/> Included
❖ 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 (except action letters), emails, faxes, telecons</i> )	various

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ 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 6/24/08
• 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> )	
❖ 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> )	
<b>Decisional and Summary Memos</b>	
❖ 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 8/30/10; 8/21/09
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8/20/10; 8/10/09; 7/15/09
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 2
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	
• Clinical review(s) ( <i>indicate date for each review</i> )	7/15/09, 6/17/09
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	7/15/09 clinical review (pg 13)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None 7/27/09, 5/19/09
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not applicable 6/26/09
❖ Risk Management	
• REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	8/30/10
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	8/21/09
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input type="checkbox"/> None 8/6/10, 8/30/10
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested 6/26/09

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

<b>Clinical Microbiology</b> <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
<b>Biostatistics</b> <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
<b>Clinical Pharmacology</b> <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 7/28/09, 6/23/09
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input type="checkbox"/> None 11/12/09, 6/29/09
<b>Nonclinical</b> <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 5/22/09, 12/4/08
❖ 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 type="checkbox"/> No carc 5/26/09
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 5/13/09 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <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 type="checkbox"/> None 8/21/09
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8/20/09, 7/7/09, 12/12/08
❖ Microbiology Reviews <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 (DMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ 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</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	7/7/09
<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) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup></i> )	Date completed: 8/20/09 <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</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>6</sup> 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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22410	ORIG-1	RECKITT BENCKISER PHARMACEUTICA LS INC	SUBOXONE (BUPRENORPHINE/NALOXONE ) sublingual film

---

**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  
09/03/2010



NDA 022410

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Reckitt Benckiser Pharmaceuticals Inc.  
10710 Midlothian Turnpike, Suite 430  
Richmond, VA 23235

Attention: John D. Pitts, R.Ph., Ph.D.  
Manager, Regulatory Affairs

Dear Dr. Pitts:

Please refer to your New Drug Application (NDA) submitted October 20, 2008, received October 21, 2008, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for buprenorphine and naloxone sublingual film.

Reference is also made to your November 24, 2009, submission, received November 30, 2009, which constituted a complete response to our August 21, 2009, action letter.

On April 30, 2010, we received your April 29, 2010, unsolicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 30, 2010.

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

Sincerely,

*{See appended electronic signature page}*

Sara E Stradley, MS  
Chief, Project Management Staff  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22410	ORIG-1	RECKITT BENCKISER PHARMACEUTICA LS INC	SUBOXONE (BUPRENORPHINE/NALOXONE ) sublingual film

---

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

---

/s/

---

SARA E STRADLEY  
05/06/2010



NDA 020732  
NDA 020733  
NDA 022410

**GENERAL ADVICE**

Reckitt Benckiser Pharmaceuticals Inc.  
10710 Midlothian Turnpike, Suite 430  
Richmond, VA 23235

Attention: John D. Pitts, R.Ph., Ph.D.  
Senior Manager, Regulatory Affairs

Dear Dr. Pitts:

Please refer to your New Drug Applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Subutex (buprenorphine HCl) sublingual tablets, Suboxone (buprenorphine HCl and naloxone HCl) sublingual tablets, and buprenorphine HCl and naloxone HCl sublingual film.

We also refer to your September 14, 2009, Type A meeting request to discuss our August 21, 2009, REMS notification [REDACTED] (b) (4) Complete Response (NDA 022410) letters.

Subsequent to this meeting request, you submitted a proposed Risk Evaluation and Mitigation Strategy (REMS) [REDACTED] (b) (4) on November 24, 2009, (NDA 022410). Based on the review of your proposed REMS, we are now providing the following responses to your questions contained in your October 5, 2009, meeting background package and providing additional comments pertinent to your proposed REMS documents.

For convenience, your questions are shown below in italics while the Division's responses are in normal text.

*Question 1: Does the FDA agree that the proposed labeling revisions and communication plan are sufficient to support the REMS?*

FDA Response:

Labeling comments have been and will continue to be conveyed in the context of review of your applications.

We note the inclusion of [REDACTED] (b) (4) in your proposed REMS. At this time, we are not requiring a [REDACTED] (b) (4) as an element of your REMS. Refer to our response to Question 2 for more information concerning the elements of the REMS.

*Question 2:*

- a) *Does the FDA agree that the proposed elements to assure safe use are adequate?*

FDA Response:



Furthermore, we believe the goals of the REMS should be changed to the following: to mitigate the risk of accidental overdose, misuse and abuse and to inform patients of the serious risks associated with the use of Subutex, Suboxone, buprenorphine HCL and naloxone HCL sublingual film.

With regard to the elements to assure safe use that will be required for the REMS, we refer you to our August 21, 2009, letters (b) (4) 022410. In those letters, we indicated that each patient using the drug should be subject to certain clinical monitoring under section 505(f)(3)(E) of the FDCA to ensure that 1) each patient is receiving the psychosocial support necessary for safe and effective use of Subutex and Suboxone, 2) each patient adheres to the conditions of safe use explained to him/her, and 3) each patient is using Subutex and Suboxone appropriately and making adequate progress towards treatment goals.

Upon further consideration, we believe that the clinical monitoring under section 505(f)(3)(E) of the FDCA will not be adequate to meet the goals of the REMS. Therefore, we have determined that the REMS for the buprenorphine products must contain an additional element to assure safe use, specifically evidence of safe-use conditions under 505-1(f)(3)(D), to ensure that the benefits of buprenorphine outweigh the risks of accidental overdose, misuse and abuse.

Based on our current understanding of the risks of buprenorphine, we have determined that the REMS must include a Medication Guide, elements to assure safe use under 505-1(f)(3)(D) and 505-1(f)(3)(E), an implementation system, and a timetable for the submission of assessments of the REMS.

The REMS must include, at a minimum, the following:

1. Reckitt Benckiser Pharmaceuticals, Inc. will ensure that Subutex, Suboxone, buprenorphine HCL and naloxone HCL sublingual film will only be dispensed to patients with documentation of the following safe use conditions:
  - a) Verification that the patient meets the diagnostic criteria for opioid dependence.
  - b) Risks described in the professional labeling and the Medication Guide have been discussed with the patient.

- c) Safe storage of the medication has been explained and reviewed.
  - d) After appropriate induction, the patient is prescribed a limited amount of medication at first visit.
2. Reckitt Benckiser Pharmaceuticals, Inc. will ensure that each patient using Subutex, Suboxone, buprenorphine HCL and naloxone HCL sublingual film will be subject to the following monitoring:
- a) Return visits are scheduled at intervals commensurate with patient stability. Weekly, or more frequent, visits are recommended for the first month.
  - b) Assessment and reinforcement of patient's compliance with the prescribed medication.
  - c) Assessment of appropriateness of dosage prescribed.
  - d) Assessment of whether patient is receiving psychosocial support, as necessary.
  - e) Assessment of whether patient is making adequate progress toward treatment goals.

We propose the attached monitoring checklist that delineates the appropriate safe use conditions and monitoring practices.

The REMS must include an implementation system to monitor and evaluate the implementation of the safe-use conditions under paragraph 1 above. As part of this implementation system, you may submit a plan to obtain information concerning the documentation of safe use conditions through the use of surveys of patients and prescribers, ongoing surveillance (including such sources as internet, street ethnography, and interviews with drug treatment program staff and patients), and evaluations of health care utilization database sources. This will enable you to determine whether prescribers are employing appropriate practices in implementing and documenting safe use conditions.

*b) Does FDA continue to concur that a single REMS can be prepared for both SUBUTEX sublingual tablets and SUBOXONE sublingual tablets?*

FDA Response:

The REMS for Subutex sublingual tablets and Suboxone sublingual tablets can be the same. For administrative purposes, submit your proposed REMS to each NDA with the respective NDA number and name of drug specified on the REMS. For your products that do not share the same Medication Guide, you may use the same REMS document and appended materials with the appropriate Medication Guide. The other appended materials may list all of the products so it remains as one system.

- c) *At the time of approval of the SUBOXONE sublingual film, does FDA continue to agree that the REMS can be operated as a single system for all three products, and that a single enrollment form and Prescriber-Patient Agreement can be used?*

FDA Response:

We agree that all three NDA products should utilize a single REMS because the risks of buprenorphine are class wide. Additionally, there is an approved generic product for buprenorphine in the treatment of opioid dependence. In accordance with section 505-1(i) of the FDCA, an abbreviated new drug application (ANDA) is required to have a REMS if the applicable listed drug has an approved REMS. Pursuant to section 505-1(i) of the FDCA, a drug that is the subject of an ANDA and the listed drug it references must use a single shared system for elements to assure safe use unless FDA waives that requirement. The ANDA Sponsor for buprenorphine for the treatment of opioid dependence is Roxane Laboratories, Inc. They will also be informed of the requirements under section 505-1(i).

- Question 3: Does the FDA agree that these measures are likely to decrease the risk of pediatric exposure for SUBOXONE and SUBUTEX Sublingual Tablets?*

FDA Response:

We agree that distribution of a Medication Guide is partially intended to address unintended pediatric exposure.

- Question 4:*

- a) *Does FDA agree that the packaging for SUBOXONE Sublingual Film provides meaningful incremental protection against pediatric exposure?*

FDA Response:

No, we do not agree that the packaging for buprenorphine HCl and naloxone HCl sublingual film provides meaningful incremental protection against pediatric exposure. Although the foil pouches fulfill the child resistant effectiveness standards and the foil pouch bears warning statements alerting patients to keep out of reach of children, no data were provided to support that these measures will encourage patients to store buprenorphine HCl and naloxone HCl sublingual film in a manner which prevents accidental pediatric ingestion. Because patients are known to divide tablets, it may be expected that patients will remove films from the package and have partial doses that are neither in the child-resistant pouch nor in a child-resistant medication bottle. Furthermore, because the film cannot be spit out (unlike a tablet) it is possible that a child who obtains access to even one dose might be more adversely affected than a child who obtains access to a single tablet.

- b) *Does FDA agree the serial numbers on the packaging of SUBOXONE Sublingual Film could be of benefit in minimizing diversion and thereby improve safe use of buprenorphine?*

FDA Response:

The Agency will not comment on whether the serial numbers would lead to a decrease in diversion of a drug product, because drug diversion issues are regulated by DEA.

*Question 5: Does FDA agree with the general system design as described?*

FDA Response:

See our response to Question 2.a.

*Question 6:*

- a) *Does FDA agree that using prescriber and patient KAB surveys is sufficient to confirm understanding of the key risks of SUBOXONE/SUBUTEX and that patients need to be appropriately monitored?*

FDA Response:

The use of knowledge, attitude and belief (KAB) surveys is sufficient to confirm patient and prescriber understanding of the key risks of Suboxone/Subutex and the requirements of the program, and could be used as part of the REMS assessments. Additionally, the KAB surveys should include questions that address the compliance with desired behaviors, such as:

- 1) Patient receives medical monitoring and psychosocial support necessary for safe and effective use.
- 2) Patient adheres to conditions of safe use.
- 3) Patient is using the drug appropriately and making adequate progress towards treatment goals.
- 4) Prescriptions are provided in amounts commensurate with patient stability.

Other sources, such as health care utilization databases, should also be used to identify relevant information about frequency of office visits, amount dispensed in prescriptions for new patients, and other indicators of adherence to practices important to safe use. This information could be included as part of REMS assessments.

*b) Does FDA agree that using a patient KAB survey is adequate to confirm dispensing of the Medication Guide to patients?*

FDA Response:

The KAB survey has the potential to confirm adequate dispensing of the Medication Guide to patients, but the survey methods will need to be reviewed.

*Question 7:*

*a) Does the Agency agree that this level of surveillance and monitoring is adequate to ensure safe use of SUBOXONE and SUBUTEX?*

FDA Response:

In general, we agree with the surveillance and monitoring program you have proposed. Your REMS should also include the “street ethnography” program that has been conducted under the Risk Management Program for Subutex and Suboxone sublingual tablets. Additionally, see our response to Question 6.a.

*b) RBP has contracted with (b) (4) to provide surveillance services. Reports from (b) (4) include data from the (b) (4) which indicates the number of single substance pediatric exposures and outcomes (death, major effect, minor effect or no effect). In addition, RBP will evaluate pediatric exposure and outcomes via internal pharmacovigilance. Does the FDA agree that this an adequate approach for evaluating pediatric exposures to SUBOXONE and SUBUTEX?*

FDA Response:

We agree with this approach.

*Question 8 Does the Agency consider this an acceptable approach to confirm appropriate distribution of Medication Guides?*

FDA Response:

You plan to audit Medication Guide distribution from wholesalers to pharmacies to confirm that these materials are available for dispensing as required. A report will be prepared on failures to adhere to distribution requirements and corrective actions taken to address noncompliance. The KAB survey should also assess whether the patients have received the Medication Guide. This is acceptable pending review of the KAB survey and methodology.

*Question 9*      *Based upon the Agency's review of the revised product labeling and the proposed REMS outlined in the Supporting Document does the Agency envision any additional features that will be necessary to include in a REMS to achieve the objectives of the REMS for SUBOXONE and SUBUTEX sublingual tablets and SUBOXONE sublingual film?*

FDA Response:  
See our response to Question 2.a.

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

Sincerely,

*{See appended electronic signature page}*

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

Enclosure: Example Appropriate Use Checklist

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22410	GI-1	RECKITT BENCKISER PHARMACEUTICA LS INC	SUBOXONE (BUPRENORPHINE/NALOXONE ) sublingual film
NDA-20732	GI-1	RECKITT BENCKISER PHARMACEUTICA LS INC	SUBUTEX (BUPRENORPHINE HCL) 2MG/8MG
NDA-20733	GI-1	RECKITT BENCKISER PHARMACEUTICA LS INC	SUBOXONE(BUPRENORPHINE HCL/NALOXONE HCL)

---

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

---

/s/

---

BOB A RAPPAPORT  
03/29/2010



NDA 022410

**ACKNOWLEDGE CLASS 2 RESPONSE**

Reckitt Benckiser Pharmaceuticals Inc.  
10710 Midlothian Turnpike, Suite 430  
Richmond, VA 23235

Attention: John D. Pitts, R.Ph., Ph.D.  
Manager, Regulatory Affairs

Dear Dr. Pitts:

We acknowledge receipt on November 30, 2009, of your November 24, 2009, resubmission to your new drug application for Suboxone (buprenorphine and naloxone) sublingual film.

We consider this a complete, class 2 response to our August 21, 2009, action letter. Therefore, the user fee goal date is May 30, 2010.

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

Sincerely,

*{See appended electronic signature page}*

Sara Stradley, MS  
Chief, Project Management Staff  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22410	ORIG-1	RECKITT BENCKISER PHARMACEUTICA LS INC	SUBOXONE (BUPRENORPHINE/NALOXONE ) sublingual film

---

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

---

/s/

---

SARA E STRADLEY  
12/11/2009



(b) (4)

**MEETING GRANTED**

NDA 022410

Reckitt Benckiser Pharmaceuticals Inc.  
10710 Midlothian Turnpike, Suite 430  
Richmond, VA 23235

Attention: John D. Pitts, R.Ph., Ph.D.  
Manager, Regulatory Affairs

Dear Dr. Pitts:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

(b) (4)

NDA 022410 Suboxone (buprenorphine and naloxone) sublingual film

We also refer to your submissions dated September 14, 2009, requesting a meeting to discuss a Risk Evaluation and Mitigation Strategy (REMS) for these products. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: October 29, 2009  
Time: 12:00 noon – 1:00 PM  
Location: Food and Drug Administration  
Bldg. 22, Room 1313  
10903 New Hampshire Ave.  
Silver Spring, MD 20903

CDER Participants: Bob A. Rappaport, MD, Director, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)  
Rigoberto Roca, MD, Deputy Division Director, DAARP  
Celia Winchell, MD, Clinical Team Leader, DAARP  
Larissa Lapteva, MD, Deputy Director for Safety, DAARP  
Claudia Karwoski, PharmD, Director, Division of Risk Assessment (DRISK), OSE  
Mary Willy, PhD, Senior Drug Risk Management Analyst, DRISK, OSE

Personnel as assigned, Controlled Substance Staff  
Matt Sullivan, MS, Regulatory Project Manager, DAARP

Please have all attendees bring photo identification (e.g. driver's license, passport) and allow 30 minutes to complete security clearance. If there are additional attendees, email that information to me at [matthew.sullivan@fda.hhs.gov](mailto:matthew.sullivan@fda.hhs.gov) so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Matt Sullivan, 301-796-1245 or the Division secretary, 301-796-2280.

If your attendees for the meeting include non-US citizens, please contact the project manager to request a Foreign Visitor Data Request Form. Please submit this completed form to the project manager no later than 12 business days prior to your meeting

Provide the background information for this meeting (one copy to each NDA) to the following address:

Food and Drug Administration/ CDER  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
5901-B Ammendale Rd.  
Beltsville, MD 20705-1266

Provide 20 desk copies to me at the following address:

Matthew Sullivan  
FDA Bldg 22, Room 3160  
10903 New Hampshire Ave  
Silver Spring, MD 20903-0002

If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by October 15, 2009, we may cancel or reschedule the meeting. If possible, submit your meeting package by September 28, 2009.

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

Sincerely,

*{See appended electronic signature page}*

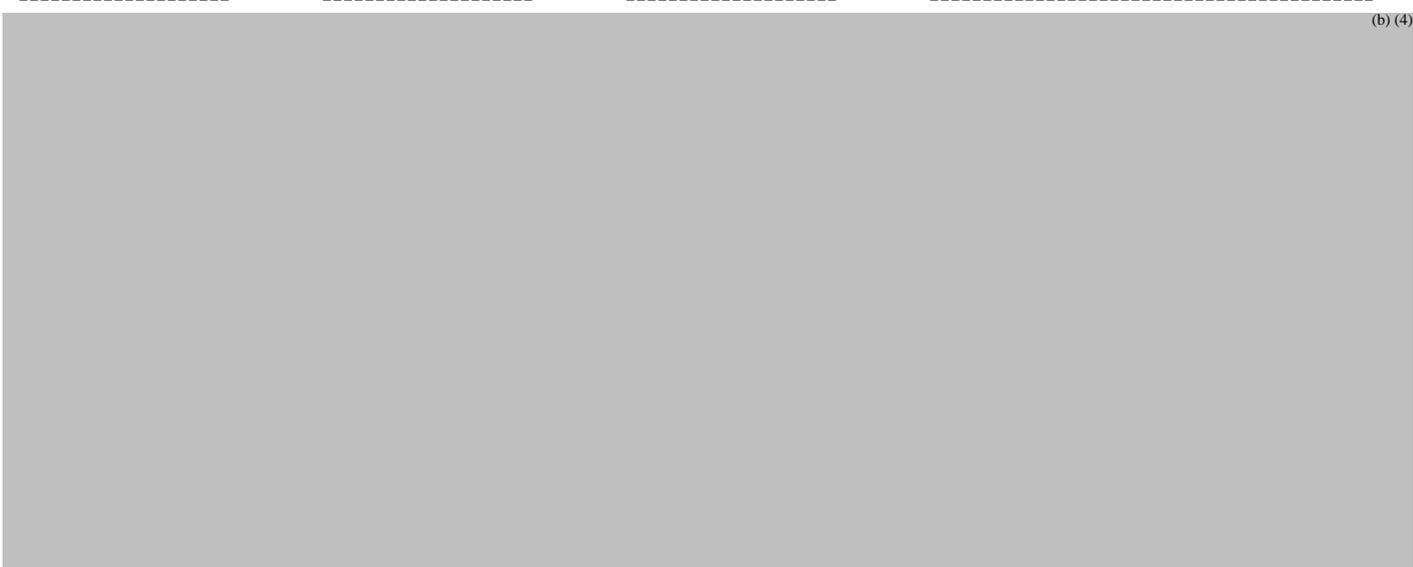
Matthew W. Sullivan  
Regulatory Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name



(b) (4)

NDA-22410

GI-1

RECKITT  
BENCKISER  
PHARMACEUTICA  
LS INC

SUBOXONE  
(BUPRENORPHINE/NALOXONE  
) sublingual film

**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  
09/24/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-410

**FILING COMMUNICATION**

Reckitt Benckiser Pharmaceuticals Inc.  
10710 Midlothian Turnpike, Suite 430  
Richmond, VA 23235

Attention: Deborah C. Moffitt  
Manager, Regulatory Affairs Operations

Dear Ms. Moffitt:

Please refer to your new drug application (NDA) dated October 20, 2008, received October 21, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Suboxone<sup>(b) (4)</sup> (buprenorphine and naloxone).

We also refer to your submissions dated October 22, and December 1, 3, 8, and 11, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is August 21, 2009.

During our filing review of your application, we have identified the following potential review issues:

1. Study RB-US-007-0001, the main study submitted to provide safety information in the intended population appears to have enrolled patients who were not taking the product as directed in the approved labeling for the referenced products, and who may not have used the product as recommended in the proposed labeling. Determining whether the submitted data provides relevant information about the safety and tolerability of the new formulation when used according to the proposed directions—<sup>(b) (4)</sup>

<sup>(b) (4)</sup>—will be a matter for review.

To facilitate this review, you should determine whether information was actually captured on the dosing regimen used by the study participants. Information on medications used prior to study entry indicates that fewer than half of the enrolled participants were taking a single daily dose of Suboxone prior to study entry. While total daily dose was recorded, it cannot be readily discerned what dosing regimen study

participants used and whether any were using a single daily dose with multiple simultaneous strips.

2. There is some lack of clarity concerning the completion of oral exams in Study RB-US-007-001. We note that you have committed to providing a clearer tabulation of the study population in which oral exams were completed; however, the adequacy of this assessment will be a matter for review.
3. Data from the study drug accountability assessment does not appear to have been analyzed or submitted. The submission indicates that this information was “deemed irrelevant given the lack of a pre-established percentage that would represent acceptable compliance.” However, because safety data from patients who were not actually using the product would not be informative, compliance data is important and should be reported. Furthermore, the study drug accountability data, beyond reflecting compliance, may provide some indication of diversion of study drug supplies. It appears that many participants failed to return study drug, and that many reported loss or theft of study drug supplies. Information on study drug accountability also provides some insight into the possibility of diversion of study drug supply. These data should be analyzed and submitted.
4. We remind you of your commitment to promptly address deficiencies in the electronic data definition files. We discussed these issues during a teleconference on December 19, 2008.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must 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/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

#### **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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the combination of buprenorphine and naloxone for this indication has orphan drug designation, you are exempt from this requirement.

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

Sincerely,

*{See appended electronic signature page}*

Bob A. Rappaport, M.D.

Director

Division of Anesthesia, Analgesia  
and Rheumatology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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

/s/

-----  
Bob Rappaport  
12/30/2008 09:28:56 AM



NDA 22-410

**NDA ACKNOWLEDGMENT**

Reckitt Benckiser Pharmaceuticals Inc.  
10710 Midlothian Turnpike, Suite 430  
Richmond, VA 23235

Attention: Deborah C. Moffitt  
Manager, Regulatory Affairs Operations

Dear Ms. Moffitt:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Suboxone (b) (4)® (buprenorphine and naloxone)

Date of Application: October 20, 2008

Date of Receipt: October 21, 2008

Our Reference Number: NDA 22-410

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 December 20, 2008, 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/oc/datacouncil/spl.html>. 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.

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  
Rheumatology 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/cder/ddms/binders.htm>.

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

Sincerely,

*{See appended electronic signature page}*

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

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

/s/

-----  
Matthew Sullivan  
11/12/2008 11:35:07 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND (b) (4)  
IND 75,811

Reckitt Benckiser Pharmaceuticals Inc.  
10710 Midlothian Turnpike, Suite 430  
Richmond, VA 23235

Attention: Deborah C. Moffitt  
Manager, Regulatory Affairs Operations

Dear Ms. Moffitt:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) buprenorphine/naloxone sublingual film strips.

We also refer to the meeting between representatives of your firm and the FDA on June 24, 2008. The purpose of the meeting was to discuss your plans for an upcoming NDA submission.

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

Enclosure - Meeting Minutes

### SPONSOR MEETING MINUTES

**MEETING DATE:** June 24, 2008

**LOCATION:** FDA White Oak Campus  
Silver Spring, MD

**APPLICATION:** IND (b) (4)  
IND 75,811

**STATUS OF APPLICATIONS:** Active

**PRODUCT:** (b) (4) buprenorphine/naloxone  
sublingual film strips

**INDICATION:** Treatment of opioid dependence

**SPONSOR:** Reckitt Benckiser Pharmaceuticals, Inc

**TYPE OF MEETING:** Type B, Pre-NDA

**MEETING CHAIR:** Celia Winchell, M.D., Division of Anesthesia, Analgesia  
and Rheumatology Products (DAARP)

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

FDA Attendees	Title
Curtis Rosebraugh, M.D.	Director, ODE II
Bob Rappaport, M.D.	Director, DAARP
Rigoberto Roca, M.D.	Deputy Director, DAARP
Celia Winchell, M.D.	Medical Team Leader, DAARP
Ricardo Dent, M.D.	Medical Officer, DAARP
Srikanth Nallani, Ph.D.	Clinical Pharmacology Reviewer, DAARP
Dionne Price, Ph.D.	Team Leader, Statistics, DAARP
Kate Meaker, Ph.D.	Statistics Reviewer, DAARP
Ali Al Hakim, Ph.D.	Chief, CMC Branch II, Office of New Drug Quality Assessment (ONDQA)
Danae Christodoulou, Ph.D.	Pharmaceutical Assessment Lead, ONDQA
Dan Mellon, Ph.D.	Supervisor, Pharmacology/Toxicology, DAARP
BeLinda Hayes, Ph.D.	Pharmacology/Toxicology Reviewer, DAARP
Matthew Sullivan, M.S.	Regulatory Project Manager, DAARP
Margarita Tossa, M.S.	Regulatory Project Manager, DAARP
Bindi Nikhar, M.D.	Medical Team Leader, DAARP
Michelle Safarik, PA-C	Risk Management Analyst (detail), Office of Surveillance and Epidemiology

<b>Reckitt Benckiser Attendees</b>	<b>Title</b>
Rolley "Ed" Johnson, Pharm.D.	Vice-President, Clinical, Scientific and Regulatory Affairs
Paul J. Fudala, Ph.D., R.Ph.	Director, Clinical and Scientific Affairs
John D. Pitts, R.Ph., Ph.D.	Manager, Regulatory Affairs
Tim Baxter, M.D.	Medical Director
Neil Hyde	Buprenorphine Development Manager
John Caruso, J.D.	Legal Counsel
(b) (4)	Consultant (Regulatory)
(b) (4)	Consultant (Pharmacokinetics)
Steve Schwartz	Clinical Project Manager
Deborah C. Moffitt	Manager Regulatory Affairs

**GENERAL DISCUSSION:** Following introductions, the meeting focused on the responses to the questions included in the May 20, 2008, meeting package for IND (b) (4) and IND 75,811. The responses to the questions were provided to the Sponsor on June 23, 2008. The questions are presented below in *italicized* text in the order in which they were addressed at the meeting. The Division's responses, prepared prior to the meeting and presented as handout, are **bolded**. Discussion is presented in normal text.

The Sponsor also noted that they intend to pursue only the Suboxone 2-mg and 8-mg formulations at this point, and only for the maintenance of patients already stabilized on buprenorphine (b) (4)

Question 1. *Reckitt Benckiser envisions the name development for this formulation proceeding in one of two ways:*

- *Developing (b) (4) in order to avoid potential confusion in the market with the current marketed product.*
- *An extension of the Suboxone name (b) (4)*

*Does the Division agree that either of these two potential approaches is acceptable?*

**FDA RESPONSE:**

**The potential for medication errors exist with either proposal.** (b) (4)

(b) (4)

**However, we also recognize that marketing the proposed product under an extension of the Suboxone name (b) (4) also has potential failure modes that may result in medication errors.**

**Thus, we recommend that you conduct a failure mode and effects analysis (FMEA) to evaluate whether (b) (4) utilization of an extension of the Suboxone name would be less error-prone. This analysis will identify the failure modes likely to occur throughout the various phases of the medication use process (i.e., procurement, prescribing, dispensing, administration and monitoring) in real use settings and the effects associated with the failure modes. This analysis will help you to determine which proposal provides the least risk of medication errors. You should submit your proposed name (i.e., (b) (4) the name Suboxone (b) (4)) and the data from the FMEA which support your decision.**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

**Question 2.** *There will be at least one complete print of the sword indicia and the dosage strength indicator (e.g. For (b) (4) For buprenorphine/naloxone - N2, N8, (b) (4) on each strip.* (b) (4)

*We believe that this meets the requirement (21 CFR 206.10) for an identification mark on each dosage unit, does the Division agree?*

**FDA RESPONSE:**

**Yes; ensure that there is a complete identification print on each dosage unit.**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

**Question 3.** *Reckitt Benckiser Pharmaceuticals Inc. currently plans for (b) (4)*

*Reckitt Benckiser will include draft product labeling and annotated labeling for the film strip products that is based upon the content of the approved labeling for Subutex and Suboxone sublingual tablets, but the film strip labeling will be formatted according to current labeling format requirements outlined in the 2006 draft FDA guidance entitled, "Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements."*

*Is this approach to creation of the film strip labeling acceptable to the Division?*

**FDA RESPONSE:**

**This approach appears acceptable.**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

***eCTD Clinical Summary Questions***

***Question 4a.*** *As discussed in the July 25, 2007 pre-IND meeting between DAARP and Reckitt Benckiser, Reckitt Benckiser plans for the film strip product label to contain identical claims as the currently approved sublingual tablet products. Because of this, additional efficacy studies will not be necessary to support the proposed film strip labeling, barring unanticipated differences between the film strip product and the tablet products.*

*To summarize efficacy information (b) (4) Reckitt Benckiser intends to include a textual summary of effectiveness information regarding (b) (4) buprenorphine/naloxone that has become available during the period starting with Subutex and Suboxone sublingual tablet approval on October 8, 2002 and ending April 30, 2008. The information for this summary will be drawn from the following sources:*

- Information about treatment induction using buprenorphine/naloxone film strips from Study RB-US-07-0002 entitled, "Induction of Opioid-Dependent Individuals onto Buprenorphine and Buprenorphine/Naloxone."*
- Published literature that has become available since Subutex and Suboxone sublingual tablet approval.*

*The efficacy summary will be incorporated into the NDA as part of the eCTD Section 2.7.3, but will not appear in the form of an ISE.*

*Does the Division agree with this plan?*

**FDA RESPONSE:**

- 1. A comprehensive literature search of efficacy studies involving buprenorphine will be neither necessary nor useful. However, if there are specific claims you envision adding to labeling based on studies in literature, note that these studies must meet the requirements for substantial evidence of efficacy. Efficacy claims that differ from the approved labeling for Subutex/Suboxone must be supported by a minimum of two adequate and well-controlled studies. Published literature generally requires right of reference with the supporting safety data including case report forms.**

**Note that, in previous applications or discussions, Reckitt Benckiser has frequently submitted publications or manuscripts involving studies that are, on face, not adequate and well-controlled, are patently unresponsive of the claim they are said to support, or do not involve the dose/population/use of interest. It is our expectation that any published articles, manuscripts, investigator-initiated studies, or other non-Reckitt Benckiser-conducted research will be carefully scrutinized by Reckitt before it is submitted in support of any claim for this application.**

**If you intend to rely on published literature to support labeling claims or other information deemed necessary for approval of your NDA applications that you do not own or have right of reference to, your application may no longer be considered a 505(b)(1) application. A 505(b)(2) application would be an acceptable approach. However, the Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.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>)).**

- 2. The Division informed Reckitt Benckiser at prior interactions that higher plasma naloxone levels from the film strip combination product as compared to Suboxone would generate concerns regarding the successful induction of patients onto treatment using the film strip product, because of the possibility that patients might experience naloxone-induced withdrawal early in treatment. Because this has proven to be the case, additional efficacy data will be needed to support this application.**
- 3. Study RB US-07-0002 is offered as additional efficacy data on the use of the film strip product in early treatment. However, preliminary results from this study suggest that symptoms consistent with precipitated withdrawal have occurred in two of eight study subjects. This further raises concerns about the appropriateness**

**of the new formulation for initiation of treatment in patients dependent on full agonists. It is not known whether the affected subjects were treated with “mono” or “combo” strips, but it is possible that even the enhanced bioavailability of buprenorphine could present a problem early in treatment, as no data on induction doses higher than 8 mg (tablet) are included in the referenced NDA. Furthermore, Study US-07-0002 is being conducted in an inpatient setting, which renders it unsuitable for determining whether patients are more or less likely to drop out of treatment prior to completing induction/stabilization when treated with the new formulation than with the old formulation. It will be necessary to provide data from a study in outpatients, showing that the differences between formulations do not translate to differences in the proportion of patients able to become successfully stabilized (e.g. induction through the first several weeks of treatment) on buprenorphine.**

Discussion:

The Sponsor sought to address the Divisions concerns with Study US-07-0002 by noting that the inpatient population studied had a much higher and more homogeneous level of dependence than would an outpatient population. Additionally, they noted that studying an outpatient population has inherent challenges, such as loss to followup. The Division acknowledged this point, but replied that outpatients are the population in whom the drug would eventually be prescribed; therefore studies would most appropriately be performed in them. Randomization at the beginning of treatment could ensure that the groups were similar at baseline with regard to inclusion of patients at various levels of dependence. Furthermore, the Division noted that symptoms of opiate withdrawal observed in the study were a concern to the extent that they might result in increased dropouts, and therefore translate to lack of efficacy in treatment of dependence. The withdrawal symptoms alone would not necessarily be cause for alarm and would not need to be directly measured.

The Sponsor also sought the Division’s opinion on the utility of continuing Study US-07-0002 as an inpatient study. The Division replied that, if the Sponsor felt that they could gain some useful information from the study, they should continue. (b) (4)

Question 4b.

(b) (4)

*A copy of the summary will be provided in each anticipated eCTD. Reckitt Benckiser also believes that the contents and volume of this (b) (4) ISS will be consistent and appropriate for insertion into the eCTD as Module 2 in accordance with 21 CFR 314.50 and the CTD M4E guidance.*

An outline of the (b) (4) ISS is provided in section 10 of this backgrounder entitled, "Proposed Safety Summary Outline for (b) (4) Buprenorphine/Naloxone Film (b) (4)"

- Does the Division agree with this proposal (b) (4) ISS outlined under the heading, "Proposed Safety Summary Outline for (b) (4) Buprenorphine/Naloxone Film (b) (4)"?
- Does the Division agree with the proposed outline for the summary and study groupings?
- Does the Division have other comments or feedback about Reckitt Benckiser's plan for developing the modified ISS?

#### **FDA RESPONSE:**

1. **The Division agrees with your plans to (b) (4) ISS. This ISS should assign unique patient IDs to all patients by treatment assignment. The safety subgroups identified appear acceptable. The Serious Adverse Events and Common Adverse Events should appear in three separate groups, that is 1) (b) (4) buprenorphine/naloxone, 2) (b) (4) and 3) buprenorphine/naloxone alone. There should be a discussion of the differences and similarities of these groups.**
2. **COSTART and MedDRA terminology cannot be used interchangeably, the dictionaries are not similar. In your ISS discussion, you should map the MedDRA terms to COSTART terms, compare the safety findings from the new formulation to the established safety profile for Subutex/Suboxone, and discuss any inconsistencies discovered.**

#### **Discussion:**

There was no additional discussion beyond the information provided in the response.

#### ***CMC Data Questions***

Question 5. *The buprenorphine hydrochloride API used in the development batches to date and intended for the marketed product is manufactured by Reckitt Benckiser Healthcare (UK) Ltd, the current manufacturer of the API used in Subutex and Suboxone sublingual tablets and also in Buprenex injection. We assume that the current DMF and existing approvals adequately support the quality of the API and only abbreviated information and a letter of access to the DMF will need to be presented in Module 3.2.S.*

*Does the Division agree with this assumption?*

**FDA RESPONSE:**

**Yes, we agree. Provide the drug substance specifications and manufacturer qualifying criteria in the NDA. In addition, include the drug substance(s) manufacturing sites in the NDA, with complete addresses, cGMP status and a statement that they are ready for inspections. For any foreign manufacturing sites, include a name contact with telephone number at the site.**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

Question 6. *The naloxone hydrochloride dihydrate used in the development and pivotal stability batches to date has been manufactured by (b) (4). However, we aim to seek approval for both (b) (4) and (b) (4) manufactured naloxone hydrochloride dihydrate.*

*(b) (4) naloxone hydrochloride dihydrate has been used since the initiation of the development program. (b) (4) had a ready supply of batches complying with the stringent limits set for the (b) (4) synthesis impurity that has the associated structural alert. At the time of initiating the development, the supply of (b) (4) API meeting this specification was very limited; however, (b) (4) is now routinely manufacturing to this quality.*

*(b) (4) naloxone hydrochloride dihydrate is currently used in the Suboxone sublingual tablets approved by the Division for the US market, and (b) (4) has an updated DMF that Reckitt Benckiser intends to reference.*

*(b) (4) has a DMF filed for their naloxone hydrochloride dihydrate and we additionally propose to cross reference this.*

*As part of the NDA we will demonstrate the equivalence of the naloxone quality from the two suppliers (both comply with USP and Ph.Eur. and the house limit on (b) (4) and provide data on at least one batch of the highest and lowest buprenorphine/naloxone film strip dosage strengths using (b) (4) naloxone hydrochloride dihydrate. These batches will form part of the stability program, but it is anticipated that limited stability data will be available at the time of submission.*

*Is this approach acceptable?*

*The Module 3.2.S for naloxone will be largely based on cross reference to the two supplier DMFs, we assume this is adequate and appropriate.*

**FDA RESPONSE:**

**Your approach to demonstrate comparability of drug product manufactured from (b) (4) naloxone hydrochloride dihydrate, is reasonable. Provide at least three months of accelerated and long term stability data including dissolution profiles.**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

Question 7. *Data will be presented in the NDA for the pivotal batches manufactured at one-third & full scale size using the industrial equipment intended for routine commercial use. Data for three batches, of each strength, with one of these at full commercial scale, will be presented. A process validation plan will be included in the NDA because the manufacturing process validation will be conducted using batches intended for commercial launch.*

*Please confirm that this meets with the Division's expectations.*

**FDA RESPONSE:**

**Yes, your proposal is acceptable.**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

Question 8.



(b) (4) *The process validation plan will comprise three consecutive batches of the low strength film and three consecutive batches of the high strength film, which will be manufactured to demonstrate reproducibility of the bulk film manufacturing process. All six batches will then be cut and the film strips will be machine pouched. The three batches of the low strength film will all be cut to 0.875 x 0.5" and pouched. The high strength bulk film batches will be cut to one of the three different sizes (b) (4) 0.875" x 0.5") for pouching – which represent the three higher strength products.*

*Does the Division view this manufacturing/packaging process validation plan as satisfactory?*

**FDA RESPONSE:**

**Yes, your approach to validation is reasonable.**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

Question 9. *Following experimental work performed during batch manufacture of buprenorphine 2mg and 8mg films, and buprenorphine 2mg/naloxone 0.5mg films at the pilot scale,* (b) (4)

(b) (4)

*Justification for* (b) (4)

*will be further provided in the NDA by reference to the weight vs. potency relationship of pilot and full scale batches. Based on previous discussions with the Division we believe the weight adjustment is appropriate and can be justified.*

*Does the Division agree with this approach for the determination of the nominal film weight?*

**FDA RESPONSE:**

**This approach is reasonable. Provide the justification and data to support the weight-versus-potency relationship. Include adequate in-process content uniformity controls during film manufacture and include all documentation in your Pharmaceutical Development Report (PDR).**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

Question 10. (b) (4)

(b) (4)

*We consider that the inclusion of batch M07ET101 in the NDA is valid and the batch is fully representative of the proposed marketed product.*

(b) (4)

Does the Division prefer this simplification to the (b) (4) compared to the (b) (4) discussed at the previous meeting?

**FDA RESPONSE:**

Should you opt to (b) (4) for your commercial batches (b) (4) provide the rationale and supporting data in the NDA. Demonstrate that (b) (4) does not impact potency. Based on adequate justification of your rationale, you may include the proposed stability batch in your registration batches.

**Discussion:**

There was no additional discussion beyond the information provided in the response.

*Question 11. Three batches of each of the proposed dosage strengths have been manufactured and are being examined in stability studies under ICH storage conditions. All batches are greater than (b) (4) of the proposed production scale and one batch, of each dosage strength, has been produced at full scale.*

*This is as previously agreed with the Division; does this approach remain acceptable?*

**FDA RESPONSE:**

**Yes, the pivotal batch scale(s) remain acceptable.**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

*Question 12. We propose to submit the NDA (b) (4). At each time point, samples from the 25 °C/60%RH (long-term), 30 °C/65% RH (intermediate) and 40 °C/75% RH (accelerated) storage conditions will be tested. We intend to (b) (4)*

*(b) (4) as previously recommended by the Division and used for the analysis of stability data supporting the (b) (4) buprenorphine:naloxone NDAs.*

*Is this approach acceptable to the Division?*

**FDA RESPONSE:**

**Note that**

(b) (4)

may not result in expiration dating sufficient for product marketing. As per ICH Q1A, we strongly recommend that you provide the maximum real-time stability data in the NDA. Expiration dating will be estimated as per ICH Q1E, based on real-time pivotal and supporting data and statistical analysis, as applicable.

Discussion:

There was no additional discussion beyond the information provided in the response.

*Question 13. Proposed product specifications will form part of the meeting package. We would like the Division to confirm that the specification parameters specified are adequate and appropriate. We accept that the available data provided in the meetings package may not be adequate for the Division to comment on the suitability of the proposed limits, but any advice in this respect would be much appreciated.*

**FDA RESPONSE:**

**The proposed specifications are sufficient. Provide adequate justification for your established limits in the NDA.**

Discussion:

There was no additional discussion beyond the information provided in the response.

*Question 14. The specification for Suboxone sublingual tablets established lower shelf life limits for the potency of buprenorphine and naloxone in unit doses. Are the same limits, if adequately justified, acceptable for the film strip products?*

*We propose to set release limits for potency on the basis of the process capability demonstrated for pilot and full scale batches.*

*Is this acceptable to the Division?*

**FDA RESPONSE:**

**This approach is reasonable. Provide justification for the different assay limits on release and stability and for why there will be no impact on product quality and performance.**

Discussion:

There was no additional discussion beyond the information provided in the response.

**Question 15.** *The degradation products of buprenorphine and naloxone currently appear to be those observed in the corresponding Suboxone sublingual tablet formulations. We propose to set specification limits for each observed individual impurity based on ICH Q3B. Specifications will be based on:*

- *Observed or predicted, “end of shelf life”, levels*
- *The ICH Q3B threshold for qualification (for those degradants not previously qualified).*
- *The previously qualified levels based on toxicological qualification performed in support of Suboxone sublingual tablets and forming part of the approved tablet NDA;*
- *The ICH Q3B identification threshold for “unspecified degradants”.*

*Does the Division agree that this approach is acceptable?*

**FDA RESPONSE:**

**This approach is reasonable. The Division notes that a specification of not more than (NMT) (b) (4) for (b) (4) was required due to positive findings in an in vitro cytogenicity assay in human lymphocytes. Although this specification will be acceptable for the current NDA submission, you should be aware that the Agency is currently requiring positive genotoxic impurities to be limited to NMT 1.5 mcg/day. For the Suboxone film strip product, a maximum daily dose of 6-mg naloxone would provide (b) (4) mcg/day [see correction below] exposure to this genotoxic impurity when limited to NMT (b) (4). Therefore, you should aggressively strive to reduce the levels of this impurity to NMT 1.5 mcg/day prior to the NDA submission or provide an outline of the step you will take to reduce the levels of this impurity in a timely manner post-approval.**

**Discussion:**

The Sponsor brought to the Division’s attention that 6 mg of naloxone would expose a patient to (b) (4) mcg/day of (b) (4), rather than (b) (4) mcg/day as stated in the response. The Division concurred, and noted that as long as the impurity levels were below 1.5 mcg/day the specification would be appropriate.

**Question 16.** *The CMC section will follow the ICH Guidance for Industry M4Q (The CTD – Quality) for this film strip product.*

*Does the Division have any expectations for further data outside the guideline requirements?*

**FDA RESPONSE:**

**We have no additional expectations. Following ICH M4Q for the CMC section is acceptable.**

Discussion:

There was no additional discussion beyond the information provided in the response.

***Clinical Studies Questions***

Question 17. *With regards to studies 20-A79-AU and 20-A90-AU, we have indicated in the Proposed NDA Table of Contents for eCTD Module 1 and also in the draft executive summaries (Attachment 1) that the studies were conducted as 3-treatment, 2-period, 2-way crossover designs as opposed to 3-treatment, 3-period, 3-way crossover designs secondary to the lack of availability of study drug for one of the study periods. These 2-way crossover designs still permitted valid comparisons of all three treatments. Further, analysis of the data indicated that the rate and extent of absorption was comparable to the other pharmacokinetic studies that have been conducted and analyzed.*

*Therefore, we believe that the designs meet the Division's request to evaluate bioequivalence at the dosage levels assessed.*

*Does the Division concur with this assessment?*

**FDA RESPONSE:**

**Based on the overall evidence, it is clear that the film strip administered by sublingual or buccal route and the approved sublingual tablet formulation are not bioequivalent. Additional studies are not necessary to address bioequivalence of film strip to the approved sublingual tablets.** (b) (4)

Discussion:

There was no additional discussion beyond the information provided in the response.

Question 18a. *The "Division Director's Review of NDA and Basis for Action" by Cynthia McCormick, Medical Officer (dated October 8, 2002) is included as Attachment 6. The background (page 2) of this document confirms that development of buprenorphine in high doses as a treatment for opioid dependence began with a sublingual ethanolic solution and that most of the clinical research was conducted using this formulation. Further, it was stated that alcohol increases the bioavailability of buprenorphine and that the tablet was less bioavailable compared to the sublingual solution.*

*Study CR88/130 (page 3 of Attachment 6) included a sublingually administered 8 mg buprenorphine dose (ethanolic solution) which was approximately comparable in buprenorphine exposure to that from 12 mg Suboxone tablets*

*given sublingually. This would equate to about a 50% increase in bioavailability of the solution compared to Suboxone tablets. On page 4 of Attachment 6 (under pharmacokinetics), it was concluded that the relative bioavailability of buprenorphine as Suboxone, compared to the solution, was relatively constant across doses of 4 mg to 16 mg Suboxone. The relative bioavailabilities for the tablet doses of 4 mg, 8 mg, and 16 mg were 0.72, 0.66, and 0.72, respectively. The bracketing of doses allowed for the clinical studies of the sublingual solution to be linked to the current NDAs (20-732 and 20-733) for Suboxone and Subutex tablets. It may be noted that these relative bioavailability values (0.72, 0.66, and 0.72) are for the tablet divided by solution. The reciprocal of these numbers (1.39, 1.51, and 1.39) provide the bioavailability of the solution relative to tablets. This approach (using tablet data in the denominator) is the more appropriate comparison when evaluating film strips compared to tablets.*

*Finally, on page 5 of Attachment 6 (clinical safety of buprenorphine) the agency stated the following: "In the context of the review of NDA 20-732 for SUBUTEX, the division previously concluded that there was evidence to support the safety of buprenorphine sublingual solution at doses up to 32 mg/day. Further examination of the buprenorphine/naloxone database as described by the Medical Officer, who teased apart the contributions of the various components of this development plan in an earlier review, confirmed this finding."*

*The labeling indicates that both Suboxone and Subutex have recommended doses (expressed as buprenorphine) of 12 to 16 mg/day; doses of 4 to 24 mg may be necessary for maintenance. The Agency previously concluded that ethanolic solution doses of buprenorphine up to 32 mg/day were safe. Since the mean ethanolic solution bioavailability was found to be 139% or more than that of the tablets, a 24 mg film strip dose with higher bioavailability than the corresponding sublingual tablet should not present any safety concerns if justified against that of the ethanolic solution.*

*Of the four buprenorphine/naloxone bioequivalency studies that have been completed/analyzed to date (20-A90-AU, 20-250-SA, 20-272-SA, and 20-273-SA), one study (20-272-SA) established that the film and tablet treatments (2 x 2/0.5 mg) were bioequivalent when drug was administered sublingually. Both  $C_{max}$  and  $AUC_{inf}$  met the 80 to 125% confidence interval criteria. Study 20-250-SA, which dosed one dosage unit (i.e., one film strip or one tablet) of the same products administered in 20-272-SA, established that sublingual buprenorphine/naloxone film strip formulations were bioequivalent to sublingual Suboxone tablets with respect to buprenorphine total exposure ( $AUC_{inf}$ ). The buprenorphine point estimate and confidence interval for  $C_{max}$  fell outside the normal bioequivalence acceptance criteria. The 8/2 mg and 16/4 mg sublingual buprenorphine/naloxone film strip formulations (studies 20-273-SA and 20-A90-AU, respectively) have 28 to 34% higher buprenorphine  $C_{max}$ , and 20 to 33 % higher buprenorphine  $AUC_{inf}$  values compared to Suboxone tablets.*

*Overall based on the mean outcomes from the four studies completed to date, the point estimates for sublingual buprenorphine/naloxone film strips compared to Suboxone sublingual tablets are 121.79% based on  $C_{max}$  and 117.67% based on  $AUC_{inf}$ . Based on plasma levels alone, the film strips should not be less efficacious than the corresponding Suboxone tablets.*

*Although the 8/2 mg 16/4 mg film formulations are not technically bioequivalent to the Suboxone tablet formulations (when administered sublingually), these small buprenorphine exposure differences are not clinically relevant.*

*Does the Division agree?*

**FDA RESPONSE:**

**Differences in bioavailability appear to be clinically relevant, especially with respect to potential treatment retention during initiation of therapy with Suboxone film strips. Although, we agree that the referenced application contains data supporting the safety of maintenance doses of buprenorphine higher than the approved doses in Suboxone and Subutex, there does not appear to be data in the referenced NDAs supporting the use of doses higher than 8-mg buprenorphine (tablet) as initial treatment.**

**For maintenance treatment, determining whether the higher exposure from the new formulation does or does not fall in the range already supported will be a matter for review.**

**Discussion:**

The Sponsor sought guidance as to how they could reanalyze or reformat the data. They noted that they believed that the Division performed a reanalysis of the PK modeling data for the original Subutex and Suboxone NDAs, and they wanted to provide similar information with the film strip NDAs to assist the Division. The Division replied that, to the best of their recollection, no reanalysis was performed.

The Sponsor noted that the 8-mg dose was just outside of the 80 – 125 % acceptable range for bioequivalence, and inquired if they could provide some supportive data to reassure the Division that the lack of bioequivalence was not clinically meaningful. The Division replied that they would need to see the data, and would only be able to make a decision on the adequacy of the data during the review cycle.

The Division also informed the Sponsor that if only 2-mg and 8-mg doses would be available, additional bioequivalence data would be needed (e.g., assess whether 2-mg + 2-mg + 8-mg is equivalent to 12-mg of Suboxone). The Sponsor acknowledged this request.

Question 18b. *For the three buprenorphine film strip bioequivalency studies that have been completed/analyzed to date (20-A78-AU, 20-A79-AU, and 20-277-SA), the norbuprenorphine film  $C_{max}$  and  $AUC_{inf}$  values were generally bioequivalent to the sublingual Subutex tablets. However, the sublingual buprenorphine  $C_{max}$  and  $AUC_{inf}$  ratios (film:tablet) range from 1.37 to 1.80, and 1.23 to 1.53, respectively. Given that the mean bioavailability (relative to tablets) of the buprenorphine ethanolic solution doses reported in the Subutex and Suboxone NDAs (20-733 and 20-732) were 139% to 151% from two separate studies, it is our belief that the bioavailability of the film strip formulations does not differ significantly from that of the ethanolic solutions and safety should not be compromised.*

*It is important to point out that patients will be individually titrated with the film product as they are with the existing sublingual tablets; the key end-point to dose titration is suppression of withdrawal effects over the interdose period, usually 24 hours. Importantly, the dose delivered by the film strip is not lower than that provided by the tablet, and if patients are switched from Subutex or Suboxone tablets to the buprenorphine film strip or buprenorphine/naloxone film strip, they should not be destabilized by emergent or unexpected withdrawal effects (i.e., the efficacy of the proposed film strip will at least match the efficacy of the sublingual tablet).*

*Therefore, assuming that the local irritation safety study (RB-US-07-0001) provides no different interpretation for safety, we believe that the bioavailability data generated, although not necessarily meeting bioequivalency criteria, provides the required comparison of the proposed (b) (4) buprenorphine/naloxone film strip dosage forms and existing Subutex and Suboxone tablets, to support the NDA.*

*Does the Division agree?*

**FDA RESPONSE:**

**Note that the local irritation study does not clearly indicate the qualifications of the personnel assessing the oral mucosa. These assessments should be made by dentists or, at a minimum, dental hygienists, as subtle changes in oral mucosa may not be detected by assessors without this level of experience.**

**As mentioned in response to Question 18a above, the failure to establish bioequivalence may well be clinically relevant.**

**Although Protocol RB-US-07-0001 has a number of design limitations (short duration of exposure, lack of placebo control, use in patients already exposed to Suboxone), we believe it should be capable of meeting its objective of detecting signals of oral irritation from the film strip formulation of Suboxone at either the buccal or sublingual site, assuming adequately-trained personnel are performing the oral evaluations (e.g., licensed dentist). The need for additional information about oral safety may be identified upon review of the application.**

Discussion:

The Division reaffirmed their concern that subtle changes to the oral mucosa were being assessed by less than ideal evaluators (i.e., Medical Doctor with a few hours of specific training). The Sponsor acknowledged this concern, but since the study is complete, they stated that there was little they could do. Dr Rappaport also noted that this issue alone would not likely hold up approval of an NDA; however, the Division might require further assessment as a Post-Marketing study.

*Question 18c. Of the four buprenorphine/naloxone bioequivalency studies that have been completed/analyzed to date (20-A90-AU, 20-250-SA, 20-272-SA, and 20-273-SA), two studies (20-250-SA and 20-272-SA) established that buprenorphine/naloxone film strip formulations, when administered sublingually, were bioequivalent to Suboxone tablets with respect to naloxone exposure. The other two studies show higher naloxone  $C_{max}$  and  $AUC_{inf}$  ratios which range from 1.41 to 1.44, and 1.21 to 1.38, respectively. Naloxone exposure in all studies is exceedingly low considering that systemic concentrations are in the picogram/mL range. Although formal dose proportionality studies are being conducted, dose proportionality data obtained from both pilot and bioequivalency studies completed/analyzed thus far (Figures 55, 58, 65, and 68) indicate that naloxone  $C_{max}$  and  $AUC_{inf}$  are dose proportional from 0.5 to 4 mg with regards to both sublingual and buccal administration.*

*Breakthrough naloxone effects would not be expected from sublingual or buccal film strips based on the small increase in  $C_{max}$  levels observed compared to Suboxone tablets. Importantly, because the film strips also give slightly increased buprenorphine  $C_{max}$  plasma levels, the average  $C_{max}$  ratios is well maintained compared to Suboxone tablets. (Mean [N=4] point estimate comparison of naloxone  $C_{max}$  / buprenorphine  $C_{max}$  is 99.8% by the sublingual route and 103.4% by the buccal route). The ratio of naloxone to the competing buprenorphine is equally important to the absolute exposure in predicting its antagonist effect.*

*Given these very low naloxone plasma concentrations, the observed dose proportionality, and the well maintained buprenorphine to naloxone  $C_{max}$  ratios, the observed increase in bioavailability is not clinically relevant.*

*Does the Division agree?*

**FDA RESPONSE:**

**As discussed in the PIND meeting, a high side failure of naloxone raises concerns about the efficacy of this new product. We do not agree that low plasma levels of naloxone are of no consequence, or that the enhanced absorption of buprenorphine mitigates concerns about the enhanced absorption of naloxone. Studies addressing the ratio of naloxone to buprenorphine focused largely on the necessary ratio for ensuring that aversive effects would occur when the drug was administered parenterally. Other studies (including the study designated *Study CR95/002* in the referenced NDA) have shown that withdrawal**

occurred with patients treated with 8-mg buprenorphine/2-mg naloxone combination (Suboxone) but not in patients treated with 4-mg buprenorphine/1-mg naloxone combination, which both include the same ratio of drug. Note also that buprenorphine itself has the potential to precipitate withdrawal, so the co-occurrence of higher doses of both naloxone and buprenorphine may be particularly problematic.

Therefore, as noted above, the differences between the film strip products and the tablet products raise concerns about the successful induction and stabilization of patients onto treatment with buprenorphine.

Discussion:

The Sponsor indicated that they planned to address this concern by proposing (b) (4)

The Division noted that this was a new proposal that had not been evaluated prior to the meeting and that there may or may not be sufficient information available to support a product labeled in this manner.

*Question 18d. We are currently conducting a study to assess opioid withdrawal signs and symptoms associated with induction onto buprenorphine and buprenorphine/naloxone film strips in persons currently opioid dependent (RB-US-07-0002).* (b) (4)

*However, if the Division agrees that the slightly elevated naloxone bioavailability observed is not clinically relevant, and the remaining buprenorphine/naloxone bioequivalence study to be analyzed (20-B20-AU) does not indicate naloxone exposure out of trend with the results from the other completed studies, can the results from study RB-US-07-0002 be submitted to the Division* (b) (4)

**FDA RESPONSE:**

The Division notes that your preliminary results indicate that two of eight completed subjects exposed to the new formulation experienced symptoms consistent with precipitated withdrawal in two study subjects. These results add to, rather than assuage, the concern about differences between the two formulations. For details, see above.

Also, prior to NDA submission, you must completely assess the safety and efficacy of your new product formulation.

Discussion:

There was no additional discussion beyond the information provided in the response.

*Question 19a. Of the four buprenorphine/naloxone bioequivalency studies that have been completed/analyzed to date (20-A90-AU, 20-250-SA, 20-272-SA, and 20-273-SA), the buccally administered film strip formulation was bioequivalent to sublingually administered tablets with respect to buprenorphine  $AUC_{inf}$  in studies 20-250-SA and 20-A90-AU. The buprenorphine  $AUC_{inf}$  ratios ranged from 1.13 to 1.24 across all four studies; the buprenorphine  $C_{max}$  ratios ranged from 1.21 to 1.34. Naloxone  $C_{max}$  met bioequivalence criteria in study 20-250-SA. Across these four studies, naloxone  $C_{max}$  and  $AUC_{inf}$  ratios (for buccally administered film products compared to sublingually administered Suboxone tablets) ranged from 1.11 to 1.54 and 1.15 to 1.37, respectively. These ranges are similar to those obtained after sublingual administration of the film product.*

(b) (4)

**FDA RESPONSE:**

(b) (4)

**Discussion:**

There was no additional discussion beyond the information provided in the response.

*Question 19b. In the three buprenorphine bioequivalency studies that have been completed/analyzed to date (20-A78-AU, 20-A79-AU, and 20-277-SA), the buccally administered film strip formulation produced  $C_{max}$  and  $AUC_{inf}$  ratios ranging from 1.25 to 1.49 and 1.28 to 1.42, respectively. As indicated above for the sublingual comparisons, these differences appear small and not clinically relevant.*

(b) (4)

**FDA RESPONSE:**

(b) (4)

Discussion:

There was no additional discussion beyond the information provided in the response.

**ADDITIONAL COMMENTS:**

- 1. Please note that, although you are correct in assuming that this product is exempt from pediatric study requirements under PREA because of Orphan Designation, in contrast to your statement in the meeting package, opioid dependence is not “an orphan drug indication.” Instead, Reckitt Benckiser has been granted Orphan Designation for *buprenorphine used for this indication*.**
- 2. The submission should contain a section specifically addressing hepatic safety, using MedDRA SMQ terms to identify all relevant cases from all sources of safety data, including post-marketing safety reports and clinical trials using all formulations of buprenorphine.**
- 3. Please refer to Attachment 1 which contains comments provided to all Sponsors at the Pre-NDA stage.**

General Discussion:

The Sponsor inquired about the submission of data in CDISC format. The Division replied that standard guidance was provided in Attachment 1 of the document, but that the Sponsor could submit a data plan to their INDs, and the Division would ask the Agency experts to review it. The Sponsor was also informed that they could discuss their plan for presentation of safety data in the same submission, and it would be similarly reviewed.

The Sponsor also reported to the Division that the immediate container (foil blister packs) will be serialized, and that should help to track diversion of the product.

The Division noted that a Risk Evaluation and Mitigation Strategy (REMS) would be needed with the NDA submission. The Sponsor asked if a template was available, and the Division replied that they would try to put something in the official meeting minutes.

The Division requested that the NDA submission include electronic data for the latest PK studies and, if available, ethanol solution single dose PK data, dose-proportionality PK study data and multiple dose PK data that were originally submitted with the Subutex and Suboxone NDAs. If information is available in previous NDA or publications, discuss the withdrawal symptoms noted in opiate addicted subjects with respect to plasma buprenorphine or naloxone levels.

Lastly, the Division informed the Sponsor that they may wish to check-in with the Division again a few months before they anticipate submission of their NDAs, particularly noting the recent change in strategy to label the product for maintenance use only. In addition, the Division noted that they may be available to informally meet with the Sponsor once the NDAs are submitted to review the navigatability of the applications.

Post-Meeting Note:

Although no REMS template is currently available, we refer you to a recently approved REMS for Entereg (alvimopan) located on the FDA www site at <http://www.fda.gov/cder/foi/label/2008/021775REMS.pdf>. You may wish to refer to this when designing your proposal.

Action Items:

1. The Sponsor will submit a CDISC and Safety data presentation plan for the Division to review.
2. The Sponsor will submit a draft REMS with their NDA. The Division will provide any available materials to assist in this effort.
3. The Sponsor is invited to communicate with the Division prior to their anticipated submission date to discuss the submission with the Division.

## **Attachment 1**

### **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) 6010.3 at: <http://www.fda.gov/cder/mapp/6010.3.pdf>.**

**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 5.3 Exposure-Response Relationships - important exposure-response assessments.**
- 3. Section 7.1.6 - Less common adverse events (between 0.1% and 1%).**
- 4. Section 7.1.7.3.1 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.**
- 5. Section 7.1.7.3.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.**
- 6. Section 7.1.7.3.3 - Marked outliers and dropouts for laboratory abnormalities.**
- 7. Section 7.1.8.3.1 - Analysis of vital signs focused on measures of central tendencies.**
- 8. Section 7.1.8.3.2 - Analysis of vital signs focused on outliers or shifts from normal to abnormal.**
- 9. Section 7.1.8.3.3 - Marked outliers for vital signs and dropouts for vital sign abnormalities.**
- 10. Section 7.1.9.1 – Overview of ECG testing in the development program, including a brief review of the nonclinical results.**
- 11. Section 7.1.9.3. – Standard analyses and explorations of ECG data.**
- 12. Section 7.1.16 – Overdose experience.**
- 13. Section 7.4.2.1 - Explorations for dose dependency for adverse findings.**

14. Section 7.4.2.2 - Explorations for time dependency for adverse findings.
15. Section 7.4.2.3 - Explorations for drug-demographic interactions.
16. Section 7.4.2.4 - Explorations for drug-disease interactions.
17. Section 7.4.2.5 - Explorations for drug-drug interactions.
18. Section 8.2 - Dosing considerations for important drug-drug interactions.
19. Section 8.3 - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

#### **Common PLR Labeling Deficiencies**

#### **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/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. 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].

7. 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)).”**

8. Please 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.
9. 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).
10. 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)].
11. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
12. 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)]
13. 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.
14. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

**Contents (Table of Contents):**

15. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
16. 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)]

17. Create subsection headings that identify the content. Avoid using the word **General, Other, or Miscellaneous** for a subsection heading.
18. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
19. When a subsection is omitted, the numbering does not change.
20. [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/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
24. Do not refer to adverse reactions as “adverse events.” Please 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/cder/guidance>.
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. There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
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. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.

34. Refer to the Institute of Safe Medication Practices' website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

**CDISC Data Requests to Sponsors  
Quantitative Safety and Pharmacoepidemiology Group**

**Safety Analysis Plan**

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, please include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis ([www.cdisc.org](http://www.cdisc.org)).

At a minimum the Safety Analysis Plan should address the following components:

- a. Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*, <http://www.fda.gov/CDER/guidance/6357fnl.pdf>).
- b. Safety endpoints for Adverse Events of Special Interest (AERI)
- c. Definition of Treatment Emergent Adverse Event (TEAE)
- d. Expert adjudication process (Expert Clinical Committee Charter)
- e. Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
- f. Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
- g. When unanticipated safety issues are identified the QSAP may be amended.

**Study Data Tabulation Model (SDTM) Issues**

1. The current published SDTM and SDTM Implementation Guide (SDTMIG) carefully should be followed. Refer to the SDTMIG section on Conformance (3.2.3)
2. Domains
  - a. There are additional domains listed below that are not included in the current DTMIG. Information on these domains may be obtained at

**www.CDISC.org** and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.

- (DV) Protocol deviations
- (DA) Drug Accountability
- (PC, PP) Pharmacokinetics
- (MB, MS) Microbiology
- (CF) Clinical Findings

b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.

- Tumor information
- Imaging Data
- Complex Inclusion/Exclusion Criteria

### 3. Variables

- a. All required variables are to be included.
- b. All expected variables should be included in all SDTM datasets.
- c. Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.
- d. A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.
- e. A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.
- f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.

### 4. Specific issues of note:

- a. SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.
- b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.
- c. These issues can be addressed through the request for ADaM datasets

### **Analysis Data Model (ADaM) Issues**

1. Please specify which ADaM datasets you intend to submit.

2. **Please include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.**
3. **Please discuss the structure of the datasets with the reviewing division and specify in the QSAP.**
4. **Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.**
5. **Please indicate which core variables will be replicated across the different datasets, if any.**
6. **SDTM and ADaM datasets should use the unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.**

### **General Items**

#### **Controlled terminology issues**

- a. **Please use a single version of MedDRA for a submission. Does not have to be most recent version**
- b. **We recommend that the WHO drug dictionary be used for concomitant medications.**
- c. **Please refer to the CDISC terminology for lab test names.**
- d. **Issues regarding ranges for laboratory measurements should be addressed.**

### Additional FDA Comments

The division requests the following for the submitted datasets:

1. **Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.**
  - a. **The integrated safety dataset that should include the following fields/variables:**
  - b. **A unique patient identifier**
  - c. **Study/protocol number**
  - d. **Patient's treatment assignment**
  - e. **Demographic characteristics, including gender, chronological age (not date of birth), and race**
  - f. **Dosing at time of adverse event**
  - g. **Dosing prior to event (if different)**
  - h. **Duration of event (or start and stop dates)**
  - i. **Days on study drug at time of event**
  - j. **Outcome of event (e.g. ongoing, resolved, led to discontinuation)**
  - k. **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).**
  - l. **Marker for serious adverse events**
  - m. **Verbatim term**
2. **The adverse event dataset should 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 should also include the Verbatim term taken from the case report form.**
3. **Please 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 should appear and does not address other content that is usually contained in the adverse event data set.**
4. **In the adverse event data set, please provide a variable that gives the numeric MedDRA code for each lower level term.**
5. **The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a**

**minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.**

- 6. Please provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.**
- 7. Please perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, please provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.**
- 8. The spelling and capitalization of MedDRA terms should match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.**
- 9. Also, for the concomitant medication dataset, you should use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.**
- 10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result should be in numeric format.**
- 11. Please perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.**
- 12. In every dataset, all dates should be formatted as ISO date format.**
- 13. Across all datasets, the same coding should be used for common variables, e.g. "PBO" for the placebo group. Datasets should 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 should be included in the datasets.**
- 14. All datasets should contain the following variables/fields (in the same format and coding):**
  - a. Each subject should have one unique ID across the entire NDA**
  - b. Study number**
  - c. Treatment assignment**

**d. Demographic characteristics (age, race, gender, etc.)**

- 15. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.**
- 16. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.**
- 17. 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.**
- 18. With reference to the table on the following page, please note that the HLGTT and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLGTT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data that is typically found in an adverse event data set.**

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		

Linked Applications

Sponsor Name

Drug Name

IND (b) (4)

RECKITT BENCKISER

(b) (4)

IND 75811

RECKITT BENCKISER

BUPRENORPHINE HCL & NALOXONE  
HCL SUBLING

-----  
**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  
07/24/2008