

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
21-306**

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 21306

SUPPL #

HFD # 170

Trade Name Butrans

Generic Name buprenorphine transdermal system

Applicant Name Purdue

Approval Date, If Known June 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?

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# 20732 Subutex

NDA# 20733 Suboxone

NDA# 18401

Buprenex

(see attachment for complete list, including approved ANDAs)

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

BUP3015: A Multicenter, Randomized, Double-blind, Active Comparator Study to Determine the Efficacy and Safety of BTDS 20 or OxyIRR versus BTDS 5 in Subjects with Moderate to Severe Low Back Pain

BUP3024: A Multi-center, Randomized, Double-blind, Placebo-controlled Study with an Open-label Run-in to Assess the Efficacy, Tolerability, and Safety of BTDS 10 or BTDS 20 Compared to Placebo in Opioid-naive Subjects with Moderate to Severe, Chronic Low Back Pain

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"):

BUP3015: A Multicenter, Randomized, Double-blind, Active Comparator Study to Determine the Efficacy and Safety of BTDS 20 or OxyIRR versus BTDS 5 in Subjects with Moderate to Severe Low Back Pain

BUP3024: A Multi-center, Randomized, Double-blind, Placebo-controlled Study with an Open-label Run-in to Assess the Efficacy, Tolerability, and Safety of BTDS 10 or BTDS 20 Compared to Placebo in Opioid-naive Subjects with Moderate to Severe, Chronic Low Back Pain

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 # 50273 YES ! NO
! Explain:
The original protocol identifies Purdue as the Sponsor.

Investigation #2
IND # 50273 YES ! NO
! Explain:
The original protocol identifies Purdue as the Sponsor.

(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: Matthew W. Sullivan

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Exclusivity Summary
Page 8

Title: Regulatory Project Manager
Date: June 22, 2010

Name of Office/Division Director signing form: Sharon Hertz, M.D.
Title: Deputy Division Director, Division of Anesthesia and Analgesia Products

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

[Quick Links: Skip to main page content](#) [Skip to Search](#) [Skip to Topics Menu](#) [Skip to Section Content Menu](#) [Skip to Common Links](#)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Active Ingredient Search Results from "OB_Rx" table for query on "buprenorphine."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
A076931	AP	No	BUPRENORPHINE HYDROCHLORIDE	INJECTABLE; INJECTION	EQ 0.3MG BASE/ML	BUPRENORPHINE HYDROCHLORIDE	BEDFORD
A074137	AP	No	BUPRENORPHINE HYDROCHLORIDE	INJECTABLE; INJECTION	EQ 0.3MG BASE/ML	BUPRENORPHINE HYDROCHLORIDE	HOSPIRA
A078331	AP	No	BUPRENORPHINE HYDROCHLORIDE	INJECTABLE; INJECTION	EQ 0.3MG BASE/ML	BUPRENORPHINE HYDROCHLORIDE	PHARMAFORCE
N018401	AP	Yes	BUPRENORPHINE HYDROCHLORIDE	INJECTABLE; INJECTION	EQ 0.3MG BASE/ML	BUPRENEX	RECKITT BENCKISER
A090360	AB	No	BUPRENORPHINE HYDROCHLORIDE	TABLET; SUBLINGUAL	EQ 2MG BASE	BUPRENORPHINE HYDROCHLORIDE	BARR
A090360	AB	No	BUPRENORPHINE HYDROCHLORIDE	TABLET; SUBLINGUAL	EQ 8MG BASE	BUPRENORPHINE HYDROCHLORIDE	BARR
N020732	AB	No	BUPRENORPHINE HYDROCHLORIDE	TABLET; SUBLINGUAL	EQ 2MG BASE	SUBUTEX	RECKITT BENCKISER
N020732	AB	Yes	BUPRENORPHINE HYDROCHLORIDE	TABLET; SUBLINGUAL	EQ 8MG BASE	SUBUTEX	RECKITT BENCKISER
A078633	AB	No	BUPRENORPHINE HYDROCHLORIDE	TABLET; SUBLINGUAL	EQ 2MG BASE	BUPRENORPHINE HYDROCHLORIDE	ROXANE
A078633	AB	No	BUPRENORPHINE HYDROCHLORIDE	TABLET; SUBLINGUAL	EQ 8MG BASE	BUPRENORPHINE HYDROCHLORIDE	ROXANE
N020733		No	BUPRENORPHINE	TABLET;	2MG;0.5MG	SUBOXONE	RECKITT

		HYDROCHLORIDE; NALOXONE HYDROCHLORIDE	SUBLINGUAL			BENCKISER
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N020733	Yes	BUPRENORPHINE HYDROCHLORIDE; NALOXONE HYDROCHLORIDE	TABLET; SUBLINGUAL	8MG;2MG	SUBOXONE	RECKITT BENCKISER
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[Return to Electronic Orange Book Home Page](#)

FDA/Center for Drug Evaluation and Research

Office of Generic Drugs

Division of Labeling and Program Support

Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through May, 2010

Patent and Generic Drug Product Data Last Updated: June 29, 2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	Butrans (buprenorphine) Transdermal System

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

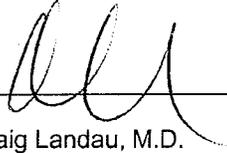
/s/

MATTHEW W SULLIVAN
06/30/2010

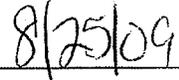
SHARON H HERTZ
06/30/2010

1.3.3. DEBARMENT CERTIFICATION

Purdue Pharma L.P. 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 connection with this application.



Craig Landau, M.D.
CMO & VP Clinical, Medical & Regulatory Affairs



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 21306 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Butrans Established/Proper Name: buprenorphine Dosage Form: transdermal system		Applicant: Purdue Pharma Agent for Applicant (if applicable):
RPM: Matthew Sullivan		Division: DAAP/ HFD170
<p>NDA: 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>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: 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><input type="checkbox"/> If no listed drug, check box and explain:</p> <p><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></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>June 30, 2010 (extended from March 30, 2010)</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None NA: August 31, 2001
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

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.

Application Characteristics ²	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan drug designation </div> <div style="width: 45%;"> <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC </div> </div> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </div> <div style="width: 45%;"> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </div> </div> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request Comments: Class 2 resubmission	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	July 6, 2010
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Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP: June 23, 2010 NA: August 31, 2001
---	---

Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	June 18, 2010
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	September 30, 2009
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 6/18/10

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use (<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 checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	September 30, 2009
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	June 18, 2010
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	January 11, 2010 Oleszczuk: June 4, 2010 January 8, 2010
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA March 5, 2010 <input checked="" type="checkbox"/> DRISK May 10, 2010 <input checked="" type="checkbox"/> DDMAC March 17, 2010 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>February 17, 2010</u> If PeRC review not necessary, explain: _____ • Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>) 	Various

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
 Version: 6/18/10

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 type="checkbox"/> N/A or no mtg November 6, 2001 April 2, 2002
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg November 18, 1998 September 15, 2008
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	
• Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	
	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None Hertz: June 30, 2010 McCormick: August 31, 2001
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None Shibuya: June 21, 2010
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None PMR -- 1 PMC -- 2
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	Levin: May 20, 2010 March 9, 2010 DalPan: August 10, 2001 December 20, 2000
• 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>)	
	Located in the following reviews: Levin: March 9, 2010 DalPan: August 10, 2001
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None Nayernama: March 10, 2010 Fizman: March 8, 2010 Garnett: December 23, 2009

⁵ Filing reviews should be filed with the discipline reviews.
Version: 6/18/10

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> Not applicable Reissig: June 29, 2010 June 23, 2010 May 7, 2010 Maust: November 22, 2002 July 26, 2001
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	June 22, 2010 Hertz: June 30, 2010 Perla: June 14, 2010 April 22, 2010
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested Leibenhaut: April 29, 2010 February 26, 2010
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Norton: March 4, 2010 Grosser: November 13, 2002 August 20, 2001 January 16, 2001
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Agarwal: March 10, 2010 Alfayoumi: July 15, 2001 December 10, 2000
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None Bond: May 11, 2010 March 10, 2010 Papoiian: August 31, 2001 July 18, 2001 December 14, 2000
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc Thomson: March 3, 2010
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None February 18, 2010
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None Peri: June 21, 2010
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None Ysern: June 17, 2010 February 26, 2010 Ghosh: June 18, 2010 May 18, 2010 Harapanhalli: August 30, 2001 Ya: December 20, 2000
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	Harapanhalli: August 30, 2001
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	

Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>	Completed: February 22, 2010 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<input checked="" type="checkbox"/> 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)

⁶ 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.



NDA 21-306

INFORMATION REQUEST

Purdue Pharma L.P.
Attention: Richard Fanelli, Ph.D.
Executive Director, Regulatory Affairs
One Stamford Forum
Stamford, CT 06901

Dear Dr. Fanelli:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BuTrans™ (Buprenorphine Transdermal System, BTDS).

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

Based on the dissolution profiles of the batches kept at the proposed storage condition at release and at 12 months, 18 months, and 24 months, we recommend the following specifications:

In Vitro Drug Release Acceptance Criteria for BTDS			
Time Point (hr)	Previous Acceptance Criteria	Sponsor's Currently Proposed Acceptance Criteria	Agency's Recommended Acceptance Criteria
0.5			(b) (4)
2			
8			
16			

If you have any questions, call Swati Patwardhan, Regulatory Management Officer, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21306

ORIG-1

PURDUE PHARMA
LP

BuTrans (buprenorphine
transdermal system)

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

/s/

PRASAD PERI
05/25/2010

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Monday, May 17, 2010 12:08 PM
To: 'Fanelli, Richard'
Subject: OSE Carton/Container Comments

Rich –

A. GENERAL COMMENTS

1. Revise all references to the unit 'hour' to be expressed as the word 'hour' to provide consistency throughout the labels and labeling and to avoid confusion that can be caused by the use of abbreviations that have multiple meanings. Currently, the labels and labeling utilize three different expressions ('h', 'hr', and 'hour') to represent the unit 'hour'. In the expression of strength (i.e. 5 mcg/h, 10 mcg/h, and 20 mcg/h) throughout the labels and labeling, the abbreviation 'h' is used to represent the unit 'hour'. On the container label the statement "Each transdermal system delivers 5 mcg buprenorphine per hr" uses the abbreviation 'hr' to represent the unit 'hour'. A similar statement "Each transdermal system delivers 5 mcg buprenorphine per hour" that appears on the carton labeling use the word 'hour' to express the unit of time. Although, we acknowledge that all three expressions can be interpreted as 'hour' in the medical community, the two abbreviations also have other recognized meanings that can be found in standard references for abbreviations. Additionally, the use of abbreviations in labels and labeling can lead to prescribing habits that may result in medication errors. If the use of an abbreviation for 'hour' is necessary because of inadequate space, revise all abbreviations to use 'hr' and be consistent whenever the abbreviation is used.
2. The controlled symbol competes for prominence with the proprietary name and strength. Reduce the size of the control symbol so it is not the most prominent information on the labels and labeling.
3. [REDACTED] (b) (4)

B. CONTAINER LABELS

1. Revise the color of the expression of strength to help differentiate the different strengths. Currently all the strengths are highlighted with (b) (4) and may be confused because of the use of the same color.
2. Revise the statement [REDACTED] (b) (4)
 (b) (4) The new statement should read "Each transdermal system delivers 5 mcg buprenorphine per hour for seven days".
3. Include the total drug content of the transdermal system in a manner that does not compete with the prominence of expression of strength or the rate of drug release.
4. Include warning statements on the principal display panel to help minimize the inappropriate use of

the transdermal system. We have seen inappropriate use with other similar transdermal systems through our postmarketing experiences and similar products list warning statements on the container label to help minimize the risk of inappropriate use of those products. (b) (4)

(b) (4)
Statements such as these warnings should be included on the principal display panel.

5. (b) (4)
Revise the net quantity statement be presented as “Contains 1 transdermal system”.

C. CARTON LABELING

1. Revise the color of the expression of strength to help differentiate the different strengths. Currently all the strengths are highlighted with (b) (4) and may be confused because of the use of the same color.
2. Revise the statement (b) (4)
The new statement should read “Each transdermal system delivers 5 mcg buprenorphine per hour for seven days”.
3. Include warning statements on the principal display panel to help minimize the inappropriate use of the transdermal system. We have seen inappropriate use with other similar transdermal systems through our postmarketing experiences similar products list warning statements on the carton labeling to help minimize the risk of inappropriate use of those products.. (b) (4)
Statements such as these warnings should be included on the principal display panel.
4. (b) (4)
Revise the net quantity statement to delete the phrase (b) (4)” and present as the net quantity as “Contains 4 transdermal systems and 4 disposal systems”.
5. The warning statement (b) (4)
Revise the warning to state “Retain systems in unopened foil pouch until ready to use.”
Additionally, the warning statement could be made more prominent by bolding the text.
6. Include the total drug content of the transdermal system in a manner that does not compete with the expression of strength or the rate of drug release.

E. DISPOSAL SYSTEM

Include a prominent statement such as “Disposal Unit: does not contain active drug” on the Disposal System to help clearly differentiate the disposal system from the patch. Such a statement should indicate what the Disposal System is and that it does not contain active drug. Since the Disposal System is in the same shape as the patch (rectangle) and is adhesive, patients may confuse the disposal system for the patch, particularly if they are unaware of the existence of a disposal system. Our postmarketing experiences with other transdermal patches

have seen similar situations where patients applied only the protective overlays that are included with those patches because the patients believed that the overlays were the actual patch.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia and
Analgesia Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	BuTrans (buprenorphine transdermal system)

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
05/17/2010

Sullivan, Matthew

From: Sullivan, Matthew

Sent: Wednesday, April 28, 2010 3:02 PM

To: 'Fanelli, Richard'

Subject: REMS comments N 21306

Attachments: Appendix D Healthcare provider clean.doc; Comments.doc; Appendix A REMS track changes.doc; Appendix B REMS clean.doc; Appendix C Healthcare provider track changes.doc

Rich –

We've gone through the REMS for NDA 21306, and have generated the attached comments.

Please confirm receipt.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia and
Analgesia Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

4/28/2010

Please see **Appendix A (Appendix B – clean version)** for our revisions to the proposed REMS which is consistent with current Agency standards.

The spelling of BuTrans has been changed to Butrans to be consistent with the PI. TM can be added after Butrans throughout the document.

The REMS Supporting Document must reflect the below changes to be consistent with the REMS document.

Please incorporate the necessary revisions and include all current versions of materials in appendices in the next submission.

A. Goals

The goals have been reviewed and found to be acceptable. We have minor editorial revisions.

B. Medication Guide

Comments on the Medication Guide will be provided under a separate review.

C. Elements to Assure Safe Use

1. The Dear Healthcare Professional (DHCP) Letter

A DHCP Letter will be included in the REMS under elements to assure safe use to inform healthcare professionals of the Butrans REMS and the need for Healthcare Provider training. Please develop and submit for review the DHCP letter.

The DHCP letter must be mailed within 60 days of the approval of Butrans to prescribers most experienced in treating chronic pain with opioid agonists, including, pain specialists, physiatrists, and primary care physicians. This letter is designed to convey and reinforce the risks of abuse, misuse, overdose, and addiction of Butrans. The mailings must also include the Butrans REMS Educational Program materials.

Additional printed educational material should be made available through field-force distribution, by calling the toll free number, and available for download at the Butrans website.

2. Healthcare Provider Training Guide (page numbers in parenthesis indicate page numbers in the HCP Guide)

Please see **Appendix C (Appendix D for clean copy)** for our revisions to the proposed Healthcare Provider Training Guide.

- i. The guide does not provide a comprehensive view of the safety information for Butrans. Place a sentence in the purpose statement section (under the goals) of the guide instructing healthcare providers to refer to

the full Prescribing Information for detailed safety information about this product. A similar statement should be used throughout the guide.

- ii. Healthcare provider training guide needs to include the risks associated to Butrans including:
 - The risk of overdose in opioid naïve patients when using initial dose greater than 5mcg/h.
 - The risk of addiction from exposure to Butrans
 - The risk of unintentional exposure to Butrans in persons for whom it was not prescribed, including accidental exposure to children.
 - The risk of temperature-dependent increases in buprenorphine released from the system resulting in possible overdose and death.
- iii. Remove the following promotional language proposed on page 3 of the training guide:



This is an inadequate communication of the indication. Although the presentation is consistent with the Highlights section of the draft PI and the limitation to its use is presented on page 4 of the proposed Guide, under “Proper Patient Selection”, the introductory presentation on page 3 does not adequately communicate the indication. Revise this presentation to include the limitations to its use relating to (b) (4), for consistency with the draft full PI.

- iv. The sequence of information within the Guide is inconsistent with the proposed PI and may minimize the risks associated with Butrans. Specifically, information on sections 17 (Patient Counseling Information), and 16 (How supplied, Storage and Handling) of the proposed PI are presented before serious and potentially fatal risk information from section 5 (Warnings and Precautions) of the draft PI. This presentation minimizes the risks being communicated. Present the information in a manner consistent with the proposed PI.
- v. The content and order of presentation of risk information within the “Risks Associated with Butrans and Opioids” section of the proposed Guide minimizes the risks associated with Butrans. For example, the risk information, including warnings and precautions are presented on page 11, under the header: (b) (4), which fails to adequately convey the severity of the potential fatal risks being communicated. (b) (4)

(b) (4) This presentation minimizes the risks being communicated. The most serious information should be presented first in a manner consistent with the proposed PI, under an appropriate header. Eliminate the heading, (b) (4) and replace it with a heading consistent with the draft PI.

- vi. Present the information regarding risks associated with Butrans prior to information on patient selection, and dosage and administration in order to prevent minimization of risk within the piece.
- vii. Proper Patient Selection/Assess All Patients for Risks of Opioid Abuse or Addiction Before Starting Treatment with BuTrans section
There are six bulleted items included in the documentation for prescribing and treatment records. It is not clear of the source for the bulleted information. They are not found in the PI. Provide a reference for the list.
- viii. Appropriate Dosing and Administration/Factors to consider when selecting the initial dose of BuTrans

(b) (4)
Please check the bullet and revise or delete.

Do not bold the information provided in the third bullet. Bolding places emphasis on the information suggesting superiority over the other bulleted items.

- ix. For patient with hepatic impairment
Use verbatim language provided in the PI. Revise the sentence

(b) (4)

- x. Side Effects/Treatment of Overdose
The PI states that Naloxone may not be effective in reversing any respiratory depression produced by buprenorphine. The Treatment of Overdose section of the guide states Naloxone, an opioid antagonist, should be administered. Please include correct information. Be sure the information in the guide is verbatim with information provided in the full PI.
- xi. Risk of Abuse, Misuse, and Addiction/BuTrans is a Schedule III Controlled Substance
The sentence, 'Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs' is found in this section of the PI. Add the sentence to the Risk of Abuse,

Misuse, and Addiction/Butrans is a Scheduled III Controlled Substance section of the guide.

xii. Revise Table of Contents

3. Butrans Educational Confirmation Form

As part of the healthcare provider training, develop a form that the healthcare providers will return to the sponsor confirming they have completed the educational training. This form may request the following Prescriber Information:

- 1) Prescriber name and credentials
- 2) DEA registration Number
- 3) Specialty
- 4) Affiliation
- 5) Address
- 6) Office Phone
- 7) Office Fax
- 8) Email
- 9) Date form completed

We recommend that you include questions that can verify prescriber's understanding of the risks associated with Butrans, the indication for use proper dosing, safety information about proper administration and storage of Butrans, and the need for patient counseling.

This form should include the following statement: "Completion of this form does not affect your ability to prescribe Butrans" Additionally, we require that you maintain a list of all prescribers that have completed the Butrans REMS Educational Program training and provide a report on the status of the training program as part of your REMS assessment.

E. Timetable for Submission of Assessment

The proposed timetable for submission of assessment is acceptable. We have minor editorial revisions

F. REMS Supporting Document

1. All Changes in REMS Document should be reflected in the REMS Supporting Document.
2. The following information needs to be included in your REMS Supporting Document under "Information Needed for Assessment:"
 - i. An evaluation of patients' understanding of the serious risks of Butrans.
 - ii. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

- iii. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
- iv. A report on the status of the training program for healthcare providers.
- v. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with Butrans (for example, through surveys of healthcare providers).
- vi. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.
- vii. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose, and addiction and any intervention taken resulting from signals of abuse, misuse, overdose, and addiction.
- viii. An analysis to evaluate Butrans (buprenorphine) utilization patterns including use in non-opioid tolerant patients.
- ix. With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

3. Survey Methodology:

Submit for review the detailed plans that will be used to evaluate patients' and prescribers' understanding about the risks associated with and safe use of Butrans. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence." The submission should include all methodologies and instruments that will be used in the evaluations.

- 1. Recruit respondents using a multi-modal approach. For example, patients might be recruited online, through physicians' offices, through pharmacies, managed care providers, or through consumer panels.
- 2. Explain how non-respondent follow-up or reminders will be completed and the planned frequency of the non-respondent follow-ups.
- 3. Explain how incentive or honorarium will be offered and the intended amount.
- 4. Explain how sites will be selected.
- 5. Submit for review any recruitment advertisements.
- 6. Define the sample size and confidence interval associated with that sample size.

7. Define the expected number of prescribers and patients to be surveyed, and how the samples will be determined (selection criteria)
8. Explain the inclusion criteria; that is, who is an eligible respondent. For example, a patient respondent might be:
 - Age 18 or older
 - Currently taking Butrans or have taken in past 3 months
 - Not currently participating in a clinical trial involving Butrans
9. Submit any screener instruments, and describe if any quotas of sub-populations will be used.
10. Explain how the surveys will be administered and the frequency of the surveys.
11. Offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy patient population. For example, surveys could be completed online, in writing or by mail, over the phone, or in person.
12. Explain how surveyors will be trained.
13. Explain controls used to compensate for the limitations or bias associated with the methodology
14. The patient sample should be demographically representative of the patients who use Butrans.
15. The prescriber sample should be demographically representative of the healthcare providers who prescribe or administer Butrans.
16. If possible and appropriate, the sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geographically
17. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey.
18. Potential respondents should be told that their answers will not affect their ability to receive or take (patients) or prescribe (prescribers) Butrans, and that their answers and personal information will be kept confidential and anonymous.
19. Respondents should not be eligible for more than one wave of the survey.
20. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).
21. Data may be stratified by any relevant demographic variable, and presented in aggregate. We encourage you to submit with your required assessments all methodology and instruments that were used to evaluate the effectiveness of the REMS.

With regard to the patient survey instrument:

22. The assessment is to evaluate the effectiveness of the REMS in achieving its goal by evaluating patients' knowledge of the serious risks associated with and safe use of Butrans. The assessment is not to evaluate consumer comprehension of the Medication Guide.
23. Respondents should not be offered an opportunity to read or see the Medication Guide again prior to taking the survey.
24. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
25. The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event.
26. Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about Butrans?" section of the Medication Guide
27. The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.
28. The order of the multiple choice responses should be randomized on each survey.
29. The order of the questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Demographic questions should be collected last or as part of any screener questions.
30. Respondents should not have the opportunity or ability to go back to previous questions in the survey if the survey is conducted by telephone or online.
31. Explain if and when any education will be offered for incorrect responses.
32. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.
33. Just prior to the questions about receipt of the Medication Guide, include text explaining what is a Medication Guide. For example,
Now we are going to ask you some questions about the Medication Guide you may have received with Butrans. The Medication Guide is a paper handout that contains important information about the risks associated with use of Butrans and how to use Butrans safely. Medication Guides always include the title "Medication Guide".

34. Use the following (or similar) questions to assess receipt and use of the Medication Guide.
- a. Who gave you the Medication Guide for Butrans? (Select all that apply)
 - a) My doctor or someone in my doctor's office
 - b) My pharmacist or someone at the pharmacy
 - c) Someone else - please explain:

 - d) I did not get a Medication Guide for Butrans
 - b. Did you read the Medication Guide?
 - All,
 - Most,
 - Some,
 - None
 - c. Did you understand what you read in the Medication Guide?
 - All,
 - Most,
 - Some,
 - None
 - d. Did someone offer to explain to you the information in the Medication Guide?
 - Yes, my doctor or someone in my doctor's office
 - Yes, my pharmacist or someone at the pharmacy
 - Yes, someone else – please explain:

 - No
 - e. Did you accept the offer? Yes or No
 - f. Did you understand the explanation that was given to you?
 - All,
 - Most,
 - Some,
 - None
 - g. Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

With regard to the prescriber survey instrument:

- 35. The assessment is to evaluate the effectiveness of the REMS in achieving its goal by evaluating prescribers' knowledge of the serious risks associated with and safe use of Butrans. The assessment is not to evaluate prescribers' comprehension of the educational materials.
- 36. Respondents should not be offered an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, videos, etc.) prior to taking the survey.

37. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.
38. The prescriber knowledge survey should include a section with questions asking about the specific risks and safety information conveyed in the educational materials.
39. Questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.
40. The order of the multiple choice responses should be randomized on each survey.
41. The order of the survey questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Demographic questions should be collected last or as part of any screener questions.
42. Respondents should not have the opportunity or ability to go back to previous questions in the survey if conducted by telephone or online.
43. Explain if and when any education will be offered for incorrect responses.
44. Use the following (or similar) questions to assess receipt and use of the educational materials.
 - a. Prior to today, which of the following were you aware of or received with regard to Butrans? (Select all that apply)

Educational Material	Aware	Received
Full Prescribing Information	<input type="checkbox"/>	<input type="checkbox"/>
Medication Guide	<input type="checkbox"/>	<input type="checkbox"/>
Dear Healthcare Provider Letter	<input type="checkbox"/>	<input type="checkbox"/>
Prescribing Butrans: A Healthcare Professional Guide	<input type="checkbox"/>	<input type="checkbox"/>
Something else - please explain:	<input type="checkbox"/>	<input type="checkbox"/>
None of the above	<input type="checkbox"/>	<input type="checkbox"/>

- b. Did you read the Full Prescribing Information?
 - o All,
 - o Most,
 - o Some,
 - o None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	BuTrans (buprenorphine transdermal system)

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/s/

MATTHEW W SULLIVAN
04/28/2010



NDA 21-306

INFORMATION REQUEST

Purdue Pharma L.P.
Attention: Richard Fanelli, Ph.D.
Executive Director, Regulatory Affairs
One Stamford Forum
Stamford, CT 06901

Dear Dr. Fanelli:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BuTrans™ (Buprenorphine Transdermal System (BTDS)).

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

1. Based on the recommendation of the Pharm-Tox review team, the acceptance criteria for (b) (4) are the following:

(b) (4)

Incorporate these limits as part of the drug product specifications. Alternatively, provide a justification based on safety considerations.

2. Provide the acceptable ranges for the in-process control of the viscosity testing of the drug-containing adhesive mass and of the drug-free adhesive mass.
3. Provide the acceptable range for the adhesion strength of the drug-containing adhesive section of the BTDS. If you are at the stage of gathering this data, provide an estimated date when this information will be conveyed to the Agency.

4. Provide an update of the drug product specifications. The updated drug product specifications should include test methods, acceptance criteria, and when the testing is not carried on the final BTDS, the stage where the test is carried out should be stated (e.g. testing for [REDACTED] ^{(b) (4)} will be performed on the drug-containing laminate and the drug-free laminate, as release specifications).

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	BuTrans (buprenorphine transdermal system)

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/s/

PRASAD PERI
04/06/2010

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Monday, April 05, 2010 2:26 PM
To: 'Fanelli, Richard'
Subject: Butrans label
Attachments: PI PLR DRAFT Butrans April 5 2010.doc

Rich -

Here is the butrans label.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia and
Analgesia Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

35 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-21306	ORIG-1	PURDUE PHARMA LP	BuTrans (buprenorphine transdermal system)

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/s/

MATTHEW W SULLIVAN
04/05/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021306

PDUFA GOAL DATE EXTENSION

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard Fanelli, Ph.D.
Executive Director, Regulatory Affairs

Dear Dr. Fanelli:

Please refer to your new drug application (NDA) submitted November 3, 2000, received November 3, 2000, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for buprenorphine transdermal system.

Reference is also made to your September 25, 2009, submission, received September 30, 2009, which constituted a complete response to our August 31, 2001, action letter.

On February 18, 2010, we received your February 18, 2010, 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 June 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, 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-21306	ORIG-1	PURDUE PHARMA LP	BuTrans (buprenorphine transdermal system)

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/s/

SARA E STRADLEY
03/05/2010

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, February 23, 2010 7:43 AM
To: 'Fanelli, Richard'
Subject: CMC IR for NDA 021306

Attachments: Picture (Metafile); Picture (Metafile)

Rich – CMC IR below for Butrans.

Thanks
matt

1. We acknowledge your request for the withdrawal of the [REDACTED] (b) (4) facility [REDACTED] (b) (4). This facility was proposed to carry out non-routine microbial testing of the drug product. Microbial testing is not part of the drug product regulatory specifications. Your request is granted.
2. Based on the provided stability data and its statistical analysis, a shelf-life of 21 months is granted for the drug product under the recommended storage conditions (Store at 25 °C (77 °F); excursions permitted between 15 °C -30 °C (59 °F – 86 °F).
3. Provide limits for the polymer components [REDACTED] (b) (4) as part of the drug product specifications. The acceptance criteria for [REDACTED] (b) (4), should be in accordance with those observed in BTDS and their safety fully justified.
4. As requested in previous letter dated August 31, 2001, provide an in-process test for viscosity of the drug-containing adhesive mass and drug-free adhesive mass. At the current time you do not have sufficient information to delete the test. Once you have generated this information on a sufficient number of batches you may choose to sunset this test via supplement.
5. Section 2.1.3 of the pharmaceutical development report (referenced in your response to Comment 35b) does not address and justify the proposed acceptance criteria for adhesion strength and release strengths. Provide a justification of the proposed acceptance criteria.
6. Provide a specification for the adhesion strength of the drug-containing adhesive section of the Buprenorphine Transdermal Patch (BTDS).
7. Provide a listing of the adhesion and release strength values of the lots used in clinical trials.
8. Provide a summary, from the clinical trials, of drug product complaints relating to the adhesiveness of the patches. For the large patches 88 % of BTDS experienced buckling (termed “System Buckled” in the Study BP9600803). Describe the system when buckled, specifically as to where on the BTDS this occurs. If it occurs in multiple sites of the patch, describe the severity of the buckle, and if it is permanent, does the patch adhere to itself?
9. Provide sufficient scientific justification to support the amount of residual drug substance in the

BTDS after use. The drug development information provided in the NDA does not demonstrate product and process understanding nor assure that a scientific, risk-based approach has been taken to minimize the amount of residual drug in a system after use. Include in the justification data demonstrating that the amount of residual drug substance is minimized consistent with the current state of technology.

10. Deficiency letters were sent to the holders of the following DMFs on February 18, 2010: DMF (b) (4), DMF (b) (4), and DMF (b) (4).
11. The following information has been submitted in the original submission:

Impact of Changes in In Vitro Release, Adhesion Strength and Release Strength over Storage on In Vivo Performance

There is a trend of decline in the in vitro release, adhesion strength and release strength for all strengths of BTDS during storage. For example, the mean amount of buprenorphine released from batch 7/00499/6 10 mg patches at 2 hours declined from 54% initially to 38% at 24 months and 36% at 36 months. However, this trend of decrease in the above mentioned attributes was not accompanied by any changes in the in vivo absorption as measured by peak exposure (C_{max}) (Figure 7) or total exposure during the 168 hour period of BTDS application (AUC_{168}) (Figure 8).

Figure 7: In Vivo Absorption as Measured by Peak Exposure (C_{max})

BTDS 10 C_{max} vs. Patch Age by Lot

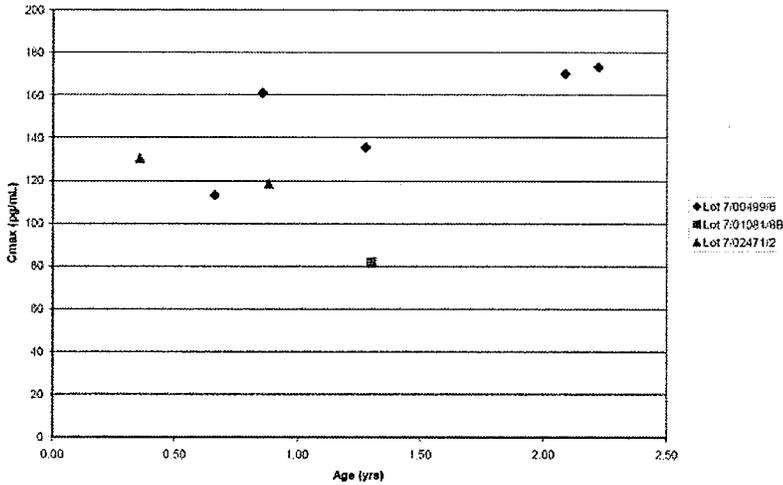
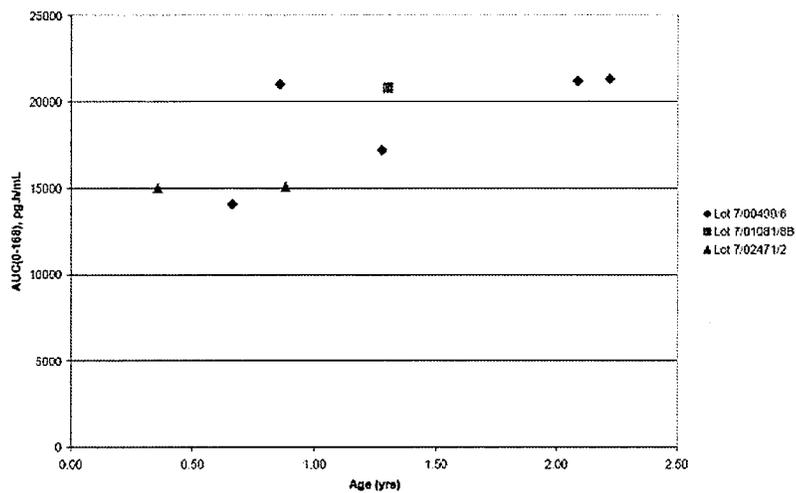


Figure 8: Total Exposure During the 168 Hour Period of BTDS Application (AUC_{168})

BTDS 10 $AUC(0-168)$ vs. Patch Age by Lot



Please provide full details of the *in-vivo* studies (Study numbers with data/results) that have been used to generate the above profiles. Also, confirm that the lots used are of clinical batches.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	BuTrans (buprenorphine transdermal system)

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/s/

MATTHEW W SULLIVAN
03/01/2010

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, March 03, 2010 2:35 PM
To: 'Fanelli, Richard'
Subject: BTDS vs MRI

Rich –

In the proposed PI, there is this warning:



Thanks,
Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21306

ORIG-1

PURDUE PHARMA
LP

BuTrans (buprenorphine
transdermal system)

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/s/

MATTHEW W SULLIVAN
04/16/2010

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, February 24, 2010 9:56 AM
To: 'Fanelli, Richard'
Subject: Clin Pharm IR NDA 21-306

Rich –

Can you provide this info for us?

Thanks
matt

Please submit the following methods (bioanalytical) in detail. These are listed as references but we would like to see them in detail (if possible).

(b) (4)

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Monday, February 01, 2010 5:57 PM
To: 'Fanelli, Richard'
Subject: REMS request

Rich –

From OSE: please submit all relevant REMS material (that has not been previously submitted) including "Prescribing BuTrans: A Healthcare Professional Guide".

4/16/2010

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, January 20, 2010 10:19 AM
To: Fanelli, Richard
Subject: N21306 IR on retained dropouts

Rich –

According to Table 5 in the Clinical Study Report for BUP3015, there were 39 subjects who discontinued study drug and completed the double-blind phase. However, A_DISPOS includes 44 subjects who are identified as retained dropouts, having the value RETDO = 'Yes'. Explain the discrepancy.

Page 23 of the Statistical Analysis Plan for BUP3015 states, "Missing 'average pain over the last 24 hours' scores at scheduled study visits subsequent to the discontinuation of study medication in the Double-blind phase will be imputed by the BOCF (baseline observation carried forward) approach." It appears that this imputation was not used for retained dropouts (i.e., subjects who discontinue double-blind medication but remain in the study). Redo Table 10 using BOCF for retained dropouts. Submit SAS code and derived data.

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, January 13, 2010 9:11 AM
To: Fanelli, Richard
Subject: CMC IR 21306

Rich –

Here is a CMC request:

Provide the weights of the (b) (4) **and the** (b) (4) **in each patch.**

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
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Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, January 05, 2010 3:51 PM
To: Fanelli, Richard
Subject: Another Stats IR

Rich –

Another one:

In the Clinical Study Report for BUP3015, Figure 3 and Table 13 define a responder using the mean pain scores at Weeks 4, 8, and 12. Redo this figure and table, defining a responder on the basis of Week 12 alone. For Figure 3 and Responder Analysis 1, impute zero improvement to any subject who withdraws prior to Week 12.

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
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Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Monday, January 04, 2010 10:13 AM
To: Fanelli, Richard
Subject: FW: Information Request for NDA 21-306

Rich –

Can you help with this?
Matt

Submit the following data files that are referenced in submitted SAS code (A_DEMO.SAS, U_TRT.SAS) for Study BUP3015:

S:\RHO\PURDUE\BUP3015\data\fromspon\invid.sas7bdat
S:\RHO\PURDUE\BUP3015\data\fromspon\bup3015.ssd01

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Thursday, December 17, 2009 3:24 PM
To: 'Fanelli, Richard'
Subject: N 21306 stats request

Rich –

The SAS code for Study BUP3015 refers to the same file names in libraries CONVERT and CONVEXT. Explain the difference between the two libraries.

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, December 09, 2009 9:43 AM
To: 'Fanelli, Richard'
Subject: Another Statistics IR NDA 021306

Rich –

In the Clinical Study Report for BUP3015, sections 10.2 and 16.2.2.1 both have listings of protocol deviations. However, some deviations are listed in one section and not the other. Moreover, section 10.2 does not always identify the subject who had the deviation. Provide a SAS data file containing a complete listing of protocol deviations which includes the subject number, description of the deviation, phase of the study, and deviation category.

Matthew W. Sullivan, M.S.
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and Rheumatology Products
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Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Monday, November 23, 2009 9:37 AM
To: 'Fanelli, Richard'
Subject: Butrans Macros and File 21306

Rich –

For Studies BUP3015 and BUP3024, submit the SAS macros that are called in the SAS code that you have previously submitted.

For Study BUP3024, submit the file named DEVSMED which is used in D_ADAP24.SAS.

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, November 20, 2009 8:40 AM
To: 'Fanelli, Richard'
Subject: FW: NDA 021306 Butrans Disposal System

Rich –

OSE has requested this. Can you provide it?

I was looking over the labels and labeling for this product and I saw that they include 4 disposal systems in each carton of 4 patches. Could we ask the Applicant to send in a working model of the disposal system and directions for use?

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, November 17, 2009 10:43 AM
To: 'Fanelli, Richard'
Subject: FW: NDA 21-306 (BuTrans) - Summary clinical PK tables

Rich – can you help?

Could you please ask the sponsor to provide me the location in the eCTD or send summary PK tables (e.g., AUC, Cmax, etc.) for clinical trials BP96-0101 & BP96-0102?

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, November 03, 2009 9:50 AM
To: 'Fanelli, Richard'
Subject: Stats IR Nov 3 for Butrans

Rich –

Several of the analysis files for Study BUP3015 appear to have "garbage" values in the USUBJID field. These files include, but may not be limited to, A_VISITS, A_DAILY, A_DLDOS, A_OXY, and A_DISPOS. For example, observation 12821 in A_VISITS.XPT has the value "*****MEMBER HEAD". Moreover, A_VISITS only has 601 unique subjects, while the full analysis set has 660 subjects. Submit a set of complete analysis files with valid values for all fields.

In regard to Study BUP3024 you state, "The Blinded Adjudication Review was performed by (b) (4) for the 172 randomized subjects who discontinued study prematurely. The review was completed prior to database lock. A separate report summarizing the adjudication process and results was prepared." Submit this report, or indicate where it can be found in the NDA.

Matt

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Monday, November 02, 2009 2:19 PM
To: 'Fanelli, Richard'
Subject: Clinical Pharm. IR 2Nov09

Rich –

The Bioanalytical Validation reports for Clin Pharm Study Bup1009 titled "A Single Center, Randomized, Double-Blind, Crossover Study to Assess Buprenorphine Accumulation and Description of Its Metabolites During Co-Medication of BTDS and Ketoconazole, Used As a CYP3A4 Inhibitor, in Healthy Subjects" are incomplete.

You submitted adequate bioanalytical validation reports (BVRs) for only 3 of the 5 moieties that were measured in that study. BVRs for bup-3-glucuronide and norbup-3-glucuronide (combined in one report) and ketoconazole are included; however BVRs for buprenorphine and norbuprenorphine are missing.

Thanks
Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, October 30, 2009 5:23 PM
To: 'Fanelli, Richard'
Subject: NDA 21306 nonclinical information request

Attachments: TgAC Data Format.pdf; Picture (Enhanced Metafile)

Rich -

Another information request. Please try to get us something in the next couple of days on this.

Thanks
matt

1) For the transgenic mouse carcinogenicity study (b) (4) study number AB26TZ.7D8T.BTL) with buprenorphine (NDA 21-306), identify the location of required information (see attached) in the statistical data transport files or create and submit required information in the required format so that FDA statistical analysis of data can be conducted.



TgAC Data
Format.pdf (34 KB)

2) For the rat carcinogenicity study (b) (4) No. 6770-290) with buprenorphine (NDA 21-306), explain the meaning of different tumor codes for the same organs for the untreated and vehicle control groups versus the treated groups (example below with tumor codes 103 and 178, respectively).

(b) (4)

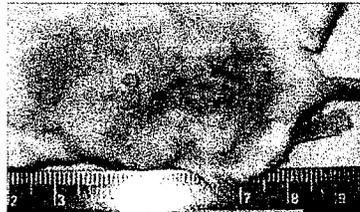
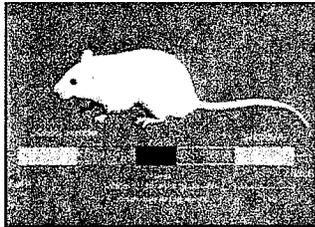
Office of Biostatistics Information Sheet for Submission of Data and for Methods of Data Analysis of Carcinogenicity Studies Using Tg.AC Transgenic Mice

The statistical reviewer responsible for this carcinogenicity-study review requests that the sponsor recreate the weekly count data of skin papillomas of individual animals as a SAS dataset in the format presented in Table 1. Numbers of skin papillomas developed on the site of application (SOA) and other sites of the body (Non-sites of application, NSOA) should be listed separately. Examples of non-sites of applications used in some previous studies are given in the table. A period (.) should be used for count of each of the weeks after death if an animal died before the end of the study.

The agency recommends that the sponsor conduct a statistical analysis of the skin papillomas weekly count data using the method proposed by Dunson et al. (2000). The paper is available on website

<http://toxsci.oxfordjournals.org/cgi/content/full/55/2/293>.

For questions related to the data format and the methods of statistical analysis, please contact Karl K. Lin, Ph.D., Room 5238, Building 22, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 301-796-0943, karl.lin@fda.hhs.gov.



(Courtesy of Dr. David Jacobson-Kram)

Table 1

**Sample Tg.AC Mouse Bioassay Data
Number of Papillomas, by Study Weeks**

Group	Gender	Animal No.	Tumor Site	1	2	3	...	26	27
2	M	16	SOA	0	0	1	...	19	19
			NSOA	0	0	0	...	0	0
			a	0	0	0	...	0	0
			b	0	0	0	...	0	0
			c	0	0	0	...	0	0
			d	0	0	0	...	0	0
			e	0	0	0	...	0	0
		f	0	0	0	...	0	0	
		17	SOA	0	0	0	...	0	0
			NSOA	0	0	0	...	0	0
			a	0	0	0	...	0	0
			b	0	0	0	...	0	0
			c	0	0	0	...	0	0
d	0		0	0	...	0	0		
...	...								
19			SOA	0	0	1	...	4	5
			NSOA	0	0	0	...	0	0
			a	0	0	0	...	0	0
			b	0	0	0	...	0	0
			c	0	0	0	...	0	0
			d	0	0	0	...	0	0
			e	0	0	0	...	0	0
			f	0	0	0	...	0	0

Note: SOA=Site of application, NSOA=Non-site of application
a=mouth, b=genital area, c=scrotal, d=vaginal, e=anal, f=abdominal

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, October 23, 2009 12:07 PM
To: 'Fanelli, Richard'
Subject: "Table 1" for the TQT study
Attachments: Table 1.pdf

Rich –
Here is the info that we need to be able to review the TQT study.

Once your colleagues have had a chance to look at it, please let me know when you think you'll be able to respond.

Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

I – For review of a Thorough QT Protocol, submit the following:

- Electronic or hard copy of the study protocol
- Electronic or hard copy of the Investigator Brochure
- A completed Highlights of Clinical Pharmacology Table (Table 1 shown below)

II – For review of a Thorough QT Study Report, submit the following:

- Electronic or hard copy of the study report
- Electronic or hard copy of the clinical protocol
- Annotated CRF
- A Define file which describes the contents of the electronic data sets
- Electronic data sets as SAS transport files
- SAS code for the primary statistical analysis
- Data set whose QT/QTc values are the average of the replicates
- Statistical programs with analysis datasets that were used to analyze the study endpoints as well as to perform exposure-response analysis
- ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- A completed Highlights of Clinical Pharmacology Table (Table 1. shown below)

For reports, please submit all data sets in CDISC SDTM format if possible.

Table 1. Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites

Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC
	Sex	Specify mean changes in C _{max} and AUC
	Race	Specify mean changes in C _{max} and AUC
	Hepatic & Renal Impairment	Specify mean changes in C _{max} and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C _{max} and AUC
	Food Effects	Specify mean changes in C _{max} and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in C _{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, October 20, 2009 2:42 PM
To: 'Fanelli, Richard'
Subject: RE: NDA 21-306: Response to FDA request: List of Tox Studies in Word format

Rich –

Thanks. That was perfect.

However, it appears that the reviewer would now like it for a few more portions of the application:

> Can you ask for a similar TOC for all of module 4 (Nonclinical) and for any nonclinical studies included in module 3 (Quality)?

Can you help us out with this too?

From: Fanelli, Richard [mailto:Richard.Fanelli@pharma.com]
Sent: Monday, October 19, 2009 2:34 PM
To: Sullivan, Matthew
Subject: NDA 21-306: Response to FDA request: List of Tox Studies in Word format

Matt –

As you requested during our phone conversation earlier today, attached please find a Word document listing the toxicology studies included in our BuTrans™ NDA 21-306. I have separated the list into 2 tables; the 1st listing toxicology studies in the original November 2000 submission, and the 2nd listing the studies included in the resubmission.

With best regards,
Rich

Richard J. Fanelli, Ph.D.
Executive Director, Regulatory Affairs
Purdue Pharma L.P.
Tel: (203) 588-8365
email: richard.fanelli@pharma.com

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, October 16, 2009 2:49 PM
To: 'Fanelli, Richard'
Subject: Stats Information Request N 21306

Rich –

IR from the Stats group:

In the clinical study report for BUP3015, you state, “Enrollment was terminated early due to administrative reasons unrelated to safety or efficacy.” Clarify what the reasons for study termination were, and state whether the treatment assignments were unblinded prior to termination.

For studies BUP3015 and BUP3024, thoroughly describe the randomization, including the methods used to make assignments within strata. These descriptions should include the details of any blocking or adaptive methods employed.

For studies BUP3015 and BUP3024, submit the SAS code used to create the analysis datasets and perform the efficacy analyses.

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021306

ACKNOWLEDGE CLASS 2 RESPONSE

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard Fanelli, Ph.D.
Executive Director, Regulatory Affairs

Dear Dr. Fanelli:

We acknowledge receipt on September 30, 2009, of your September 25, 2009, resubmission to your new drug application for buprenorphine transdermal system.

We consider this a complete, class 2 response to our August 31, 2001, action letter. Therefore, the user fee goal date is March 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, M.S.
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-21306

ORIG-1

PURDUE PHARMA
LP

BUPRENORPHINE
TRANSDERMAL SYSTEM

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
10/14/2009

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, October 13, 2009 3:51 PM
To: 'Fanelli, Richard'
Subject: DMF deficiencies/ N21306

Rich –

I left you a VM just now on this. We need to know the dates that these DMF deficiencies were addressed in their respective DMF applications.

Please provide a statement confirming that the DMF holders of DMF (b) (4), DMF (b) (4) and DMF (b) (4) have provided response to the Agency's DMF deficiency letters. The response to Item 50 should include the dates the DMF holders responded to the deficiencies questions

We need this, in partial part, to determine that your response is "complete".

Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-306

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard Fanelli, PhD
Executive Director, U.S. Regulatory Affairs

Dear Dr. Fanelli:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for buprenorphine transdermal system (BTDS).

We also refer to the meeting between representatives of your firm and the FDA on September 15, 2008. The purpose of the meeting was to discuss your plans for submission of a complete response to our August 31, 2001, Not Approvable (NA) letter.

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

SPONSOR MEETING MINUTES

MEETING DATE: September 15, 2008

TIME: 2:00 pm to 3:00 pm

LOCATION: FDA White Oak Campus
Silver Spring, MD

APPLICATION: NDA 21-306

PRODUCT: BuTrans (buprenorphine transdermal system (BTDS))

INDICATIONS: Moderate to severe pain requiring continuous opioid analgesia

SPONSOR: Purdue Pharma L.P.

TYPE OF MEETING: Type B, Pre-NDA

MEETING CHAIR: Sharon Hertz, M.D., Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

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

FDA Attendees	Title
Sharon Hertz, M.D.	Deputy Director, DAARP
Ellen Fields, M.D., MPH	Medical Team Leader, DAARP
Lei Zhang, Ph.D.	Clinical Pharmacology Reviewer, DAARP
Sheetal Agarwal, Ph.D.	Clinical Pharmacology Reviewer, DAARP
R. Dan Mellon, Ph.D.	Pharmacology/ Toxicology Supervisor, DAARP
BeLinda Hayes, Ph.D.	Pharmacology/ Toxicology Reviewer
Katherine Bonson., Ph.D.	Pharmacologist, Controlled Substance Staff (CSS)
Prasad Peri, Ph.D.	Pharmaceutical Assessment Lead, Office of New Drug Quality Assurance
Afrouz Nayernama	Safety Evaluator, Office of Surveillance and Epidemiology
Kate Meaker, M.S.	Biostatistics Reviewer, DAARP
Matthew Sullivan, M.S.	Regulatory Project Manager, DAARP
Purdue Attendees	Title
Brian Burke, PhD	Executive Director, Project Management
Richard J. Fanelli, PhD	Executive Director, Regulatory Affairs

J. David Haddox, DDS, MD	VP Health Policy
Stephen Harris, MD	Executive Medical Director, Clinical Pharmacology
Craig Landau, MD	CMO & VP Clinical, Medical & Regulatory
Catherine Munera, PhD	Director, Biostatistics
Steven Ripa, MD	Executive Medical Director, Medical Research
John H. Stewart	President
Jack Henningfield, PhD	VP, Research and Health Policy, Pinney Associates

Background:

The Sponsor submitted a meeting package on July 31, 2008, in support of the September 15, 2008, meeting to discuss plans for submission of a complete response to our August 31, 2001, Not Approvable (NA) letter. The Division provided written responses to the questions in the meeting package on September 12, 2008.

The Attachment at the end of this document provides general comments provided to all Sponsors at the Pre-NDA meeting. These comments have not been tailored to your specific application.

The questions are presented below in *italicized* text in the order in which they were addressed at the meeting. The Division's responses are **bolded**, and the discussion is presented in normal text.

General/Regulatory Questions

Question 1. Does the Agency agree that this is a Complete Response to be submitted in eCTD format and that the full November 2000 NDA submission does not need to be included?

FDA Response:

The full November 2000 NDA submission does not need to be included in the eCTD format of the Complete Response. However, all parts of the original NDA submission referenced in the Complete Response should be provided in eCTD format.

Discussion:

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

Question 2. Does the Agency agree that the package insert should be revised and submitted according to the PLR?

FDA Response:

It is preferable that the package insert is revised and submitted in PLR format.

Discussion:

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

Question 3. Does the Agency agree that with PPLP's plan to submit a revised PPSR after submission of the complete response?

FDA Response:

You should be aware that "The Food and Drug Administration Amendments Act of 2007," which includes regulations regarding pediatric studies under the "Pediatric Research Equity Act of 2007" and "Best Pharmaceuticals for Children Act of 2007" was enacted on Sept 27, 2007.

As part of this act you must submit a pediatric plan including proposed studies and requests for deferrals and/or waivers (with justifications) as part of the complete response.

These are evaluated by Pediatric Equity Research Committee (PERC) as part of the review process.

Discussion:

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

Clinical Questions

Question 4. Does the Agency agree with the proposed plan for presentation of the clinical data?

FDA Response:

The outlined plan for presentation of clinical data appears reasonable. Detailed documentation should be provided on how derived variables were created. Submit a well-formed define.pdf or define.xml document as described in FDA guidances.

Discussion:

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

Question 5. Does the Agency agree with the planned grouping of controlled and uncontrolled multiple-dose studies in chronic pain and with the additional pools of adverse event data planned for in the ISS?

FDA Response:

In the primary pool for safety analysis, including the "Non-enriched titration-to-effect studies pool" and "Enriched fixed duration studies pool,"

present adverse events by treatment group (i.e. placebo or active comparator and BTDS dose received). Perform separate analyses for the controlled double-blind and open label phases.

Present exposure and disposition data by BTDS dose and include placebo and active comparator treatment groups.

Discussion:

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

Question 6. Does the Agency agree with the planned approach to the evaluation of the effect of dose on safety data?

FDA Response:

Include placebo and active comparators in the dose-response safety analysis. Present open-label and double-blind data analyses separately.

To better understand tolerability of BTDS, include non-enriched, titration-to-effect studies in the dose-response analysis.

Discussion:

The Sponsor sought clarification on the request for non-enriched studies to be included in the dose-response analysis. They specifically noted that the adverse events may be related to the dose at onset, and might not be an accurate reflection of the events over the course of the study. The Division replied that data may help to inform the label by providing an overall picture of adverse events during the titration and maintenance periods of use.

The Division asked the Sponsor to include both the dose at onset, and the dose at the end of titration.

Additional Safety Data-Related Questions

Question 7. Does the Division agree with the planned approach to presenting addendum reports for the updated safety database and analyses for each individual study?

FDA Response:

Your proposal appears reasonable.

Discussion:

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

Question 8. Does the Agency agree that patient profiles are not necessary as part of the Complete Response to the NA letter?

FDA Response:

Yes, we agree that safety profiles are not necessary.

Discussion:

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

Question 9. Does the Agency agree that the submission of the most recent PSUR, line listings for cases not included in the current PSUR, a summary of past PSURs, and a detailed summary of published case reports associated with buprenorphine will be a satisfactory summary of worldwide safety?

FDA Response:

Section 5.3.6 of the NDA (“Reports of postmarketing experience”) must contain a written summary of the post-marketing experience with BTDS since initial time of marketing. The PSUR is not adequate to meet this NDA requirement because it discusses the safety experience over the previous 6 months since the last PSUR, and because it is comprised predominantly of line listings and/or summary tabulations.

Discussion:

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

Abuse Potential and Risk Management-Related Questions

Question 10. Does the Agency agree that a Premarketing Risk Assessment and the development of a RiskMAP with these goals are sufficient to address the abuse liability issues in the NA letter?

FDA Response:

You propose a RiskMAP which is outlined in the briefing package. Any proposal including a Medication Guide, Communication Plan, and/or Elements to Assure Safe Use as described under 505-1(e) of the Food and Drug Administration Amendments Act (FDAAA) should be submitted as a proposed Risk Evaluation and Mitigation Strategy (REMS). However, a complete review of your Complete Response (CR) will be necessary to determine whether a REMS is needed to ensure that the benefits of the drug outweigh the risks and what components will be essential to assure safe use.

For information on the format and content of a REMS, we refer you to the approval letter for Entereg (available at <http://www.fda.gov/cder/foi/label/2008/021775REMS.pdf>).

Remember to submit all planned materials identified within the proposed REMS that will be necessary to implement your proposal. Education should emphasize the safety messages important for safe use of the product. Product marketing materials generally are not appropriate to educate about product risks.

Deficiency 60 of the NA letter addressed the need for a study to evaluate the bioavailability and pharmacokinetic profile of buprenorphine through the buccal mucosal route in the presence of alcohol, which is frequently misused with other drugs of abuse. As agreed in the February 2002 End-of-Review meeting, this issue has been completely addressed, dependent on your receiving right of reference regarding access to the buccal absorption data discussed in the November 6, 2001 meeting. Evidence of right of reference to these data should be provided.

Deficiency 60 of the NA letter also addressed the need for a human abuse potential study with BTDS. As agreed in the February 2002 End-of-Review meeting, the rescheduling of buprenorphine from Schedule V to Schedule III of the Controlled Substances Act (CSA) in October 2002 obviated the need for a human abuse potential study with BTDS.

Deficiency 61 of the NA letter addressed the potential for significant diversion of buprenorphine from BTDS and the need to redesign the patch or modify the BTDS matrix to limit residual buprenorphine in an individual BTDS upon completion of dosing and to reduce significantly the potential for extraction of buprenorphine from the BTDS matrix. No information was provided in the briefing document regarding this issue. Thus, the response to this issue is incomplete.

In the briefing document, the Premarketing Risk Assessment and the RiskMAP were submitted in outline form only. Given the lack of specific details and lack of primary data in the submitted materials, we are unable to determine whether these plans are sufficient to address the abuse potential issues raised in the NA letter. Thus, the adequacy of these materials will be a review issue when the NDA is resubmitted.

Discussion:

The Sponsor acknowledged that the RiskMAP submitted with the meeting package was an outline with "high-level" thoughts, and asked how future communications regarding RiskMAPs should be handled. The Division noted that all communications should be channeled through the Regulatory Project Manager.

The Division also reminded the Sponsor that a REMS proposal should be submitted with the upcoming NDA resubmission. This document should be complete and all educational materials should be included. The Division stated that they would try to work with the

Sponsor prior to submission to ensure that the proposal is adequate. The Controlled Substance Staff noted that they would work with the Division in this endeavor as well.

Question 11. Does the Agency agree that these 2 disposal options are sufficient to address concerns regarding the safe disposal of used BTDS patches? What are the Agency's recommendations concerning the type of information related to the BTDS disposal system it would prefer to review in the Complete Response?

FDA Response:

Refer to our response to Question #10.

The “fold and flush” disposal method is recommended for use with other opioid patches (such as the fentanyl patch) and may be appropriate for BTDS. However, the Agency is in the process of reviewing all drug labels with disposal directions to assure that the recommended methods are still appropriate. Since no details were provided regarding the complete methods proposed for disposal of BTDS, the adequacy of these methods will be a review issue when the NDA is re-submitted.

Discussion:

See the discussion to Question 10.

Question 12. Does the Agency agree that the planned approach to conducting a Premarketing Risk Assessment is acceptable for identifying the main risks associated with BTDS and formulating a predicted benefit/risk analysis? What modifications and/or additional components would the Agency recommend?

FDA Response:

Refer to our response to Question #10.

Discussion:

See the discussion to Question 10.

Question 13. Does the Agency agree that the planned RiskMAP outline is acceptable for managing the main risks associated with BTDS? What modifications and/or additional components (ie, goals, objectives, RiskMAP tools, evaluation strategies) would the Agency recommend?

FDA Response:

Refer to our response to Question #10.

Discussion:

See the discussion to Question 10.

Preclinical Question

Question 14. Does the Agency agree that these additional nonclinical studies with an updated summary should be included in the Complete Response and that nothing additional is needed?

FDA Response:

Yes, with the following caveats.

- 1. In addition to final study reports, you must submit the carcinogenicity study data in SAS XPORT format. For information regarding the specifications for submitting a tumor dataset, refer to the following URL: <http://www.fda.gov/cder/regulatory/ersr/Studydata.pdf>.**
- 2. Specifications for drug product impurities, including (b) (4) must not exceed the acceptable Q3B qualification thresholds based on the maximal feasible daily exposure. If this or any other impurity exceeds this specification, adequate safety qualification must be provided. Adequate qualification would include the following:**
 - a. Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**
 - b. Repeat dose toxicology of 90-day duration in the most appropriate species to support the proposed chronic indication.**

Should this qualification produce positive or equivocal results, the impurity specification should be set at NMT (b) (4) mcg/day, or otherwise justified. Justification may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

Discussion:

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

CMC Question

Question 15. Does the Agency agree that submission of responses to CMC items in the NA letter and current versions of specifications, testing methods, and CoAs are sufficient for the Complete Response?

FDA Response: Your proposal appears reasonable. In the resubmission, highlight any changes to the drug substance and drug product information including specifications, testing methods, and Certificates of Analysis (CoAs).

With respect to the following items, refer to the deficiencies in our August 31, 2001, letter. Some of our comments reflect policy changes and changes to compendial monographs which have occurred since 2001.

1. With respect to deficiencies 2 through 6, refer to the current ICH Q3A Guidance (February 2003). Follow the recommended reporting, identification and qualification criteria. (b) (4) could be classified as a structural alert.
2. Report all impurities in drug substances with two significant figures (e.g., (b) (4)).
3. With respect to deficiencies 7 and 15, note that the proposed acceptance criteria will be evaluated in the NDA in collaboration with the Pharmacology /Toxicology reviewers.
4. Note that the current monograph for Buprenorphine EP specifies a number of impurities. Please evaluate this and update your proposed specification if applicable.
5. With respect to deficiencies 9, 13, and 40, provide the Detection and Quantitation limits for impurities in the drug substance and drug product. Refer to ICH Q2A and ICH Q2B for additional information on Method Validation.
6. For deficiency 10, please clarify that no new batches were manufactured between (b) (4) and used to make drug product. If they were used, include the impurity profile of all drug substance batches.
7. For deficiency 17, clarify if the source of oleyl oleate is a plant or animal.
8. For deficiencies 22 and 23, provide the results from scale-up studies, validation studies, and early development batches that form the basis for your rationale for not monitoring the proposed parameters in the NDA.
9. With respect to deficiencies 26 and 44, clarify if the foil pouch (b) (4) Provide the results for these either in the NDA or in the DMF.

10. For deficiencies 29-33, refer to the current revision of ICH Q3B (July 2006). Follow the Reporting, Identification and Qualification Thresholds listed in Attachment 1. The qualification limit is ^{(b) (4)}% or ^{(b) (4)} mcg TDI whichever is lower.
11. For deficiency 35c, provide details on all complaints for all patches used in clinical trials, not just the top-line review of the products.
12. For deficiency 42, provide the qualitative and quantitative composition and dimensional information of the ^{(b) (4)} laminates.
13. For deficiency 46, provide the available PK data (for all strengths of patches) vs. patch age. Your response will be evaluated from a CMC perspective and in collaboration with the Clinical Pharmacology reviewers as needed. We also note that you plan to provide a discussion of a lack of IVIVC (deficiency 48a).
14. Please provide a statement in the NDA from your DMF holders indicating to the Agency that they have responded to all the deficiency letters. Include the dates of the responses to each letter in the NDA.

Provide tabular summaries of your stability data, organized by test parameter, and separated by manufacturing site, batch, storage condition, and container closure system. Provide graphical summaries of any trending stability data, organized by test parameter, including mean and individual data.

Include a well-documented Pharmaceutical Development Report as per ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.

At the beginning of the CMC section, include a table of all facilities, specifically including the function of each facility, the contact name and address, the CFN number, and the complete name and address of the facility.

Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming this in the NDA cover letter.

Relevant Guidances for Industry are listed below for your convenience:

Guidance for Industry ICH Q3A (R) Impurities in New Drug Substances available at <http://www.fda.gov/cder/guidance/4164fnl.htm>

Guidance for Industry ICH Q3B (R2) Impurities in New Drug Products available at <http://www.fda.gov/cder/guidance/7385fnl.htm>

Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/122900d.htm>

**Guidance for Industry Container Closure Systems for Packaging
Human Drugs and Biologics Chemistry, Manufacturing and Controls
Documentation available at**

<http://www.fda.gov/cder/guidance/1714fnl.htm>

**Guidance for Industry Text on Validation of Analytical Procedures
available at <http://www.fda.gov/cder/guidance/ichq2a.pdf>.**

**Guidance for Industry Validation of Analytical Procedures:
methodology available at**

<http://www.fda.gov/cder/guidance/1320fnl.pdf>

Discussion:

The Sponsor requested clarification on item number one which noted that (b) (4) could be classified as a structural alert. The Division replied that (b) (4) are usually structural alerts, but that the Sponsor should provide justification as to how (b) (4) is to be classified in this setting. The Division also noted that if (b) (4) is a metabolite, there might be less concern.

Post-Meeting Note:

After internal discussion within ONDQA, it is determined that (b) (4) is not considered a structural alert.

General Discussion:

The Sponsor stated that they may have some technical CDISC/STDM questions as they assemble their NDA resubmission, and wondered how they could get them addressed. The Division replied that the Regulatory Project Manager could assist with this.

The Sponsor informed the Division that they anticipate resubmitting the NDA during the second or third quarter of 2009.

Action Items:

1. The Sponsor will include the non-enriched population in their dose-response analysis. Dose at onset and dose at end of titration will be also included.
2. The Sponsor will provide a REMS proposal with the NDA resubmission. The Division will provide assistance, as resources allow, to ensure that the REMS is adequate.

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.

Sites for Inspection

To assist the clinical reviewer in selecting sites for inspection, include a table in the original NDA for each of the completed Phase 3 clinical trials that has the following columns:

1. Site number
2. Principle investigator
3. Location: City State, Country
4. Number of subjects screened
5. Number of subjects randomized
6. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites)
7. Number of protocol violations (Major, minor, definition)

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. 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.” 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, 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).

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 (AESI)
- c. Definition of Treatment Emergent Adverse Event (TEAE)
- d. Expert adjudication process (Expert Clinical Committee Charter)
- e. Data/Safety Monitoring Committee (DSMC): (Submit charter for FDA review) by

- f. Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
- g. When unanticipated safety issues are identified the Quantitative Safety Analysis Plan may be amended. Amendments should be filed in accordance with FDA regulations.

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, 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 must be included in all SDTM datasets.
 - c. Variables (expected or permissible) for which no values will be submitted must 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 must 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 must 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 must 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 SUPQUAL dataset or an ADaM dataset.
 - c. These issues can be addressed through the request for ADaM datasets

Analysis Data Model (ADaM) Issues

- 1. Specify which ADaM datasets you intend to submit.
- 2. Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.
- 3. Discuss the structure of the datasets with the reviewing division and specify in the QSAP.
- 4. Within each adverse event analysis dataset, include all levels of the MedDRA hierarchy as well as verbatim term.
- 5. Indicate which core variables will be replicated across the different datasets, if any.
- 6. SDTM and ADaM datasets must use the unique subject ID (USUBJID). Each unique subject identifier must be retained across the entire submission.

General Items

Controlled terminology issues

- a. 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. Refer to the CDISC terminology for lab test names.
- d. Issues regarding ranges for laboratory measurements must be addressed.

Integrated Summary of Effectiveness

Please refer to the Guidance for Industry located at the following web page
<http://www.fda.gov/cder/guidance/7694dft.pdf>

Dataset 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.

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

- a. A unique patient identifier
 - b. Study/protocol number
 - c. Patient's treatment assignment
 - d. Demographic characteristics, including gender, chronological age (not date of birth), and race
 - e. Dosing at time of adverse event
 - f. Dosing prior to event (if different)
 - g. Duration of event (or start and stop dates)
 - h. Days on study drug at time of event
 - i. Outcome of event (e.g. ongoing, resolved, led to discontinuation)
 - j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
 - k. Marker for serious adverse events
 - l. Verbatim term
2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group

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

11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. In every dataset, all dates must be formatted as ISO date format.
13. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.
14. All datasets must contain the following variables/fields (in the same format and coding):
 - a. Each subject must have one unique ID across the entire NDA
 - b. Study number
 - c. Treatment assignment
 - d. Demographic characteristics (age, race, gender, etc.)
15. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. Also, a listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.
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, note that the HLG T and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLG T terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

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this page is the manifestation of the electronic signature.**

/s/

Matthew Sullivan
10/17/2008 05:01:49 PM



NDA 21-306

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Derek Williams, RAC
Associate Director, US Regulatory Affairs

Dear Mr. Williams:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norspan (buprenorphine transdermal system).

We also refer to your September 25, 2002 submission, containing an assessment of the extractability of buprenorphine from intact patches.

We have reviewed the referenced material and have the following comments and recommendations from the Controlled Substance Staff.

1. Specify the number and strengths of patches that will be used.
2. The amount of buprenorphine extracted will depend on the length of the extraction. Extractability of buprenorphine at 2 hours as proposed is not adequate. Measure the amount of buprenorphine extracted at 12, 18 and 24 hours under the conditions indicated in the protocol (use of various solvents at room temperature and higher temperatures).
3. In addition to using 10 ml of the various solvents, measure extractability using 50 ml of the solvents for patches with 10 mg or lower amount of drug and 100 ml of the solvents for patches with a higher content of drug.
4. Determine the effect of using unfolded pieces of patches under the conditions specified in the protocol.
5. Describe and justify the assay methodology used to quantify buprenorphine.
6. Indicate which component of the risk management plan will address the ease of extraction.

The labeling must include appropriate warnings to prevent abuse and diversion of the patches and must not underestimate the abuse potential of the formulation. The high concentration of buprenorphine in the formulation, the ease of extraction of buprenorphine from the patches, and the fact that the amount of buprenorphine absorbed can be increased by either applying heat to the patch, by reapplying a patch to a site recently used, or by chewing of the patch, are factors that may increase the abuse potential of this formulation.

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
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NDA 21-306

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Derek Williams, RAC
Associate Director, U.S. Regulatory Affairs

Dear Mr. Williams:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norspan (buprenorphine transdermal system).

We also refer to your July 22, 2002, containing a request that the Division reconsider its decision that the clinical study BP96-0604 'fail[ed] to demonstrate the effectiveness of the product for the management of patients with pain requiring continuous opioid analgesia.'

We have reviewed the referenced material and have the following comments and recommendations.

1. You have not provided substantial evidence that Norspan (BTDS) will have its intended clinical effect.
2. You make several valid points. In particular, the completer analysis does violate the intent-to-treat principle. It is often compared to intent-to-treat analyses as a rough check, but we agree that it should not be relied upon in reaching conclusions. Also, the by-time-point analysis without LOCF (last observation carried forward) is indeed not very reliable in itself because, as you indicate, it excludes the large number of subjects who drop out by day 60. In that sense, it, too, violates the intent-to-treat principle.
3. We do not agree that LOCF, the use of the last recorded pain observation for each subject, or comparison of on-study means are sufficient analyses in this situation. The sensitivity approach suggested in this submission that uses the subject's mean of on-study responses as the dependent variable is equivalent to imputing an average value for each dropout. Imputing, whether with the last value (LOCF) or an average value, does not take into account the information provided by the fact of dropping out due to a poor response to treatment and the shortened time on study. Nor does endpoint analysis. A repeated measures analysis without imputation was also suggested by the FDA as rough

check. While it may take into account the differing times on study, it more importantly does not treat the dropouts as fundamentally different.

4. While pain data are missing for a large number of subjects, there is full and relevant information on each subject at the end of the study in the full analysis set. Each subject in the ITT population was either a dropout or a completer. For a subject who dropped out due to adverse events or lack of efficacy (23 of 27 and 22 of 24 dropouts in the placebo and BTDS group, respectively), we know that BTDS does not provide acceptable treatment of pain relative to placebo over the time frame of the study, and this information is more important than the pain scores prior to drop-out. For each completer, we have a full series of relevant pain scores, but the final scores do not differ significantly between the Norspan and the placebo groups. While you indicate in Attachment 3, p. 15 of your response that this may be due to “more of an unexpected placebo group pattern on or after day 60 relative to both active treatment groups rather than an issue of concern regarding the efficacy of BTDS,” it may as likely be the opposite. Placebo control groups are crucial as comparators in clinical trials for this reason.
5. We have in each group comparable numbers of failures of treatment, either by lack of efficacy or by toxicity, as well as comparable pain scores among patients who did not fail in this way. A more formal analysis along these lines could be done as described by Gould or Senn (see *Statistics in Medicine* 2001; 20:3931-3946 for more details). In this approach, ranks are assigned to everyone in the full analysis set, with dropouts given the lowest ranks, and a test performed on the ranks.
6. As to the dropout rates and patterns, we suggest that they are not important in themselves. Rather, our concern is that they make it impossible to discern a treatment effect with appropriate confidence.
7. You correctly quote ICH E9 in this submission:

“Imputation techniques, ranging from the carrying forward of the last observation to the use of complex mathematical models, may also be used in an attempt to compensate for missing data.”

but it goes on to say,

“The use of any of these strategies should be described and justified in the statistical section of the protocol and the assumptions underlying any mathematical models employed should be clearly explained.”

The ICH document is clearly discussing LOCF as one of a number of more or less problematic ways of dealing with missing data, rather than as a general solution to the problem. Moreover, your plan for use of LOCF did not include an adequate justification of certain key aspects of the analysis of the imputed data, an important part of the imputation strategy. In the primary analysis, LOCF was used in conjunction with a repeated measures analysis that assumed an auto-regressive covariance structure. An

auto-regressive structure theoretically does not describe data where half of the observations for half of the subjects have been carried forward—all the imputed values for an individual are exactly the same as his last observed value, and so the within-subject correlation is a constant of one rather than falling off exponentially with time. Even using an unstructured covariance matrix, as you did in a sensitivity analysis, poses problems. It assumes that all subjects have the same covariance, but as indicated above, LOCF necessarily forces a different structure upon the dropouts.

8. The argument regarding effect size, which you have calculated and compared to the effect size in other clinical trials, is not supportive of your overall argument, as it relies on your primarily analysis, which, as noted above, remains problematic.

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Bob Rappaport
11/8/02 10:40:04 AM



NDA 21-306

Purdue Pharma
One Stamford Forum
Stamford, CT 06901-3431

Attention: J. Christopher Prue, R.Ph.
Sr. Director, US Regulatory Affairs

Dear Mr. Prue:

Please refer to the meeting between representatives of your firm and FDA on April 2, 2002. The purpose of this second End-of-Review meeting was to discuss abuse liability issues from the Not Approvable letter dated August 31, 2001.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Shepherd
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: April 2, 2002

Location: Parklawn Building, Conference Room C (1:00-3:00 PM)

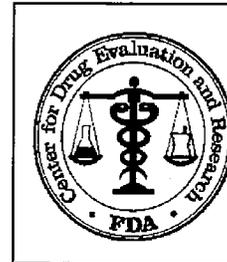
Sponsor: Purdue Pharma L.P.

NDA: NDA 21-306 (Norspan, [buprenorphine TDS])

Type of Meeting: End of Review Meeting /Guidance

Meeting Chair: Cynthia McCormick, M.D. Director
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

Meeting Recorder: Sara E. Shepherd, Regulatory Project Manager



Purdue Pharma	Title
Brian Burke, Ph.D.	Sr. Director, Project Management
Lynn Kramer, M.D.	Vice President, Medical Research
Alton Kremer, M.D.	Executive Medical Director
Steven Ripa, M.D.	Medical Director
Anthony Santopolo, M.D.	Vice President, US Regulatory Affairs
Paul Goldenheim, M.D.	Executive Vice President, Worldwide R&D
Thomas Hille	Project Leader, LTS Lohmann, Andernach Germany
J. Christopher Prue, R.Ph.	Senior Director, US Regulatory Affairs
Derek Williams, RAC	Associate Director, US Regulatory Affairs
David Wu	Assistant Director, Regulatory Affairs, CMC
Glenn Van Buskirk	Vice President, Non-Clinical Drug Development
DACCADP	Title
Cynthia McCormick M.D.	Division Director
Bob Rappaport, M.D.	Deputy Director
Gerald Dal Pan, M.D.	Medical Reviewer
Suresh Doddapaneni, Ph.D.	Pharmacokinetics Team Leader
Suliman Al Fayoumi, Ph.D.	Pharmacokinetics Reviewer
Ravi Harapanhalli, Ph.D.	Chemistry Reviewer
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Controlled Substance Staff	Title
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Katherine Bonson, Ph.D.	Pharmacologist
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Meeting Objective: The primary objective of this second End of Review meeting was to discuss the abuse liability issues from the August 31, 2001, not approvable letter for Norspan (buprenorphine transdermal system).

General Discussion: Following introductions, the discussion focused on comments from the primary reviewers from the Division of Anesthetic, Critical Care and Addiction Drug Products and the Controlled Substance Staff concerning the meeting package dated February 28, 2002. Each issue from the August 31, 2001, not approvable letter, addressed in the information package, is listed below in italics.

Issue 60 (August 31, 2001 NA letter)

Further characterize the abuse potential and risk of overdose of buprenorphine in the transdermal formulation. Examples of issues that need to be addressed, include, but are not necessarily limited to the following.

- a. *Characterize the bioavailability and pharmacokinetic profile of buprenorphine through the buccal mucosal route in the presence of alcohol, a common accompaniment for orally or transmucosally abused drugs.*
- b. *The human abuse liability study was reviewed and found to be inconclusive because of the failure to investigate a full range of doses in order to produce low, moderate, and high reinforcing responses to buprenorphine. Failure to use a standard comparator, such as morphine, and failure to obtain plasma levels of buprenorphine renders the study uninterpretable. Repeat this study taking into consideration these design issues.*

The Sponsor's Questions (meeting package dated February 28, 2002)

1. The Division has requested that Purdue further characterize the abuse potential and risk of overdose of buprenorphine. Paragraphs A and B are designated as examples of issues, but it appears that the issues are not necessarily limited to A and B. Purdue requests that all deficiencies in NDA 21-306 be set forth in sufficient detail so that a response and/or specific corrective action can be taken to place the application in condition for approval.
2. Purdue requests clarification and support as to why parenteral buprenorphine is not considered a standard comparator given that 1) buprenorphine is a marketed substance that is already controlled and 2) new drugs containing substances already scheduled are routinely compared to scheduled product.
3. The Division has requested investigation of a full range of doses (Issue 60b). The transdermal dose employed in the abuse liability study was two times the maximum dose proposed for use in the intended population and that this dose separated from

active control. Therefore Purdue requests specifics from the Division for the dosing requested here and its relationship to the abuse potential of this product.

Agency's Response

The Agency stated that there are additional risks presented by the buprenorphine transdermal system (BTDS) that are different from the risks presented by the substance itself, and these will be noted when question #61 is discussed. The FDA's recommendation and DEA's recent publication of the rescheduling of buprenorphine substance to Schedule III (Federal Register, Vol 67, No. 55, pages 13114-6: March 21, 2002) changes the context for the discussion of BTDS. The Agency stated that provided that buprenorphine is placed in Schedule III, an additional human abuse liability study is no longer needed. If buprenorphine is placed in a less restrictive schedule, an additional Norspan human abuse liability study may be needed.

Regardless of the schedule in which buprenorphine is finally placed, the Agency reminded the Sponsor that the risk management plan will be critical in reducing the risks associated with BTDS.

Discussion

The Agency reassured the Sponsor that the DEA is unlikely to down schedule the buprenorphine substance. Thus, another abuse liability study would not be needed. However, if the FDA's recommendation to reschedule the buprenorphine substance to Schedule III is not accepted, then the Sponsor should contact the Agency for further discussion.

Dr. Leiderman also advised the Sponsor that the buprenorphine substance is going to be reviewed for an international schedule by the World Health Organization (WHO). If moved under the Single Convention on Narcotic Drugs all countries will be required to move to the most restrictive domestic schedule. If the Sponsor wants to prove there is a difference in their product versus the buprenorphine substance, the Sponsor would need to generate data to support their argument. However, the Agency also stated that the Sponsor's surveillance program should allow them to collect the necessary data to address this issue.

In summary, it was agreed that no study would be needed if the buprenorphine substance was placed in Schedule III, but the Sponsor would contact the Agency if buprenorphine was placed in a less restrictive schedule.

Sponsor's Question (meeting package - February 28, 2002)

4. During the 6 November meeting, the Division indicated that the buccal absorption data referenced in the pre-meeting package were appropriate to address the concerns in this section. The Division asked for clarification from Purdue regarding access to

the buccal data. Assuming right of reference, does the Division agree that this item has been satisfactorily resolved?

Agency's Response

Yes, we agree.

Discussion

No further discussion was needed.

Sponsor's Question (meeting package - February 28, 2002)

5. Does the Division believe that the buprenorphine contained in the transdermal system poses a greater potential for diversion or abuse than other dosage forms? If so, please explain the basis for this conclusion.

Agency's Response

BTDS presents additional potential risks over and above other dosage forms, because it can be used for its intended therapeutic purpose and removed, and BTDS still contains a significant amount of abusable buprenorphine.

Discussion

The Agency expressed concern over the amount of buprenorphine remaining (b) (4) in the patch after the full therapeutic dose. The amount of residual buprenorphine in the BTDS presents a significant safety risk as well as abuse risk. Accidental ingestion or inadvertent patch application by a child or vulnerable adult of an already "used" BTDS represents a significant amount of abusable buprenorphine. The Sponsor questioned this concern. As an example, the Agency presented data to compare the fentanyl patch with Norspan.

For pain relief, 0.1 mg fentanyl = 0.3 mg buprenorphine = 10 mg morphine for IM, IV, SC routes of administration. Therefore, Fentanyl is 3X more potent than buprenorphine. The amount of fentanyl leftover in each patch is (b) (4) mg per 10.0 mg patch) and the amount of buprenorphine is (b) (4) mg out of 20.0 mg patch). Furthermore, the (b) (4) mg of fentanyl represents (b) (4) dosages of 0.1 mg and there is (b) (4) mg leftover of buprenorphine which represents (b) (4) dosages of 0.3 mg. Thus there is twice as much buprenorphine leftover in the Norspan patch than there is fentanyl leftover in the Duragesic patch.

The Sponsor stated that (b) (4) of fentanyl would be fatal and that (b) (4) mg of buprenorphine would not be fatal and requested clarification of this comparison. The Agency clarified that the main concern was the abusability of the leftover buprenorphine in the Norspan patch. The Agency stated that there is no Agency policy about how much drug should remain in the patch and reminded the Sponsor to

consider what is good for the public health. The Agency is concerned about the abuse/diversion of the remaining buprenorphine in the used patch. The Agency stated that the Sponsor should improve the patch to minimize the risk of abuse. The Sponsor asserted that in their clinical trials the patch has been shown to be safe and questioned the Agency's request for reformulation of the patch. Since there are no set standards for accepting/rejecting a patch based on the residual drug, the Sponsor asked if the current formulation could be approvable if all other issues were addressed in the deficiency letter. The Agency replied that the current formulation could be approved (if all other issues were resolved) because there are no set standards for residual drugs in the patch. The Agency advised the Sponsor to be more proactive by finding a solution to the residual buprenorphine in the patch and minimize the risk to the public.

The Sponsor asked for advice on methods to address the used patch. The Agency replied that the current disposal system described by the Sponsor in their Risk Management Plan was not sufficient (flush the used patch down the toilet). The Agency stated they realize that the patch will never have 0% residual buprenorphine but the Sponsor should develop a means to reduce the residual drug in the used patch. The Sponsor stated they have reviewed the issue of the level of residual buprenorphine and do not believe it to be a problem. The Agency again reiterated their concern that from a public health standpoint there may be a problem with the abuse/diversion potential of the used patch and that the Sponsor should be more concerned.

To address the issues of reformulation the Agency presented the following:

Typically, residual drug in transdermal patches (TDS) patches of various drugs are in the range 30-60 %. Residual buprenorphine is about (b) (4) for Norspan, On the other hand, following the 3-day application of Duragesic, there is about (b) (4) residual fentanyl. The Agency stated that there are inadequacies in the pharmaceutical development report in the NDA. The Agency questioned the limitations of the current formulation, the amine-compatibility of the DuroTak polymeric adhesives, and the reasons for not exploring the use of penetration enhancers.

The Agency discussed the limitation of the current formulation.

Drug flux $J = DKC/h$

- D = diffusion coefficient of the drug in the skin.
- K = skin-vehicle partition coefficient of the drug.
- C = drug concentration in the delivery system.
- h = Thickness of the skin.

K is not sufficient enough to drive the drug efficiently because of the matrix containing levulinic acid, oleyl oleate, povidone and DuroTak (b) (4) adhesives. Saturation concentration (Cs) is (b) (4)%, whereas the drug content in the matrix is (b) (4).

The Agency questioned if the DuroTak (b) (4) adhesives are amine-compatible?

A near 5% drop in potency at the end of 24 months with no concomitant increase in the degradation products indicates the binding of the drug to polymeric adhesive of the patch.

Chemically DuroTak adhesives used in Norspan are (b) (4) based polymer containing (b) (4). Compositionally, there are (b) (4) molecules of (b) (4) per molecule of buprenorphine.

The Agency stated other considerations for pressure sensitive adhesives. In lieu of (b) (4) groups needed for adhesion strength, various tackifiers should have been investigated. The Agency questioned whether other adhesives were investigated before finalizing the Duro Taks and if amine-compatible silicone-based adhesives containing silicate tackifiers were investigated.

The Agency asked if skin penetrations enhancers were examined. The drug flux J is also a function of the skin permeability (P) and drug concentration at saturation in the skin (C) provided there is an excess supply of drug in the delivery system ($J = PC$). Agents such as DMSO and azone act by changing the diffusion coefficient (permeability) of the skin whereas ethanol and macrocyclic ketones and lactones act by increasing the drug solubility in the skin.

Discussion

The Sponsor stated they accept the recommendations and the theories proposed by the Agency. However, the Sponsor stated that the drug load is only a certain portion of the patch and the Agency's calculations are based on the entire patch. The Agency asked if there is data to support the adhesiveness of the patch. The Sponsor stated that there is no in-vitro assay to correlate to in-vivo data. The Sponsor explained that a steel plate test was used to demonstrate adhesion strength. However, the Sponsor stated that drug uptake and its presence in human plasma is related to the adhesiveness of the patch and demonstrated by their PK study. It was unclear during the discussion if skin contact with the inner patch containing the drug is the same as the outer portion of the patch.

The Sponsor stated that the concentration of drug in the drug portion of the patch is close to saturation. Furthermore, tackifiers are derived from naturally occurring components and the use of such components as nickel may produce an allergic reaction in the patient. The Sponsor stated they used the most modern methods available to develop their patch. (b) (4) were used because they provide good tack to the skin and are amine-resistant. The Sponsor stated that the use of skin penetration enhancers, such as DMSO, may cause harm to the patient and therefore they did not pursue this in their development of the patch.

The Sponsor questioned why BTDS was compared to Duragesic. The Agency replied that it was a comparison to a marketed opioid-containing patch and they realize Duragesic was not a gold standard. The high level of residual buprenorphine after the

therapeutic dose makes the BTDS product unique as compared to other patches on the market. The Agency reminded the Sponsor that MS Contin was never as problematic as Oxycontin and thus it is hard to define if/when a drug will be abused. The Sponsor denied that Oxycontin is a problem. The Agency reiterated that the formulation issue cannot prevent the product from being marketed and reminded the Sponsor of the risk if they ignore the possibilities for the potential for diversion/abuse of BTDS. The issue of abuse/diversion must be incorporated into the risk management plan.

The Agency questioned if the Sponsor could improve the efficacy of the delivery system. The Sponsor stated that they believe their system is one of the best modern delivery systems and reminded the Agency about the residual found in hormone patches. The Agency reminded the Sponsor that the focus is on controlled substances, not hormones.

The Sponsor stated that reformulation would not be feasible, as they had explored alternatives already and asked if some type of disposal system would work.

The Agency suggested the Sponsor explore the use of tracers to identify their product. It would benefit the Sponsor to pursue some type of system to enable them to determine that if abuse or diversion does occur, the Sponsor could determine if the abused buprenorphine substances was derived from their product, a counterfeit product, or another company's product. (b) (4)

(b) (4)

(b) (4)

The Agency questioned if some chemical process could be developed to breakdown the buprenorphine after the patch was removed. The Sponsor stated they have examined the possibility of (b) (4) The adhesive layer would be strong enough to prevent removal.

The Agency asked about the possibility of using a heavy isotope to label the buprenorphine. The Sponsor stated they will explore this option as well.

Sponsor's Question (meeting package - February 28, 2002)

6. Purdue notes that there are extensive data on the actual abuse of buprenorphine from more than 20 years of medical use. This includes data on actual abuse of

buprenorphine given parenterally, which would result in substantially higher and more rapid exposure to buprenorphine than is possible using either transdermal or buccal delivery. Please explain why these data are not given precedence over a clinical laboratory study in the assessment of the abuse liability of buprenorphine.

Agency's Response

All data, including chemical, pharmacological, human abuse liability, and epidemiological, are taken into consideration when making a scheduling recommendation. With regard to buprenorphine, data on actual abuse of buprenorphine dosage forms in other countries were also relied upon.

Discussion

This issue was addressed in Issue 60.

Issue 61 (August 31, 2001 NA letter)

The potential for significant diversion of buprenorphine from Norspan is unacceptable for a controlled substance. This risk should be properly addressed by redesigning the patch or modifying the BTDS matrix to limit the residual buprenorphine upon completion of dosing and to reduce significantly the potential for extraction of buprenorphine from the matrix.

Sponsor's Questions (meeting package - February 28, 2002)

1. Purdue understands that a finding of significant potential for abuse or diversion is implicit in the definition of a controlled substance. Therefore, Purdue requests clarification as to what is meant by "potential for significant diversion" and the basis for the Division's determination that the risk of buprenorphine diversion from Norspan is unacceptable. Purdue is unaware of any information either contained within our NDA or through other sources that would lead to such a conclusion.

Agency's Response

The major problem is that BTDS can be used for its intended purpose and then diverted. A substantial number of 0.3 mg buprenorphine doses remain in a 20 mg BTDS after it has been used. Buprenorphine can be easily extracted from used and unused patches and abused.

In addition, the plasma concentration of buprenorphine can be increased by applying heat to BTDS, by applying it to a site that has recently been a BTDS application site, by applying multiple BTDS patches, and by chewing or altering BTDS in other ways and then allowing absorption of the drug to occur through the buccal mucosa.

Discussion

This was addressed in Issue 60

Sponsor's Question (meeting package - February 28, 2002)

2. The Division appears to believe that limiting the residual buprenorphine upon completion of dosing is a potential remedy to the Division's concern of diversion. Purdue requests clarification as to the acceptable limit of residual buprenorphine in a transdermal system and further requests specific clarification as to how this limit was determined.
3. The Division has noted that the system should be re-designed to address diversion risk. Purdue requests clarification as to how the Division has determined that such a step is necessary for this product as distinct from other controlled substances, including other transdermal systems. Purdue also requests clarification as to the specific characteristics that would be considered acceptable as no guidance is contained in the paragraph and the company is unaware of any approved transdermal systems with such characteristics.

Agency's Response

In its current form, the formulation is able to deliver only about (b) (4) of the drug, leaving behind nearly (b) (4) of undeliverable drug in the TDS patch. While it is true that the process is diffusion controlled, typically the transdermal systems deliver much more efficiently than is delivered by Norspan. In our opinion, a good pharmaceutical development program should have investigated various approaches for efficient delivery of buprenorphine.

Discussion

This was addressed in the discussion of Issue 60

Issue 62 (August 31, 2001 NA letter)

Adequate adhesion characteristics of the patch should be ensured. This deficiency may affect the efficacy and diversion potential of this product.

Sponsor's Question (meeting package-February 28, 2002)

1. Adhesion characteristics have been documented in prospectively collected data as part of clinical pharmacology studies BP96-0702, BP96-0803, and BP98-1204. These studies were provided as part of NDA 21-306. During efficacy studies, no treatment-limiting adhesion problems were identified. Please identify the specific deficiencies the Division has identified in this data or any other data in our application and list the specific reasons why these deficiencies are considered to render Norspan not approvable.

Agency's Response

The question relates to drug product quality and has been covered in the CMC question # 35 of the Agency letter dated August 31, 2001.

Meeting minutes concurred by meeting chair, Cynthia McCormick, M.D. (4/24/02)

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/s/

Sara Shepherd
4/26/02 12:24:41 PM



NDA 21-306

Purdue Pharma
One Stamford Forum
Stamford, CT 06901-3431

Attention: J. Christopher Prue, RPh
Sr. Director, US Regulatory Affairs

Dear Mr. Prue:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norspan (buprenorphine transdermal system).

We also refer to your January 8, 2002, correspondence containing your disagreements to our November 28, 2001, meeting minutes from the November 6, 2001, end-of-review meeting.

In the following discussion, the statements that the Division acknowledges Purdue's comments on or changes to the minutes is not necessarily an agreement on the contents of those statements.

We have reviewed the referenced material and have the following comments.

1. *“Question 52*

Your analyses of the hepatic impairment study were based on pooled data that do not allow for a reasonable understanding of the correlation between the clinical stage of disease and the pharmacokinetic profile. Reanalyze the data by degree of hepatic impairment into separate subgroups for mild and moderate hepatic impairment.

Purdue Pharma stated that the data were being re-analyzed and will be submitted. The Division replied this was acceptable.”

- The Division acknowledges that there were no points of disagreement.

2. *“Question 53*

The assay used in study BP95-0901 was not validated and therefore, the pharmacokinetic data from that study were not reported. As a trend toward an exposure-response relationship was noted, samples from this study should be reassayed and the data specifically analyzed to assess pharmacokinetic/pharmacodynamic relationships.

Purdue stated there were no remaining blood samples from this study, thus re-analysis of samples was not feasible. The Division concurred with this assessment.”

- The Division acknowledges that there were no points of disagreement.

3. “Question 54

You have not adequately addressed concerns pertaining to potential drug-drug interactions between CYP450 inhibitors and BTDS. Provide data to adequately address these concerns either from available literature or from in vivo drug-drug interaction studies.

Purdue proposed to conduct an *in vivo* drug-drug interaction (DDI) study. The Division stated this was an acceptable approach. Due to time constraints, it was decided that details of the study could be discussed later in a teleconference, if needed.”

Purdue proposed the following revisions:

Purdue proposed to conduct an *in vivo* drug-drug interaction (DDI) study in volunteers using buprenorphine and ketaconazole. The Division stated this was an acceptable approach. Due to time constraints, it was decided that details of the study could be discussed later in a teleconference, if needed.

- The Division acknowledges the revision.

4. “Question 55

You have not provided substantial evidence that the drug will have its intended clinical effect.

In Study BP99-0203, patients were counted as “successfully” treated if their pain evaluations indicated pain relief using a last-observation-carried-forward (LOCF) methodology, regardless of the reason for discontinuation. When patients who were discontinued due to a drug-related adverse event were re-classified as treatment failures, the difference between Norspan and placebo was no longer clinically or statistically significant. While the protocol specified a sample size that was to be sufficient for the demonstration of a statistically significant effect in both hip and knee subgroups, there was no beneficial effect of Norspan in patients with osteoarthritis of the hip compared to placebo in your analysis. In your primary efficacy analysis, the between-group difference in treatment successes is not very large, about 12%, which is notably different from the 30% between-treatment difference specified in the protocol.

While Study BP96-0604 met its protocol-specified primary endpoint, further review of the data calls into question the clinical relevance of the findings. The relatively favorable efficacy results in Norspan patients who dropped out (relative to placebo patients who dropped out) was a factor in the statistical demonstration of a superior effect of Norspan over placebo. Further review of the data indicates that both an endpoint analysis (i.e., an analysis using the last recorded observation on each randomized patient) and a

completers' analysis (i.e., an analysis using the last observation only on patients who completed the protocol) indicate no statistically significant difference between Norspan and placebo. Using only observed data (i.e., no LOCF), there is no clinically meaningful difference in pain reduction after day 60 between placebo- and Norspan-treated patients. Additionally, the magnitude of effect of the between-group difference in mean change from baseline for Pain on the Average and Pain Right Now is of questionable clinical significance.

These findings from Studies BP99-0203 and BP96-0604, coupled with the negative findings from Studies BP96-0101 and BP96-0102, fail to demonstrate the effectiveness of the product for the "management of patients with pain requiring continuous opioid analgesia."

Submit the results of additional adequate and well-controlled studies of appropriate duration and in relevant target populations to provide evidence of the effectiveness of the product and the durability of the treatment effect.

The Division provided the following comments concerning study BP99-0203.

- a. The observed between-group (Norspan vs. placebo) difference in success rate in the overall analysis was 12% (44%-32%), a value that was much less than the protocol-specified anticipated 30% between-group difference.
- b. The observed between-group (Norspan vs. placebo) differences in success rate in the knee subgroup (15%) and the hip subgroup (7%) were both less than the anticipated protocol-specified 30% between-group difference.
- c. The power calculation was based on the ability of the study to show a clinically and statistically significant effect in each stratum.
- d. The protocol appeared to define both the combined population (hip+knee) analysis and the separate analyses of hip and knee as primary endpoints.
- e. The study report treated the analysis of the combined population as the primary endpoint, and the analyses of each joint site as secondary analyses.
- f. The Division concluded that Study BP99-0203 did not demonstrate effectiveness of the product.

The Division described the patterns of discontinuation noted in study BP99-0203. Forty-five patients discontinued due to drug-related adverse events (AE). Of the 31 patients in the Norspan-treated group, 15 were treated "successfully" and 16 were treated "unsuccessfully." Of the 14 placebo-treated patients, 4 were treated "successfully" and 10 were treated "unsuccessfully." It was noted by the Division that patients that could not tolerate the drug and dropped out of the study were

called “successful.” However, if the results with all drug-related discontinuations were changed to “treated unsuccessfully,” the data demonstrated a higher rate of failure in both Norspan and placebo as noted in Table 1.

Table 1

Treatment	Success (n/N) %	Failure (n/N) %	Ratio
Norspan (n/N) %	(50/149) 34%	(99/149) 66%	0.51
Placebo (n/N) %	(48/162) 30%	(114/162) 70%	0.42
Observed Odds Ratio (Ratio Norspan/Ratio Placebo)			1.20

The Division stated that study BP99-0604 was more complex. The primary efficacy analysis (repeated measures [RM] with LOCF) was statistically significant, but appeared driven by stronger efficacy in Norspan dropouts than in placebo dropouts (see Table 2). The least-squares (LS) mean difference was less than the 1.5 planned in the protocol. The RM without LOCF was statistically significant, but there was no difference between Norspan and placebo after day 60; this analysis was more heavily weighted with earlier visits. The endpoint analysis and completers analysis were not statistically significant.

Table 2

	Placebo		Oxy/APAP		Norspan	
	N	%	N	%	N	%
Enrolled	45	100.0	43	100.0	46	100.0
Related to Test Medication	6	13.3	11	25.6	15	32.6
Ineffective Treatment	16	35.6	1	2.3	7	15.2
<i>Source: Sponsor Table 14.1.1.1E</i>						

Purdue presented their arguments about what “meaningful change” is in a clinical trial. Purdue stated that in 21CFR314.126, “the purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.” Purdue was concerned that the Division was too focused over the small difference noted between Norspan and placebo in the clinical trial. Purdue stated that this did not seem consistent with Office or ICH/FDA policy. Purdue stated that the treatment difference was a function of the trial design as well as the drug effect. Purdue stated that in an April 28, 2000 letter from Dr. John Jenkins to R. Crosswell, Dr Jenkins stated “ The Division has appropriately determined that analgesics are examples of drugs for which the minimum expected effect size versus placebo cannot be adequately and reliably determined. This is based on

the fact that there are numerous studies of analgesics that are known to be effective where the analgesic cannot be shown to be superior to placebo.”

[Post Meeting Note: Upon further review of this quote from Dr. Jenkins, the Division would like to state that this quote was taken out of context. The quote relates to the fact that one cannot rely on active control trials that did not show a difference as evidence of effectiveness.]

Purdue further reflected on past data that supported a small treatment difference and used the following examples:

For a medication for refractory seizure disorders a 9% to 15% increase in “adequate seizure control” was acceptable for approval (Neurontin Advisory Committee Meeting, Medical Officer: C McCormick).

For several medications for the treatment of progressive dementia, an effect on cognitive function of about 2.6 units on a 0-70 scale (3.7%) was adequate for approval.

Purdue continued their argument and stated that the FDA has not generally decided that a trial with a statistically significant result on a primary clinical endpoint shows “too small” an effect. This is because the magnitude of the effect seen in “a clinical trial” reflects both clinical effectiveness of a drug and sensitivity of the clinical trial.

Purdue pointed out with data from monotherapy and an add-on therapy, that the latter yielded smaller treatment differences. Purdue concluded that the observed treatment difference was the size expected with an opioid analgesic in these trial designs. No actual data were presented, though Purdue indicated that it planned to submit a summary of multiple analgesic trials in the future.

The Division replied that the issue was not just a treatment effect size. It was difficult to determine the clinically relevant effect size in the clinical trials. A big dilemma was the large dropout rate early in the trial. Purdue should focus on the clinical trial design to avoid AEs in the beginning and consider a possible titration scheme. The Division advised that the small effect could be attributed to the effects of the patients that dropped out. Overall, it was not easy to see effect in patients who continued.

Purdue wondered if the issue was related to robustness and cited ICH E9 1.2, “Robustness implies that the treatment effect and primary conclusions of the trial are not substantially affected when analyses are carried out based on alternative assumptions or analytic approaches.” Purdue presented data on a priori analysis of the clinical trials generating data for repeated measure, last observation and mean of observed pain. The Division agreed that these were useful approaches to looking at data, but noted that these three techniques do not look at everything. All three have one feature in common. All assign a good score for patients who

then drop out of the study. The approaches provide good observation for patients but not AEs. If dropouts due to AEs are included and considered “failures,” then the treatment effect goes away.

Purdue stated that the Division has proposed a new primary outcome measure, global assessment, for BP96-0203 (combination of DOLE and DOAE) and stated that, based on ICH E9 sec 2.2.3, “global assessment variables could lead to 2 products being declared equivalent despite their having very different profiles of beneficial and adverse effects... It is therefore not advisable.” The Division replied that global assessment is not being proposed.

Purdue realized that the objectives for study BP96-0203 were unclear. Purdue questioned whether or not the two subgroups in the trial (hip, knee) could be separated and stated the knee trial had good results. The Division advised Purdue to send in a proposal for comment and suggested that another clinical trial should be considered.

Purdue wanted to know if the Division was raising the hurdles to get the drug approved. The Division advised Purdue that public policy was not changing.”

- Purdue provided several comments to the meeting minutes for issue #55 and the Division has the following responses:
 - a. The Division acknowledges that Purdue stated that they did not believe BP99-0203 and BP96-0604 had failed to show efficacy.
 - b. The Division acknowledges that Study BP99-0203 was incorrectly referred to as BP96-0203 in the minutes.
 - c. The Division acknowledges that Purdue maintains that the quotation from Dr. John Jenkins’ letter is appropriate in the context in which it was presented by Purdue at the end-of-review meeting. The Division maintains that Dr. Jenkins’ statement quoted by Purdue in the statement of “PPLP Significant Differences” is not applicable if for no other reason than that Norspan has not yet been shown to be effective. Clinically and statistically significant superiority of Norspan over placebo must be demonstrated in clinical trials before Norspan can be considered effective. Furthermore, the Division notes that Dr. Jenkins’ letter was not written regarding issues related to the Norspan NDA (21-306) and thus Purdue should submit a copy of this letter to NDA 21-306 if Purdue wishes to use it as a point of discussion.
 - d. The Division acknowledges that the sentence, “The approaches provide good observation for patients but not for AEs,” is not

clear. The point of this sentence is that the analytical approaches that rely on imputation allow for favorable pain scores to be imputed for patients who drop out because of drug-related adverse events.

- e. The Division acknowledges that Study BP99-0203 used a binary (ie, success/failure) outcome as the primary outcome while Study BP96-0604 used pain scores as the primary outcome.
- f. The Division notes that in describing Studies BP96-0101 and BP96-0102 as “negative”, the Division simply meant that the studies failed to show superiority of Norspan over placebo. The Division acknowledges that Purdue maintain that these studies failed to show a difference between treatment and placebo because they lacked sensitivity. The Division has not reviewed the studies in sufficient detail to determine the reason for their being failed studies.
- g. The Division acknowledges the Post Meeting Note: Purdue will provide a package summarizing the company’s position on effect size and robustness in these trials for future discussion in a face-to-face meeting or teleconference.

5. *“Question 56*

The extent of errors and inconsistencies in the safety database and in the safety analyses, especially the clinical laboratory data, preclude meaningful interpretation of the safety data.

- a. Submit safety data in clinical study reports and in an Integrated Summary of Safety (ISS) that are accurate and presented in a clear manner. Safety data in this context refer to the primary safety database, the tables and listings of safety data in the text of the reports and ISS, the tables and listings in appendices, and the text of the reports and of the ISS and their appendices.
- b. Adverse events were not coded consistently. Code all adverse events in the safety database in a consistent manner across all studies.
- c. The intercurrent diseases and conditions that were reported in some of the studies appear to be adverse events. Include in the analysis of adverse events an analysis of intercurrent diseases and conditions, and address how not classifying these events as adverse events may impact the reported rates of adverse events.

As part of this analysis, review all of the events classified under intercurrent diseases and conditions to insure that none meet criteria for a serious adverse event.

The Division advised Purdue it only pointed out some of the data errors and inconsistencies that were found during the review process. Purdue was urged to perform

a full check of all data, analyses, summaries, tables, and listings in all of the study reports. Purdue agreed to check the database thoroughly.”

- The Division acknowledges that there were no points of disagreement.

6. “*Question 57*

The safety analyses did not analyze the effect of BTDS dose on safety outcomes. For all safety measures, include analyses in the ISS that focus on the relationship between BTDS dose at the time of a safety measure and the outcome of the safety measure.

The Division stated that all safety data (adverse events, lab data, vital signs, and other safety measures) should be analyzed by dose being received at the time the event or measure occurred. Purdue agreed.”

- The Division acknowledges that there were no points of disagreement.

7. “*Question 58*

The electrocardiogram data do not analyze electrocardiographic intervals. Include in the ISS analyses of electrocardiographic intervals (e.g., PR, QRS, QT, QTc, etc) in view of reports of cardiotoxicity associated with other opioids.

The Division advised that high-quality ECG data, including analysis of electrocardiographic intervals, was required, even in the absence of any “signal” during *in vitro* testing. Purdue stated that they only have photo copies of the ECG data, making it difficult to analyze the intervals and suggested an *in vitro* electrophysiological study. Their on-going open-label study has a limited number of patients. Purdue stated that if the pre-clinical data were clean, then what was the point of checking the ECGs? The Division advised Purdue to collect the ECG data and suggested searching the public domain for the information. Any data from the public domain raises the issue of whether the NDA is 505(b)(1) or a 505(b)(2) application.”

Purdue proposed the following revisions:

The Division advised that high-quality ECG data, including analysis of electrocardiographic intervals, was required, even in the absence of any “signal” during *in vitro* testing. Purdue stated that they might be able to retrieve photocopies of the ECG data from the archives at some clinical sites, only have photo-copies of the ECG data, making it difficult to analyze the intervals and suggested an *in vitro* electrophysiological study. Purdue stated that they believe that the preclinical information from in vitro electrophysiology experiments is sufficient but if they run additional clinical studies, ECG data will be collected. ~~that they believe Their on-going open-label study has a limited number of patients. Purdue stated that if the pre-clinical data were clean, then what was the point of checking the ECGs?~~ The Division advised Purdue to collect the ECG data and suggested searching the public domain for the information. Any data

from the public domain raises the issue of whether the NDA is 505(b)(1) or a 505(b)(2) application.

- The Division acknowledges these revisions.

8. *“Question 59*

A potential problem with the design of studies BP96-0604 and BP99-0203 was the fact that during the titration period, patients could escalate from one dose to the next dose before seven days – in fact, as early as three days after a dose had been applied. Given the pharmacokinetic characteristics of BTDS, which suggest that the maximum concentration is reached at about 107 hours, titration to a higher dose after only 3 or 4 days on a lower dose may be premature, and may lead to either excessive toxicity, overestimation of the minimum effective dose for a given patient, or both. Address this issue, both in regard to the completed studies, and in the design of future studies.

Purdue provided a detailed response to this issue in the meeting package. It was decided that this could be addressed in a teleconference, if needed. This information will be addressed in the label.”

Purdue proposed the following revisions

Purdue provided a detailed response to this issue in the pre-meeting package. A statement that FDA agreed with Purdue’s position that three days was adequate time for dosing escalation initiated discussion of this item. The data, which was discussed in some detail, showed that plateau buprenorphine concentration is reached mostly on Day 2 using both raw data and Clinical Trial Simulations.. In addition, using the validated population pharmacokinetic model, PPLP provided the population prediction that confirmed dose escalation every 3 days is not premature because buprenorphine concentrations on Day 3 of BTDS wear are similar to buprenorphine concentration on Day 7 of BTDS wear. Dr. Rappaport stated that he found the outlier data interesting and suggested it might be addressed in a separate teleconference. It was decided that this could be addressed in a teleconference, if needed. This information will be addressed in the label.

- The Division acknowledges these revisions but also reminds Purdue that there are outliers that are unaccounted for by their population PK model.

9. *“Question 60*

Further characterize the abuse potential and risk of overdose of buprenorphine in the transdermal formulation. Examples of issues that need to be addressed, include, but are not necessarily limited to the following.

Characterize the bioavailability and pharmacokinetic profile of buprenorphine through the buccal mucosal route in the presence of alcohol, a common accompaniment for orally or transmucosally abused drugs.

The human abuse liability study was reviewed and found to be inconclusive because of the failure to investigate a full range of doses in order to produce low, moderate, and high reinforcing responses to buprenorphine. Failure to use a standard comparator, such as morphine, and failure to obtain plasma levels of buprenorphine renders the study uninterpretable. Repeat this study taking into consideration these design issues.

The Division asked for clarification from Purdue regarding their access to the buccal data since this may relate to 505(b)(1) vs. 505(b)(2).

The Division advised that full characterization include investigation of a full range of doses (and corresponding plasma levels) that would produce low, moderate and high reinforcing responses to buprenorphine. The Division stated that it was important to characterize the physiological effects of a range of Norspan doses to determine the relationship between reinforcing and respiratory depressant effects. Labeling should reflect this.

The Division informed Purdue that rescheduling of the buprenorphine drug substance was in process. The current formulation may require an even higher schedule than originally considered. The Division advised Purdue that the rescheduling may hold up the drug since it cannot be marketed when there is a scheduling action pending.”

Purdue proposed the following revisions:

The Division asked for clarification from Purdue regarding their access to the buccal data since this may relate to 505(b)(1) vs. 505(b)(2). The FDA indicated that the buccal absorption data referenced in the pre-meeting package were appropriate to address the concerns in part A of Question 60 and asked for clarification from Purdue regarding their access to these data since this may relate to 505(b)(1) vs. 505(b)(2).

Purdue requested a face-to-face meeting with the Division and the Controlled Substance Staff for further discussion of these issues.

- The Division acknowledges the revisions.

10. *“Question 61*

The potential for significant diversion of buprenorphine from Norspan is unacceptable for a controlled substance. This risk should be properly addressed by redesigning the patch or modifying the BTDS matrix to limit the residual buprenorphine upon completion of dosing and to reduce significantly the potential for extraction of buprenorphine from the matrix.

The Division stated that the Risk Management Plan has many strong points. Through further discussion over time the details can be finalized. In concept, it has the essential features that are important in a Risk Management Plan (RMP). The Division requested that Purdue submit a detailed proposal for review by the Division and Controlled Substance Staff. A future teleconference may be needed to discuss the details of the plan.

The Division stated that the reformulation may be the definitive approach versus the RMP and advised Purdue that approval may be based on Subpart H.

The Division further advised that the elements proposed in the RMP to address the challenges associated with this formulation, regarding residual buprenorphine in the patch and ease of extraction, do not effectively remedy the problem. Purdue replied that they are developing a prototype disposal system.”

Although Purdue views new clinical trials as a high hurdle at this point, they have considered this option. The Division suggested that, in future development for clinical efficacy, titration to tolerated dose might be a useful approach to minimize the dropout rates associated with these studies.

Purdue proposed the following revisions:

It was agreed that the Division, Controlled Substance Staff, and PPLP would meet in the near future to discuss the Risk Management issue for Norspan.

Post Meeting Note--Purdue believes buprenorphine is inherently safer than some other marketed opioid analgesics when used as directed and that the concern regarding residual can be handled through the RMP.

- The Division acknowledges the revisions and the Post Meeting Note.

11. “POST MEETING NOTE: (this issue was not addressed in the meeting due to time constraints)

Question 62

Adequate adhesion characteristics of the patch should be ensured. This deficiency may affect the efficacy and diversion potential of this product.

Transdermal absorption is in part a function of the degree of skin contact. Hence, adhesion strength is critical to the product’s efficacy. See issue # 35 from the NA letter for the requested technical details. There is additional concern of accidental exposure to unintended persons, such as children, if the patch does not adhere well to the skin.”

Purdue proposed the following:

As a Post Meeting Note, Purdue stated they will address this issue in their response to issue #35 from the NA letter.

- The Division acknowledges the revision.

12. "Action Items/Outcomes

1. Purdue will re-analyze the hepatic impairment study (issue #52).
2. No blood samples remain from BP95-0901, hence reanalysis of samples are not feasible (issue # 53).
3. If needed, Purdue will request a teleconference to discuss the *in vivo* drug-drug interaction study (issue #54).
4. Purdue will send in a proposal for comment about the possibility of separating BP96-0203 into two separate studies (issue #55).
5. Purdue will check the entire ISS database for errors (issue #56).
6. Purdue will analyze the safety data (adverse events, lab data, vital signs and other safety measure) by dose being received at the time the event or measure occurred (issue #57).
7. The Division advised Purdue to collect ECG data (issue #58).
8. If needed, Purdue will request a teleconference to discuss the titration period for studies BP96-0604 and BP99-0203 (issue #59).
9. Purdue will submit a proposal for the RMP to be reviewed by the Division and the Controlled Substance Staff. A teleconference may be needed (issue #60/61)."

Purdue proposed the following revisions:

1. Purdue will re-analyze the hepatic impairment study (issue #52).
2. No blood samples remain from BP95-0901, hence reanalysis of samples are not feasible (issue # 53).
3. If needed, Purdue will request a teleconference to discuss the *in vivo* drug-drug interaction study (issue #54).
4. Purdue will send in a proposal for comment about the possibility of separating BP96-0203 into two separate studies (issue #55).

5. If the FDA statement that “if dropouts due to AEs are considered failures...” Relates to study BP99-0203 rather than BP96-0604, Purdue will submit a response and request further discussion (issue #55).
6. Purdue will submit a summary of multiple analgesic trials (issue #55).
7. Purdue will check the entire ISS database for errors (issue #56).
8. Purdue will analyze the safety data (adverse events, lab data, vital signs and other safety measure) by dose being received at the time the event or measure occurred (issue #57).
9. The Division advised Purdue to collect ECG data in any upcoming studies (issue #58).
10. If requested by FDA, Purdue <will> provide additional information on the outlier analysis, however a teleconference in the issue of adequacy of the dosing interval is not required (issue #59).
11. ~~If needed, Purdue will request a teleconference to discuss the titration period for studies BP96-0604 and BP99-0203 (issue #59).~~
11. Purdue will submit a proposal for the RMP to be reviewed by the Division and the Controlled Substance Staff. ~~A teleconference may be needed (issue #60/61).~~ A meeting with the Division and the Controlled Substances Staff will be held to review risk management issues in detail.

- The Division acknowledges these revisions.

If you have any questions, call Sara E. Shepherd, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Cynthia McCormick
4/2/02 10:01:35 PM



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 (301) 827-7410

REVIEW AND EVALUATION OF CLINICAL DATA

NDA #	21-306
Sponsor	Purdue Pharma, LLP
Generic Name	Buprenorphine Transdermal System
Proprietary Name	Norspan™
Pharmacologic Class	Opioid analgesic
Proposed Indication	“Norspan™ is indicated for the management of patients with pain requiring continuous opioid analgesia”
Submission Date	January 8, 2002
Review Date	January 17, 2002
Medical Reviewer	Gerald J. Dal Pan, MD, MHS
Supervisory Medical Reviewer	Bob Rappaport, MD
Project Manager:	Sara Shepherd

1 Background

The NDA for Norspan™ was found to be Non-Approvable on September 30, 2001. On November 6, 2002, the Sponsor and the Division had an End-of-Review Meeting to discuss the clinical and biopharmaceutics issues in the Non-approvable letter. These were items 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, and 62. On January 8, 2002, the Sponsor submitted a letter detailing points of disagreement with the Division’s meeting minutes. This review responds to those points of disagreement.

2 Responses to Sponsor’s Points of Disagreement

Question 52

Sponsor had no points of disagreement. No Agency response required.

Question 53

Sponsor had no points of disagreement. No Agency response required.

Question 54

Sponsor's points of disagreement relate to clinical pharmacology. The clinical pharmacology staff will review this point and provide any required response.

Question 55

Sponsor's points of disagreement relate to various issues regarding the Division's determination that Studies BP96-0604 and BP99-0203 failed to demonstrate the effectiveness of the product. The Division's responses to the Sponsor's comments are as follows:

The Division acknowledges that Purdue stated that it did not believe BP99-0203 and BP96-0604 had failed to show efficacy.

The Division acknowledges that Study BP 99-0203 was incorrectly referred to as BP96-0203 in the minutes.

The Division acknowledges that Purdue maintains that the quotation from Dr. John Jenkins' letter is appropriate in the context in which it was presented by Purdue at the End-of-Review meeting. The Division maintains that Dr. Jenkins' statement quoted by Purdue in its statement of "PPLP Significant Differences" is not applicable if for no other reason than Norspan has not yet been shown to be effective. Clinically and statistically significant superiority of Norspan over placebo must be demonstrated in clinical trials before Norspan can be considered effective. Furthermore, the Division notes that Dr. Jenkins' letter was not written regarding issues related to the Norspan NDA (21-306) and thus the Sponsor should submit a copy of this letter to NDA 21-306 if it wishes to use it as a point of discussion.

The Division acknowledges that the sentence "The approaches provide good observation for patients but not for AEs" is not clear. The point of this sentence is that the analytical approaches that rely on imputation allow for favorable pain scores to be imputed for patients who drop out because of drug-related adverse events.

The Division acknowledges that Study BP99-0203 used a binary (ie, success/failure) outcome as the primary outcome while Study BP96-0604 used pain scores as the primary outcome.

The Division notes that in describing Studies BP96-0101 and BP96-0102 as "negative", it simply meant that the studies failed to show superiority of Norspan over placebo. The Division acknowledges that Purdue maintains that these studies failed to show a difference between treatment and placebo because they lacked sensitivity. The Division

has not reviewed the studies in sufficient detail to determine the reason for their being failed studies.

Question 56

Sponsor had no points of disagreement. No Agency response required.

Question 57

Sponsor had no points of disagreement. No Agency response required.

Question 58

The Division acknowledges that Purdue will see if they have ECG data in the archives at some clinical sites. The Division also acknowledges that Purdue stated that Purdue believes that preclinical information from in vitro electrophysiology studies is sufficient, but that if additional clinical studies are conducted, ECG data will be collected.

Question 59

Sponsor's points of disagreement relate to clinical pharmacology. The clinical pharmacology staff will review this point and provide any required response.

Question 60

Sponsor's points of disagreement with regard to Question 60a relate to clinical pharmacology. The clinical pharmacology staff will review this point and provide any required response.

With regard to Question 60b, the Division acknowledges that Purdue expressed its intent to request face-to-face meeting with the Division and the Controlled Substances staff to discuss further the human abuse liability study. A meeting, however, will only be scheduled once a formal request has been submitted to the Division.

Question 61

The Division acknowledges that Purdue expressed its intent to request face-to-face meeting with the Division and the Controlled Substances staff to discuss further the Risk Management issues. A meeting, however, will only be scheduled once a formal request has been submitted to the Division.

Question 62

The Division acknowledges that Purdue intends to address the issues in Question 62 in its response to Item 35.

Action Items – Item 5

The Division acknowledges Purdue's proposal to submit a response regarding Study BP99-0203. If at the time of submission, Purdue believes that further discussion of this issue is necessary, Purdue can submit a request for a meeting, which the Division will review.

Action Items – Item 6

The Division acknowledges Purdue's proposal to submit a summary of multiple analgesic trials.

Action Items – Item 9

The Division acknowledges it advised Purdue to collect ECG data in any upcoming studies.

Action Items – Item 10

The Division accepts Purdue's proposal to submit written information on the outlier analysis. The Division agrees that a teleconference on this issue is not necessary at this time.

Action Items – Item 11

The Division acknowledges that Purdue expressed its intent to request face-to-face meeting with the Division and the Controlled Substances staff to discuss further the Risk Management issues. A meeting, however, will only be scheduled once a formal request has been submitted to the Division.

3 Reviewer's Comments

The above comments should be forwarded to the Sponsor.

RECOMMENDATION – Forward comments to Sponsor.

Gerald J. Dal Pan, MD, MHS Date
Medical Officer

Bob Rappaport, MD Date
Deputy Director, DACCADP

CC: **NDA #21-306**
 HFD-170: Division File
 HFD-170: B. Rappaport, MD
 HFD-170: G. Dal Pan, MD, MHS

HFD-170: S. Shepherd, MS

Appears this way on original

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/s/

Gerald DalPan
1/18/02 11:19:25 AM
MEDICAL OFFICER

You've already initialed for entry into DFS.

Bob Rappaport
1/18/02 01:47:45 PM
MEDICAL OFFICER



NDA 21-306
Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Lois Hinman
Sr. Director, US Regulatory Affairs

Dear Dr. Hinman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norspan (buprenorphine transdermal system).

We also refer to your October 15, 2001, submission containing a request for clarification on issues #31 and #32 from the August 31, 2001, not approvable letter.

We have reviewed the referenced material and have the following comments.

Issues #31 and #32 from the not approvable letter pertain to the degradation products in the drug product. The synthetic process impurities and by-products should be controlled in the drug substance. The following thresholds apply to the drug product:

- a. Individual specified impurities: (b) (4)
- b. Individual unspecified impurity: (b) (4)
- c. Individual identified impurity: (b) (4)
whichever is lower.
- d. Individual qualified impurity: (b) (4)

If you have any questions, call Sara E. Shepherd, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Cynthia McCormick
11/20/01 06:34:28 PM



NDA 21-306

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Lois Hinman
Sr. Director, US Regulatory Affairs

Dear Dr. Hinman:

Please refer to the teleconference between Dr. Hinman and Ms. Shepherd on November 9, 2001. The purpose of the meeting was to reach an agreement on the meeting minutes dated October 26, 2001, from the September 26, 2001, teleconference.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Shepherd
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECON

In a November 5, 2001, submission, Purdue requested the following statement be added to the meeting minutes from the September 26, 2001, teleconference concerning issue #51 (pharmacology/toxicology) from the August 31, 2001, not approvable letter.

“Purdue is committed to moving forward with the carcinogenicity program as quickly as possible. If however, Purdue Pharma does not fully address other deficiencies in the non-approvable letter prior to the anticipated 2005 completion of the carcinogenicity studies, the carcinogenicity studies can be completed as a post marketing commitment, as per previous agreement with FDA.”

Ms. Shepherd informed Purdue Pharma during a telephone conversation on November 9, 2001, that the Division agreed to amend the meeting minutes, dated October 26, 2001.

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/s/

Sara Shepherd
11/14/01 10:20:56 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-306

Purdue Pharma
One Stamford Forum
Stamford, CT 06901-3431

Attention: Lois Hinman
Sr. Director, US Regulatory Affairs

Dear Dr. Hinman:

Please refer to the meeting between representatives of your firm and FDA on November 6, 2001. The purpose of the End-of-Review meeting was to discuss clinical issues from the not approvable letter dated August 31, 2001.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Shepherd
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: November 6, 2001

Location: Parklawn Building, Conference Room K (1:00-2:30 PM)

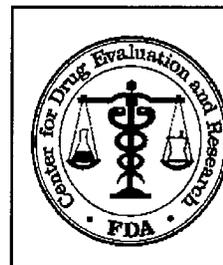
Sponsor: Purdue Pharma L.P.

NDA: NDA 21-306 (Norspan, [buprenorphine transdermal system])

Type of Meeting: End-of-Review meeting

Meeting Chair: Cynthia McCormick, M.D.
Division of Anesthetics, Critical Care and Addiction Drug Products

Meeting Recorder: Sara E. Shepherd, Regulatory Project Manager



Purdue Pharma	Title
Dr. Edward Bryant	Ex. Director, Biostatistics and Clinical Program
Dr. Brian Burke	Sr. Director, Project Management
Dr. Lois Hinman	Sr. Director, US Regulatory Affairs
Dr. Lynn Kramer	Vice President, Medical Research
Dr. Alton Kremer	Executive Medical Director
Dr. Bruce Reidenberg	Medical Director
Dr. Steven Ripa	Medical Director
Dr. Anthony Santopolo	Vice President, US Regulatory Affairs
Dr. Minggao Shi	Sr. Manager, Biostatistics
Dr. Daniel Spyker	Sr. Medical Director
Dr. Paul Goldenheim	Executive VP, R&D
Dr. Ahmed El-Tahtamy	Assoc. Director, Clinical PK
DACCADP	Title
Cynthia McCormick M.D.	Division Director
Bob Rappaport, M.D.	Deputy Director
Gerald Dal Pan, M.D.	Medical Reviewer
Tom Permutt, Ph.D.	Biometrics/Statistician Team Leader
Yaron Harel, M.D.	Medical Reviewer
Suliman Al Fayoumi, Ph.D.	Pharmacokinetics Reviewer
Ravi Harapanhalli, Ph.D.	Chemistry Reviewer
Sara Shepherd, M.S.	Regulatory Project Manager
Hellen Kiruthl	Pharmacy Student
Controlled Substance Staff	Title
Deborah B. Leiderman, M.D.	Director
Ann-Kathryn Maust, M.D.	Medical Reviewer
Kit Bonson, Ph.D.	Pharmacologist
Corinne Moody	Science Policy Analyst

Meeting Objective: The primary objective of the End of Review meeting was to discuss the clinical issues from the August 31, 2001, not approvable letter for Norspan (buprenorphine transdermal system).

General Discussion: Following introductions, the discussion focused on comments from the primary reviewers concerning the information package dated October 8, 2001. Each issue from the August 31, 2001, not approvable letter, addressed in the information package, is listed below in italics.

Question 52

Your analyses of the hepatic impairment study were based on pooled data that do not allow for a reasonable understanding of the correlation between the clinical stage of disease and the pharmacokinetic profile. Reanalyze the data by degree of hepatic impairment into separate subgroups for mild and moderate hepatic impairment.

Purdue Pharma stated that the data were being re-analyzed and will be submitted. The Division replied this was acceptable.

Question 53

The assay used in study BP95-0901 was not validated and therefore, the pharmacokinetic data from that study were not reported. As a trend toward an exposure-response relationship was noted, samples from this study should be reassayed and the data specifically analyzed to assess pharmacokinetic/pharmacodynamic relationships.

Purdue stated there were no remaining blood samples from this study, thus re-analysis of samples was not feasible. The Division concurred with this assessment.

Question 54

You have not adequately addressed concerns pertaining to potential drug-drug interactions between CYP450 inhibitors and BTDS. Provide data to adequately address these concerns either from available literature or from in vivo drug-drug interaction studies.

Purdue proposed to conduct an *in vivo* drug-drug interaction (DDI) study. The Division stated this was an acceptable approach. Due to time constraints, it was decided that details of the study could be discussed later in a teleconference, if needed.

Question 55

You have not provided substantial evidence that the drug will have its intended clinical effect.

In Study BP99-0203, patients were counted as “successfully” treated if their pain evaluations indicated pain relief using a last-observation-carried-forward (LOCF) methodology, regardless of the reason for discontinuation. When patients who were discontinued due to a drug-related adverse event were re-classified as treatment failures, the difference between Norspan and placebo was no longer clinically or statistically significant. While the protocol specified a

sample size that was to be sufficient for the demonstration of a statistically significant effect in both hip and knee subgroups, there was no beneficial effect of Norspan in patients with osteoarthritis of the hip compared to placebo in your analysis. In your primary efficacy analysis, the between-group difference in treatment successes is not very large, about 12%, which is notably different from the 30% between-treatment difference specified in the protocol.

While Study BP96-0604 met its protocol-specified primary endpoint, further review of the data calls into question the clinical relevance of the findings. The relatively favorable efficacy results in Norspan patients who dropped out (relative to placebo patients who dropped out) was a factor in the statistical demonstration of a superior effect of Norspan over placebo. Further review of the data indicates that both an endpoint analysis (i.e., an analysis using the last recorded observation on each randomized patient) and a completers' analysis (i.e., an analysis using the last observation only on patients who completed the protocol) indicate no statistically significant difference between Norspan and placebo. Using only observed data (i.e., no LOCF), there is no clinically meaningful difference in pain reduction after day 60 between placebo- and Norspan-treated patients. Additionally, the magnitude of effect of the between-group difference in mean change from baseline for Pain on the Average and Pain Right Now is of questionable clinical significance.

These findings from Studies BP99-0203 and BP96-0604, coupled with the negative findings from Studies BP96-0101 and BP96-0102, fail to demonstrate the effectiveness of the product for the "management of patients with pain requiring continuous opioid analgesia."

Submit the results of additional adequate and well-controlled studies of appropriate duration and in relevant target populations to provide evidence of the effectiveness of the product and the durability of the treatment effect.

The Division provided the following comments concerning study BP99-0203.

- a. The observed between-group (Norspan vs. placebo) difference in success rate in the overall analysis was 12% (44%-32%), a value that was much less than the protocol-specified anticipated 30% between-group difference.
- b. The observed between-group (Norspan vs. placebo) differences in success rate in the knee subgroup (15%) and the hip subgroup (7%) were both less than the anticipated protocol-specified 30% between-group difference.
- c. The power calculation was based on the ability of the study to show a clinically and statistically significant effect in each stratum.
- d. The protocol appeared to define both the combined population (hip+knee) analysis and the separate analyses of hip and knee as primary endpoints.
- e. The study report treated the analysis of the combined population as the primary endpoint, and the analyses of each joint site as secondary analyses.
- f. The Division concluded that Study BP99-0203 did not demonstrate effectiveness of the product.

The Division described the patterns of discontinuation noted in study BP99-0203. Forty-five patients discontinued due to drug-related adverse events (AE). Of the 31 patients in the Norspan-treated group, 15 were treated “successfully” and 16 were treated “unsuccessfully.” Of the 14 placebo-treated patients, 4 were treated “successfully” and 10 were treated “unsuccessfully.” It was noted by the Division that patients that could not tolerate the drug and dropped out of the study were called “successful.” However, if the results with all drug-related discontinuations were changed to “treated unsuccessfully,” the data demonstrated a higher rate of failure in both Norspan and placebo as noted in Table 1.

Table 1

Treatment	Success (n/N) %	Failure (n/N) %	Ratio
Norspan (n/N) %	(50/149) 34%	(99/149) 66%	0.51
Placebo (n/N) %	(48/162) 30%	(114/162) 70%	0.42
Observed Odds Ratio (Ratio Norspan/Ratio Placebo)			1.20

The Division stated that study BP99-0604 was more complex. The primary efficacy analysis (repeated measures [RM] with LOCF) was statistically significant, but appeared driven by stronger efficacy in Norspan dropouts than in placebo dropouts (see Table 2). The least-squares (LS) mean difference was less than the 1.5 planned in the protocol. The RM without LOCF was statistically significant, but there was no difference between Norspan and placebo after day 60; this analysis was more heavily weighted with earlier visits. The endpoint analysis and completers analysis were not statistically significant.

Table 2

	Placebo		Oxy/APAP		Norspan	
	N	%	N	%	N	%
Enrolled	45	100.0	43	100.0	46	100.0
Related to Test Medication	6	13.3	11	25.6	15	32.6
Ineffective Treatment	16	35.6	1	2.3	7	15.2
<i>Source: Sponsor Table 14.1.1.1E</i>						

Purdue presented their arguments about what “meaningful change” is in a clinical trial. Purdue stated that in 21CFR314.126, “the purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.” Purdue was concerned that the Division was too focused over the small difference noted between Norspan and placebo in the clinical trial. Purdue stated that this did not seem consistent with Office or ICH/FDA policy. Purdue stated that the treatment difference was a

function of the trial design as well as the drug effect. Purdue stated that in an April 28, 2000 letter from Dr. John Jenkins to R. Crosswell, Dr Jenkins stated “ The Division has appropriately determined that analgesics are examples of drugs for which the minimum expected effect size versus placebo cannot be adequately and reliably determined. This is based on the fact that there are numerous studies of analgesics that are known to be effective where the analgesic cannot be shown to be superior to placebo.”

[Post Meeting Note: Upon further review of this quote from Dr. Jenkins, the Division would like to state that this quote was taken out of context. The quote relates to the fact that one cannot rely on active control trials that did not show a difference as evidence of effectiveness.]

Purdue further reflected on past data that supported a small treatment difference and used the following examples:

For a medication for refractory seizure disorders a 9% to 15% increase in “adequate seizure control” was acceptable for approval (Neurontin Advisory Committee Meeting, Medical Officer: C McCormick).

For several medications for the treatment of progressive dementia, an effect on cognitive function of about 2.6 units on a 0-70 scale (3.7%) was adequate for approval.

Purdue continued their argument and stated that the FDA has not generally decided that a trial with a statistically significant result on a primary clinical endpoint shows “too small” an effect. This is because the magnitude of the effect seen in “a clinical trial” reflects both clinical effectiveness of a drug and sensitivity of the clinical trial.

Purdue pointed out with data from monotherapy and an add-on therapy, that the latter yielded smaller treatment differences. Purdue concluded that the observed treatment difference was the size expected with an opioid analgesic in these trial designs. No actual data were presented, though Purdue indicated that it planned to submit a summary of multiple analgesic trials in the future.

The Division replied that the issue was not just a treatment effect size. It was difficult to determine the clinically relevant effect size in the clinical trials. A big dilemma was the large dropout rate early in the trial. Purdue should focus on the clinical trial design to avoid AEs in the beginning and consider a possible titration scheme. The Division advised that the small effect could be attributed to the effects of the patients that dropped out. Overall, it was not easy to see effect in patients who continued.

Purdue wondered if the issue was related to robustness and cited ICH E9 1.2, “Robustness implies that the treatment effect and primary conclusions of the trial are not substantially affected when analyses are carried out based on alternative assumptions or analytic approaches.” Purdue presented data on a priori analysis of the clinical trials generating data for repeated measure, last observation and mean of observed pain. The Division agreed that these were useful approaches to looking at data, but noted that these

three techniques do not look at everything. All three have one feature in common. All assign a good score for patients who then drop out of the study. The approaches provide good observation for patients but not AEs. If dropouts due to AEs are included and considered “failures,” then the treatment effect goes away.

Purdue stated that the Division has proposed a new primary outcome measure, global assessment, for BP96-0203 (combination of DOLE and DOAE) and stated that, based on ICH E9 sec 2.2.3, “global assessment variables could lead to 2 products being declared equivalent despite their having very different profiles of beneficial and adverse effects... It is therefore not advisable.” The Division replied that global assessment is not being proposed.

Purdue realized that the objectives for study BP96-0203 were unclear. Purdue questioned whether or not the two subgroups in the trial (hip, knee) could be separated and stated the knee trial had good results. The Division advised Purdue to send in a proposal for comment and suggested that another clinical trial should be considered.

Purdue wanted to know if the Division was raising the hurdles to get the drug approved. The Division advised Purdue that public policy was not changing.

Question 56

The extent of errors and inconsistencies in the safety database and in the safety analyses, especially the clinical laboratory data, preclude meaningful interpretation of the safety data.

a. Submit safety data in clinical study reports and in an Integrated Summary of Safety (ISS) that are accurate and presented in a clear manner. Safety data in this context refer to the primary safety database, the tables and listings of safety data in the text of the reports and ISS, the tables and listings in appendices, and the text of the reports and of the ISS and their appendices.

b. Adverse events were not coded consistently. Code all adverse events in the safety database in a consistent manner across all studies.

c. The intercurrent diseases and conditions that were reported in some of the studies appear to be adverse events. Include in the analysis of adverse events an analysis of intercurrent diseases and conditions, and address how not classifying these events as adverse events may impact the reported rates of adverse events.

As part of this analysis, review all of the events classified under intercurrent diseases and conditions to insure that none meet criteria for a serious adverse event.

The Division advised Purdue it only pointed out some of the data errors and inconsistencies that were found during the review process. Purdue was urged to perform a full check of all data, analyses, summaries, tables, and listings in all of the study reports. Purdue agreed to check the database thoroughly.

Question 57

The safety analyses did not analyze the effect of BTDS dose on safety outcomes. For all safety measures, include analyses in the ISS that focus on the relationship between BTDS dose at the time of a safety measure and the outcome of the safety measure.

The Division stated that all safety data (adverse events, lab data, vital signs, and other safety measures) should be analyzed by dose being received at the time the event or measure occurred. Purdue agreed.

Question 58

The electrocardiogram data do not analyze electrocardiographic intervals. Include in the ISS analyses of electrocardiographic intervals (e.g., PR, QRS, QT, QTc, etc) in view of reports of cardiotoxicity associated with other opioids.

The Division advised that high-quality ECG data, including analysis of electrocardiographic intervals, was required, even in the absence of any “signal” during *in vitro* testing. Purdue stated that they only have photo copies of the ECG data, making it difficult to analyze the intervals and suggested an *in vitro* electrophysiological study. Their on-going open-label study has a limited number of patients. Purdue stated that if the pre-clinical data were clean, then what was the point of checking the ECGs? The Division advised Purdue to collect the ECG data and suggested searching the public domain for the information. Any data from the public domain raises the issue of whether the NDA is 505(b)(1) or a 505(b)(2) application.

Question 59

A potential problem with the design of studies BP96-0604 and BP99-0203 was the fact that during the titration period, patients could escalate from one dose to the next dose before seven days – in fact, as early as three days after a dose had been applied. Given the pharmacokinetic characteristics of BTDS, which suggest that the maximum concentration is reached at about 107 hours, titration to a higher dose after only 3 or 4 days on a lower dose may be premature, and may lead to either excessive toxicity, overestimation of the minimum effective dose for a given patient, or both. Address this issue, both in regard to the completed studies, and in the design of future studies.

Purdue provided a detailed response to this issue in the meeting package. It was decided that this could be addressed in a teleconference, if needed. This information will be addressed in the label.

Question 60

Further characterize the abuse potential and risk of overdose of buprenorphine in the transdermal formulation. Examples of issues that need to be addressed, include, but are not necessarily limited to the following.

Characterize the bioavailability and pharmacokinetic profile of buprenorphine through the buccal mucosal route in the presence of alcohol, a common accompaniment for orally or transmucosally abused drugs.

The human abuse liability study was reviewed and found to be inconclusive because of the failure to investigate a full range of doses in order to produce low, moderate, and high reinforcing responses to buprenorphine. Failure to use a standard comparator, such as morphine, and failure to obtain plasma levels of buprenorphine renders the study uninterpretable. Repeat this study taking into consideration these design issues.

The Division asked for clarification from Purdue regarding their access to the buccal data since this may relate to 505(b)(1) vs. 505(b)(2).

The Division advised that full characterization include investigation of a full range of doses (and corresponding plasma levels) that would produce low, moderate and high reinforcing responses to buprenorphine. The Division stated that it was important to characterize the physiological effects of a range of Norspan doses to determine the relationship between reinforcing and respiratory depressant effects. Labeling should reflect this.

The Division informed Purdue that rescheduling of the buprenorphine drug substance was in process. The current formulation may require an even higher schedule than originally considered. The Division advised Purdue that the rescheduling may hold up the drug since it cannot be marketed when there is a scheduling action pending.

Question 61

The potential for significant diversion of buprenorphine from Norspan is unacceptable for a controlled substance. This risk should be properly addressed by redesigning the patch or modifying the BTDS matrix to limit the residual buprenorphine upon completion of dosing and to reduce significantly the potential for extraction of buprenorphine from the matrix.

The Division stated that the Risk Management Plan has many strong points. Through further discussion over time the details can be finalized. In concept, it has the essential features that are important in a Risk Management Plan (RMP). The Division requested that Purdue submit a detailed proposal for review by the Division and Controlled Substance Staff. A future teleconference may be needed to discuss the details of the plan.

The Division stated that the reformulation may be the definitive approach versus the RMP and advised Purdue that approval may be based on Subpart H.

The Division further advised that the elements proposed in the RMP to address the challenges associated with this formulation, regarding residual buprenorphine in the patch and ease of extraction, do not effectively remedy the problem. Purdue replied that they are developing a prototype disposal system.

Although Purdue views new clinical trials as a high hurdle at this point, they have considered this option. The Division suggested that, in future development for clinical efficacy, titration to tolerated dose might be a useful approach to minimize the dropout rates associated with these studies.

POST MEETING NOTE: (this issue was not addressed in the meeting due to time constraints)

Question 62

Adequate adhesion characteristics of the patch should be ensured. This deficiency may affect the efficacy and diversion potential of this product.

Transdermal absorption is in part a function of the degree of skin contact. Hence, adhesion strength is critical to the product's efficacy. See issue # 35 from the NA letter for the requested technical details. There is additional concern of accidental exposure to unintended persons, such as children, if the patch does not adhere well to the skin.

Action Items/Outcomes

1. Purdue will re-analyze the hepatic impairment study (issue #52).
2. No blood samples remain from BP95-0901, hence reanalysis of samples are not feasible (issue # 53).
3. If needed, Purdue will request a teleconference to discuss the *in vivo* drug-drug interaction study (issue #54).
4. Purdue will send in a proposal for comment about the possibility of separating BP96-0203 into two separate studies (issue #55).
5. Purdue will check the entire ISS database for errors (issue #56).
6. Purdue will analyze the safety data (adverse events, lab data, vital signs and other safety measure) by dose being received at the time the event or measure occurred (issue #57).
7. The Division advised Purdue to collect ECG data (issue #58).
8. If needed, Purdue will request a teleconference to discuss the titration period for studies BP96-0604 and BP99-0203 (issue #59).
9. Purdue will submit a proposal for the RMP to be reviewed by the Division and the Controlled Substance Staff. A teleconference may be needed (issue #60/61).

Meeting minutes concurred by meeting chair, Cynthia McCormick, M.D. (November 26, 2001)

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/s/

Sara Shepherd
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**DEPARTMENT OF HEALTH & HUMAN
SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-306

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Lois Hinman, Ph.D.
Sr. Director, US Regulatory Affairs

Dear Dr. Hinman:

Please refer to the teleconference between representatives of your firm and the FDA on September 26, 2001. The purpose of the telecon was to address issue #51 (pharm/tox) from the August 31, 2001, not approvable letter.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, contact me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Shepherd
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

MEMORANDUM OF TELECON

DATE: Sept. 26, 2001

APPLICATION NUMBER: NDA 21-306

DRUGS: Norspan (buprenorphine TDS)

BETWEEN: Purdue Pharma

Name: Dr. Lois Hinman, Sr. Director, U.S. Regulatory Affairs
Dr. Tony Santopolo, V.P., Regulatory Affairs
Dr. Brian Burke, Sr. Director, Project Management
Dr. Viny Srinivasan, Manager, Non-Clinical Drug Safety Evaluation
Dr. Stanley Stadnicki, Sr. Research Fellow, Non-Clinical Drug Safety Evaluation
Dr. Timothy Sullivan, Executive Director, Non-Clinical Drug Safety Evaluation
Dr. Glenn Van Buskirk, Vice President, Non-Clinical Drug Safety Evaluation

AND

Name: Division of Anesthetic, Critical Care, and Addiction Drug Products
Cynthia McCormick, M.D., Director
Bob Rappaport, M.D., Deputy Director
Gerald Dal Pan, M.D., Medical Reviewer
Thomas Papoian, Ph.D., Supervisory Pharmacologist
Sara E. Shepherd, Regulatory Project Manager

SUBJECT: Purdue submitted a teleconference request on September 18, 2001, to address issue #51 from the August 31, 2001, not approvable letter. Specific questions were sent September 21, 2001.

51. Given the wide variability in plasma drug levels in the chronic toxicity studies conducted in animals, and the fact that humans may require higher doses of buprenorphine as they become tolerant to its effects, conduct an additional 6-month chronic toxicity study in either rabbits or dogs at a maximum tolerated dose to fully assess potential systemic toxicities that may be unrelated to buprenorphine's known pharmacological effects.

After a brief introduction, the discussion focused on question #3 posed by Purdue Pharma in the September 21, 2001, submission.

“We note our Phase IV (sic) commitment to conduct carcinogenicity studies in rat and mouse. We expect to justify dose selection based on achievement of exposure ratios well in excess of 25X clinical plasma concentrations. We believe that conduct of these

carcinogenicity studies could satisfy the request in Question #51, providing a 25-fold safety margin noted above.”

The Division was concerned about the adequacy of the nonclinical data. The plasma levels obtained in the rabbit, mini-pig and dog were variable. There were minimal signs of toxicity. The dermal route chosen for the studies limited the ability to probe for systemic toxicity. If tolerance develops, then other forms of administration may need to be explored to increase the systemic exposure or reach the maximum tolerated dose (MTD).

As mentioned, another issue of concern for the Division was tolerance. The animal studies were completed with a reasonable safety margin relative to the proposed maximum dose of Norspan 20 every week. However, the Division was concerned that people might use higher doses, which would reduce the safety margin, and therefore the animal data would no longer be supportive. Purdue Pharma should conduct an additional animal study with higher systemic exposures.

Purdue Pharma stated that few patients changed their doses during the clinical trials. If tolerance were reached, Purdue Pharma felt that patients would change to another product and not increase the number of patches. However, Purdue's clinicians were not available to discuss this data.

Purdue Pharma stated that their literature survey revealed that buprenorphine has a low intrinsic toxicity and requires a large dose to get a toxic effect. Minimal clinical signs were noted in the animals. The Division stated that there was not much information about long-term exposure and toxicity to buprenorphine. Humans have wider exposures. Two cases of neutropenia were noted in the clinical trials and were of concern to the Division. Purdue Pharma stated the margin of safety range was 3-8X and higher in rabbits versus dogs. One study in dogs had a safety margin of 19X, but minimal histopathology was done in this study and the high rates were from buccal exposure only. In the dog buccal study, Purdue Pharma was looking at routine clinical signs as evidence of pharmacological activity. The Division inquired if any nonpharmacological effects were examined in that study. Purdue Pharma replied that toxicology would be limited. Purdue Pharma could not dose animals for long periods of time by the subcutaneous route due to local irritation.

Purdue Pharma stated they were relying on historical human data from parenteral buprenorphine and looking for novel effects (i.e., localized versus systemic effects) in animals. Purdue Pharma felt they achieved the highest possible exposure using the patch. They would like to obtain higher exposure but are comfortable with the data based on historical data in humans with parenteral buprenorphine. The Division stated that information from a previously approved drug product was not theirs to access. The Division acknowledged that Purdue Pharma could resubmit the NDA as a 505(b)(2) if they needed to rely on the parenteral buprenorphine data. The parenteral buprenorphine, however, was approved for acute pain and the Division stated that the Purdue Pharma product, Norspan, was submitted as a 505(b)(1) application.

The Division informed Purdue Pharma that carcinogenicity studies would no longer be regarded as post marketing study commitments, but now were required for approval. Purdue Pharma replied that they were surprised by this decision to make the carcinogenicity studies a requirement for approval versus a post marketing study commitment since the reproductive

toxicity and carcinogenicity studies were previously agreed to be post marketing commitments. The Division replied that they no longer waive carcinogenicity studies for chronic use products and that the previous decision to make the carcinogenicity studies a post marketing commitment was to not hold up the NDA for a prolonged period of time. Assuming that the timing of the response to the other deficiencies in the not approvable letter may take several years to complete, it is reasonable that the carcinogenicity study not be a post marketing commitment requirement. The Division asked for clarification on the status of the studies. Purdue Pharma replied that initial studies and feasibility studies are ongoing and that it would not be until at least 2005 before all of the studies are completed and all data are analyzed. Specifically, the 28-day study was completed and the 3-month dose range-finding study has been started.

Purdue Pharma asked if interim results from the carcinogenicity studies would be sufficient to fulfill issue #51 from the not approvable letter. The Division agreed this was an acceptable approach. A study in rats, sacrificed at 6 months, with full histopathology would satisfy the Division's concern about systemic toxicity. The Division stated the data would be required for resubmission. Purdue Pharma was still concerned about reaching MTD. The Division stated that a 25X systemic exposure relative to the clinical exposure at the maximum buprenorphine dose would be sufficient. Thus, it was agreed that the 2-year carcinogenicity study could include a group that could be sacrificed at 6 months for interim analysis.

Purdue Pharma requested clarification that the Division was not concerned about the intact product but with the active ingredient. The Division concurred that the issue was addressing possible systemic toxicity to buprenorphine. The carcinogenicity 6-month interim sacrifice study would provide additional information on the systemic toxicity of the active ingredient. Skin painting was discussed as an option since the dermal patch may not achieve the levels needed. Purdue Pharma plans to move forward with the carcinogenicity feasibility studies.

Purdue Pharma will work on developing the carcinogenicity protocols for the Executive Carcinogenicity Assessment Committee (CAC). The 2-year carcinogenicity study will include a 6-month rat interim sacrifice study at a greater than 25X the clinical systemic exposure with full histopathology. However, the Division suggested that Purdue Pharma separate the two protocols since the Executive CAC may have other issues that may delay initiation of the carcinogenicity study. Purdue Pharma agreed to submit the carcinogenicity protocol and the Division agreed to review it in a timely manner. Also Purdue Pharma agreed that a 6-month chronic toxicity study in rats could be conducted separate from the carcinogenicity study to satisfy the Division's concern for addressing possible systemic toxicity of buprenorphine.

Meeting minutes recorded by Sara E. Shepherd

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/s/

Sara Shepherd
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NDA 21-306

DISCIPLINE REVIEW LETTER

Purdue Pharma
One Stamford Forum
Stamford, CT 06901-3431

Attention: Lois Hinman
Sr. Director, US Regulatory Affairs

Dear Dr. Hinman:

Please refer to your November 3, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norspan (buprenorphine TDS).

Our review of the clinical pharmacology and biopharmaceutics section of your submission is complete, and we have identified the following deficiencies:

1. Re-analyze data in study BP97-1102 by hepatic impairment subgroup (i.e.-mild and moderate hepatic impairment subgroups) instead of using pooled data.
2. Re-analyze any samples still available from study BP95-0901 using a validated assay and evaluate the data for PK/PD relationships.
3. Since CYP3A4 is a major determinant of buprenorphine metabolism, address potential drug-drug interactions between CYP450 inhibitors and BTDS.

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

NDA 21-306
Page 2

If you have any questions, call Sara E. Shepherd, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Cathie Schumaker, R.Ph.,
Chief, Project Management Staff
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Cathie Schumaker
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**DEPARTMENT OF HEALTH & HUMAN
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Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-306

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Lois Hinman, Ph.D.
Sr. Director, US Regulatory Affairs

Dear Dr. Hinman:

Please refer to the teleconference between representatives of your firm and the FDA on July 17, 2001. The purpose of the telecon was to discuss several clinical issues raised in your June 18, June 26, and June 28, 2001, submissions regarding 505b(1) vs 505b(2).

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, contact Sara Shepherd, Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Shepherd
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

MEMORANDUM OF TELECON

DATE: July 17, 2001

APPLICATION NUMBER: NDA 21-306

DRUGS: Norspan (buprenorphine TDS)

BETWEEN: Purdue Pharma

Name: Dr. Lois Hinman, Sr. Director, U.S. Regulatory Affairs
Dr. Lynn Kramer, V.P., Medical Research
Dr. Tony Santopolo, V.P., Regulatory Affairs

AND

Name: Division of Anesthetic, Critical Care, and Addiction Drug Products
Cynthia McCormick, M.D., Director
Bob Rappaport, M.D., Deputy Director
Gerald Dal Pan, M.D., Medical Reviewer
Cathie Schumaker, Chief, Project Management Staff
Sara E. Shepherd, Project Manager

SUBJECT: Purdue submitted a teleconference request on June 18, 2001, to address their concerns about the long-term safety database and the 505b(1) vs b(2) issues raised in the teleconferences of December 14 and December 19, 2000. Additional information was sent on June 26, and June 28, 2001, as requested by the Division.

1. *Are there advantages/disadvantages to 505b(1) vs 505b(2)?*

The Division stated that changing NDA 21-306 to a 505b(2) application did not provide any advantages over a 505b(1) application. The Division confirmed that NDA 21-306 qualified as a 505b(1) and regarded the application as complete/fileable.

2. *Is the safety database adequate?*

The extent of the exposure in the safety database is adequate. The database is currently under review.

3. *Other issues?*

- a. A risk management plan was submitted on July 16, 2001. ✓
- b. Purdue will be submitting a final safety report by mid-August (PDUFA date-September 3, 2001). ✓
- c. Purdue will have responses to all outstanding clinical questions by July 27, 2001. ✓

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/s/

Sara Shepherd
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DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG
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Date: *7-16-01*

Pages: *3*
(INCLUDING THIS COVER SHEET)

From: *Sara*

Subject: *NDA 21-306*

Comments: *Questions - Clinical*

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NDA 21-306
Norspan™
Clinical Review of NDA
July 16, 2001

Questions for Sponsor

- 1) Does Table 8.13.7.2.2E in the ISS (Shift Tables of Subject changes in the Clinical Pharmacology Studies) include both placebo-treated and BTDS-treated patients? The ISS methodology (page 267 of the ISS) notes that a “Shift table of screening vs final (end-of-study) values by treatment group” will be provided. The Shift tables provided in Tables 8.14.1.3.1.1 through 8.14.1.3.1.7 appear to be for “All Treatments”. Please explain.
- 2) Were data from Study BP96-0104 included in ISS Table 8.13.7.2.3.1A, since the data listings in Table 8.14.2.3.5.1 in the ISS includes patients from Study BP96-0104?
- 3) Review of hepatic function data from Study 96-0103 indicates that two subjects had isolated marked abnormalities of total bilirubin: Subject 21361 had an end-of-study value of 6.9 mg/dl (no follow-up values available), and Subject 2307 has a value of 7.3 mg/dl, which returned to normal (0.5 mg/dl) at the end of the study. In each case, review of the CRFs revealed that these values were recorded in the “Value Within Normal Range” column, not in the “Abnormal Value” Column. In each case there was no entry in the “Indicate Clinical Significance of Abnormal Value”. In each case, the patient’s total protein value (in g/dl) at the visit was identical to the total bilirubin value (in mg/dl). Is it possible that these two total bilirubin values are data entry errors – for example, transcription errors from the original lab report form to the CRFs? Why was there no comment for such markedly abnormal values? Is there a follow-up total bilirubin value for Subject 21361?
- 4) What was the cut-off time period after the last dose of study medication for including abnormal laboratory values in the analysis of hepatic function tests? For example, Patient 2119 in Study BP99-0203 had mildly elevated AST and ALT at screening (72 and 77 U/L, respectively), which increased to 120 and 122 U/L, respectively, at the end of the study. Neither of these values is more than 3 X ULN (ULN = 48). However, repeat values measured about one week later were above 3 X ULN (AST and ALT were 154 and 152 U/L, respectively). No additional measurements were reported. This patient is not reported in Table 8.14.2.3.5.1 in the ISS – is this because of a time cut-off? Is there any further follow-up laboratory data for this patient?
- 5) Is any further information regarding hepatic function known for the following subjects in the clinical pharmacology studies: Subject 9 in Study BP95-0901, Subject 22 in Study BP95-0901, Subject 8 in Study BP96-1102, and Subject 76 in Study BP98-0201?

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/s/

Sara Shepherd
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DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG
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Rockville, Maryland 20857
Office: 301-827-7410
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To: *Lois Hinman*

Date: *7-10-01*

Fax #: *203 588 6229*

Pages: *4*
(INCLUDING THIS COVER SHEET)

From: *Sara Shepherd*

Subject: *UDA 21306 Clinical Quest*

Comments: *Please respond to these questions
as soon as possible Thanks*

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NDA 21-306
Norspan™
Clinical Review of NDA
July 10, 2001

Questions for Sponsor

- 1) For the Phase 2/3 controlled studies, the open-label study BP96-0103, and the clinical pharmacology studies, generate data listings of all clinically significant abnormal laboratory values (see Section 8.13.7.2.3 of the ISS). Include columns for lab test, protocol number, investigator, patient, normal range, baseline value, most abnormal post-baseline value, final value, study day of most abnormal value, study day of final value, name of study medication, and for BTDS the dose of study medication at the time of the most abnormal value. For each of the three study groupings above, generate two versions of the listing: the first sorted by protocol, investigator, patient, and lab test, and the second sorted by lab test, protocol, investigator, and patient number.
- 2) Review of Table 8.14.2.3.3.1 of the ISS (Laboratory Tests and Their Change From Screening – Summary Statistics) reveals that the mean change from baseline for Specific Gravity in the Placebo group in the forced titration studies is 234.65. Other clinically implausible values include a maximum final value of 20000, a screening mean value of 19.15, and final mean value of 248.69. The minimum and maximum values at screening are 3 and 31, respectively. By way of example, review of the patient data listings (Data Listing 16.2.8 in Study BP96-0101) reveals that Patient 4001 (Investigator 100) had an End of Study specific gravity of 25.00, with normal range for that test reported as LOW – 1.00 and HIGH – 30.00. That patient's case report form (CRF), however, indicates a specific gravity value at that time of 1.025, with no normal ranges reported on the CRF. Further review of the LAB3_A dataset reveals that certain studies, such as BP96-0101 and BP96-0102 have LOW values ranging from 0.00 to 15.00, while the LOW value for BP96-0104 is 10.00 and the corresponding value for BP96-0604 is 1.00. Similarly, the HIGH values for studies BP96-0101 and BP96-0102 range from 25.00 to 35.00, while the HIGH value for study BP96-0104 is 30.00 and the HIGH value for study BP96-0604 is 1.03. Explain the deviation of the specific gravity results in the data listings from those on the CRFs. Also, explain the clinical interpretation of specific gravity measures that do not use the standard 1.000-1.030 scale.
- 3) In the analysis of mean change from baseline for urinalysis values, how were qualitative values such as GLUCOSE – 3+ handled?
- 4) Review of Tables 8.14.1.3.3.1, 8.14.2.3.3.1 (ISS) and 14.3.4.5 (BP96-0103) reveals some values suggestive of data entry errors, which might affect the summary statistics. Address these values, examples of which are presented in the table below:

Table	Laboratory Test	Summary Statistic	Time Point	Value
8.14.1.3.3.1 (ISS)	Globulin	Maximum	Final	38
8.14.1.3.3.1 (ISS)	Phosphorus Inorganic	Maximum	Final	547.99
8.14.2.3.3.1 (ISS)	Hematocrit %	Maximum	Final	399
8.14.2.3.3.1 (ISS)	Chloride	Maximum	Screening	711
14.3.4.5 (BP96-0103)	Calcium	Maximum	Worst Case High Value	94.0
14.3.4.5 (BP96-0103)	Phosphate	Maximum	Baseline	43.0

- 5) Section 8.13.7.2.1 of the ISS notes that “There were no clinically meaningful changes in mean values for any laboratory parameter.” Reference is made to Table 14.3.4.2C in Clinical Study Report BP96-0104. That table is a shift table, not a table of mean changes from baseline. Indicate the location in the NDA of the supporting data for this statement. If a table of mean changes from baseline for laboratory values exists for Phase 2 study BP96-0104, indicate its location in the NDA. If not, generate a table for this study, similar information to Table 8.14.2.3.3.1 in the ISS.

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/s/

Sara Shepherd
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NDA 21-306

DISCIPLINE REVIEW LETTER

Purdue Pharma
One Stamford Forum
Stamford, CT 06901-3431

Attention: Lois Hinman
Sr. Director, US Regulatory Affairs

Dear Dr. Hinman:

Please refer to your November 3, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norspan (buprenorphine TDS).

The Office of Post Marketing Drug Risk Assessment's (OPDRA) review of the proposed tradename, Norspan, and draft carton/containers for your product is complete, and we have identified the following deficiencies:

1. The use of the proprietary name "Norspan" is acceptable at this time. However, if approval of the NDA is delayed beyond 90 days from the date of this letter, the name must be reevaluated. A re-review of the name prior to NDA approval will rule out any objections based on approval of other proprietary names/NDA's.
2. According to the package insert, container labels, and carton labeling, the proprietary name will be associated with the strength of the drug product (Norspan 5, Norspan 10, and Norspan 20). This practice is not recommended (using the number without the unit of measurement) since a practitioner may confuse the number to mean that the patient should use that many patches at one time, giving the patient an overdose of the medication. Also, a pharmacist may view that the number may mean the dispensing amount.
3. For the carton and container labeling (5 mg, 10 mg, and 20 mg), the abbreviation for micrograms must be "mcg" instead of "(b) (4)". The statement (b) (4) should be revised to state "5 mcg buprenorphine/hr" since the (b) (4) can be mistaken as "mg".
4. The symbol "C" for the controlled substance may be confused to be part of the proprietary name. The symbol should be moved to the lower right hand corner for easier visibility on the container and carton.

5. The statement (b) (4)
should be revised to state “Usual Dose: See package insert.”

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

If you have any questions, call Sara E. Shepherd, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Cathie Schumaker, R.Ph.,
Chief, Project Management Staff
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Cathie Schumaker

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Date: *7-6-01*

Fax #: *2035886229*

Pages: *3*
(INCLUDING THIS COVER SHEET)

From: *Sara Shepherd*

Subject: *NDA 21306 Clin. Questions*

Comments:

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NDA 21-306
Norspan™
Clinical Review of NDA
July 6, 2001

Questions for Sponsor

- 1) Apart from the section on "Post-study Analgesics" in each of the Phase 3 protocols, did any of the Phase 3 protocols specify any further directions for post-study treatment with opioid or non-opioid analgesics? Did any of the Phase 3 studies have protocol-specified visits after treatment was discontinued to evaluate patients for withdrawal? ✓
- 2) Explain in more detail the algorithm used to identify patients with suggestions of overdose, abuse, or withdrawal based on COSTART terms (see Section 8.15.6.2.1.1 of the Abuse Liability section of the NDA, page 57). Specifically, explain the phrase "and then dividing by the maximum adverse event score in that body system." Does this refer to the single highest AE score in that body system among all patients? Does this refer to the highest possible AE score in that body system? ✓
- 3) The comment on the Discontinuation page (dataset: DISCON) for Patient No. 4313 in Study BP96-0103 notes "Patient discontinued from study per sponsor request." What was the reason for this request? ✓
- 4) Adverse events for the Phase 3 studies are presented separately for the forced-titration and titration-to-effect studies in the main body of the NDA. In a follow-up submission on May 4, 2001, pooled adverse event data for the Phase 3 studies are presented, including BTDS dose-specific rates for adverse events. None of these analyses, however, provides for an analysis of pooled Phase 3 placebo-controlled studies (BP96-0101, BP96-0102, BP96-0604, and BP99-0203, but excluding BP98-1201). Please provide tables similar in format to those in Attachment 3 and Attachment 4 of the May 4 submission for the pooled Phase 3 placebo-controlled studies.
- 5) Generate a table similar to Table 8.13.5.3D in the ISS for the pooled Phase 3 placebo-controlled studies (BP96-0101, BP96-0102, BP96-0604, and BP99-0203). Include columns for "BTDS 5", "BTDS 10", "BTDS 20" (where those labels refer to the dose at which the AE occurred), "BTDS Total", "Placebo", and "% BTDS Minus % Placebo" (using the BTDS Total value for this comparison). Include all AEs occurring in 2% or more of patients in any of the four BTDS groups listed above, sorted by descending order of frequency in the "BTDS Total" group.
- 6) Generate a table similar to Table 8.13.5.3E in the ISS for the open-label Phase 3 study (BP96-0103). Include columns for "BTDS 5", "BTDS 10", "BTDS 20" (where those labels refer to the dose at which the AE occurred), and "BTDS Total". Include all AEs occurring in one or more patients in any of the four BTDS groups listed above, sorted by descending order of frequency in the "BTDS Total" group.

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/s/

Sara Shepherd
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From: Sara Shepherd

Subject: NDA 21-306 Clinical questions

Comments:

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NDA 21-306
Norspan™
Clinical Review of NDA
June 29, 2001

Questions for Sponsor

- 1) If adverse events (AEs) that led to discontinuations were analyzed and summarized by dose at which the AE occurred in the Phase 3 trials, identify the location of these analyses in the NDA. If not, regenerate Tables 8.14.2.2.20.1 and 8.14.2.2.20.2 in the ISS, Table 8.14.2.2.20.4 in the 120-Day Safety Update, and Table 14.3.2.5 in the BP96-0103 Study Report with additional columns for BTDS 5, BTDS 10, and BTDS 20, so that the incidence of adverse events that led to study discontinuation is presented by dose level at which the AE occurred. In addition, regenerate Table 12.3.1.3C in Study Report BP960103 to include the dose at which the AE occurred, and the dose at which study drug was discontinued.
- 2) If adverse events (AEs) that led to discontinuations were analyzed and summarized by dose at which the study medication was discontinued in the Phase 3 trials, identify the location of these analyses in the NDA. If not, regenerate Tables 8.14.2.2.20.1 and 8.14.2.2.20.2 in the ISS, Table 8.14.2.2.20.4 in the 120-Day Safety Update, and Table 14.3.2.5 in the BP96-0103 Study Report with additional columns for BTDS 5, BTDS 10, and BTDS 20, so that the incidence of adverse events that led to study discontinuation is presented by dose level at which study drug discontinuation occurred. (This table will be similar to the table requested in #1 above if the study drug was discontinued at the same dose at which the AE occurred. If, for example, a patient developed moderate nausea on BTDS 5, which continued at the same severity while on BTDS 10, and the drug was discontinued while on BTDS 10, then the event will be assigned to BTDS 5 in the first table and to BTDS 10 in the second table.)
- 3) If adverse events (AEs) that led to drug interruption were analyzed and summarized by dose at which the AE occurred in the Phase 3 trials, identify the location of these analyses in the NDA. If not, regenerate Table 8.14.2.2.21.1 in the ISS so that the BTDS dose under the TREATMENT heading corresponds to the dose received at the time of the AE that led to drug interruption. Regenerate Table 8.14.2.2.21.2 the ISS and Table 14.3.2.6 in the BP96-0103 study report with three additional columns (BTDS 5, BTDS 10, and BTDS 20), so that the incidence of AEs that lead to drug interruption is presented by dose level at which the AE occurred.
- 4) If adverse events (AEs) that led to drug interruption were analyzed and summarized by dose at which study medication was interrupted in the Phase 3 trials, identify the location of these analyses in the NDA. If not, regenerate Table 8.14.2.2.21.1 in the ISS so that the BTDS dose under the TREATMENT heading corresponds to the dose received at the time of drug interruption. Regenerate Table 8.14.2.2.21.2 the ISS and Table 14.3.2.6 in the BP96-0103 study report with three additional columns (BTDS 5, BTDS 10, and BTDS 20), so that the incidence of AEs that lead to drug interruption

is presented by dose level at which drug interruption occurred. (This table will be similar to the table requested in #3 above if the study drug was interrupted at the same dose at which the AE occurred).

- 5) If adverse events (AEs) that led to dose reduction were analyzed and summarized by dose which required dose reduction in the Phase 3 trials, identify the location of these analyses in the NDA. If not, regenerate Table 8.14.2.2.22.2 the ISS and Table 14.3.2.7 in the BP96-0103 study report with three additional columns (BTDS 5, BTDS 10, and BTDS 20), so that the incidence of AEs that lead to dose reduction is presented by dose level which required reduction.

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/s/

Sara Shepherd
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From: *Sara*

Subject: *more clinical questions*

Comments:

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NDA 21-306
Norspan™
Clinical Review of NDA
June 12, 2001

Questions for Sponsor

- 1) Please send the case report forms (CRFs) for Patient 20209 (Investigator No. 1627) in Study BP960102. (This patient died while participating in open-label study BP96-0103 [patient no. 20304, investigator no, 1627], and CRFs were sent only for the open-label study.)
- 2) The narrative of the death of patient 20304 (investigator no. 1627) in Study BP96-0103 notes that on Study Day 481, she fell at home, and was admitted to the hospital with shortness of breath and a lumbar fracture. Review of adverse event data for this patient indicates that the shortness of breath and lumbar fracture were not reported as either adverse events or serious adverse events. Similarly, the post-hospitalization events leading to her deterioration (atrial fibrillation, anteroseptal infarct, inferior wall infarct, pulmonary edema, and myopathy) are mentioned in the narrative, but are not recorded as serious adverse events in the adverse event dataset. What is the source of this information, and why were these events not in the adverse event database as serious adverse events?
- 3) Some of the clinical studies have a case report form (CRF) for Intercurrent Diseases and Conditions, in addition to CRFs for adverse events. What is the definition of an “intercurrent disease or condition”, and how does this differ from an adverse event? What instructions were investigators given to distinguish between “adverse events” and “intercurrent diseases and conditions”? For example, in Study BP96-0103, Patient 4302 (Investigator No. 100) had an intercurrent illness of “kidney infection” which started on [REDACTED] (b) (6). This event, which started before the patient’s last dose of study medication on [REDACTED] (b) (6), was not recorded on the adverse event CRF. At baseline, this patient had no urogenital medical conditions reported. Why was this kidney infection counted as an “intercurrent illness” and not as an adverse event? How many studies (Phases 1, 2, or 3) used both an “Intercurrent Illness” CRF and an “Adverse Event” CRF? How many patients in each such study had at least one intercurrent illness recorded? How many intercurrent illnesses were recorded in each study? Were these intercurrent illnesses reported in the adverse event database and were they counted in the adverse event frequency tables? Why or why not? Apart from the brief discussion of intercurrent illnesses on page 53 of the ISS, are intercurrent illnesses discussed elsewhere in the ISS?

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/s/

Sara Shepherd
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From: *Sara Shepherd*

Subject: *NDA 21-306*

Comments: *Clin. Quest*

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Questions for Sponsor

- 1) Table 8.13.6.3.2 of the ISS indicates that the serious adverse event (SAE) “cerebrovascular accident” occurring in Patient 2165/2063 was reported to the FDA, but not included in the database. Explain why this SAE was not included in the database. What steps were taken to insure that all adverse events that were serious were reported in the NDA? Was an adverse event designated as serious based solely on the investigators’ designation, or were all adverse events reviewed by the Sponsor for seriousness? Was the investigator’s determination of seriousness re-classified by the Sponsor for any adverse event?

- 2) As was discussed briefly in a telephone conversation between the Division and the Sponsor on Friday, June 7, 2001, the assignment of COSTART terms (variable name ENGLISH in the CO_ADR3 dataset) is not always apparent when looking at the investigator verbatim term (variable name ADR in the CO_ADR3 dataset). The example of pruritus was discussed, and the Sponsor explained that an algorithm was used to classify pruritus-related AEs to either PRURITUS or to PRURITUS AT SITE. Review of several pruritus-related AEs reveals many whose coded term is not evident from the investigator verbatim term (see Attachment I). Some of these are presented in the accompanying table. While a few of the investigator verbatim terms corresponding to the coded term PRURITUS AT SITE can probably be explained by the algorithm briefly presented by the Sponsor in the phone conversation, many can not be explained. Explain the algorithm for coding pruritus-related AEs, and explain how that algorithm results in the coding of AEs in the examples in Attachment I.

- 3) Review of the CO-ADR3 dataset indicates that most AEs of edema in the limbs were coded to the COSTART term PERIPHERAL EDEMA. However, the following terms were coded to EDEMA. Explain this choice of coding terms.

PROTOCOL	INO	PNO	ADR	ENGLISH
BP960101	1215	21005	RIGHT LEG SWOLLEN	EDEMA
BP960101	1248	3027	SWOLLEN LEGS	EDEMA
BP960101	1630	7004	BILAT DECREASED EXT. EDEMA	EDEMA
BP960101	1630	7014	EDEMA LOWER EXT.	EDEMA
BP960101	1630	7027	EDEMA LOWER EXT	EDEMA
BP960101	1692	5010	BILATERAL LE EDEMA	EDEMA
BP960604	1723	3607	SWELLING BOTH HANDS	EDEMA
BP990203	1995	1101	1+ EDEMA LEFT FOOT	EDEMA
BP990203	2062	1057	1+ PITY EDEMA PRE-TIBIAL	EDEMA
BP990203	2062	2058	LOWER LEG EDEMA	EDEMA

- 4) Explain the variable coding if investigator terms “cold”, “cold symptoms”, and related terms:

PROTOCOL	INO	PNO	ADR	ENGLISH	BODYSYS	COMMENT1
BP960101	131	8023	COLD	CHILLS	BODY	
BP960101	131	8023	COLD	CHILLS	BODY	
BP960102	1627	20230	COLD	CHILLS	BODY	
BP960102	1756	29201	COLD	CHILLS	BODY	
BP960102	302	28213	COLD SYMPTOMS	FLU SYNDROME	BODY	
BP960102	1721	26217	COLD SYMPTOMS	FLU SYNDROME	BODY	
BP960604	1820	16607	COLD SYMPTOMS	FLU SYNDROME	BODY	RUNNY NOSE, SORE THROAT, CONGESTED
BP960604	1820	16619	COLD SYMPTOMS	FLU SYNDROME	BODY	
BP960101	100	4021	COLD-LIKE SYMPTONS	INFECTION	BODY	
BP981201	1878	2022	COLD	PHARYNGITIS	RES	PT. TOOK NYQUIL FOR RELIEF
BP990203	1215	2017	COLD	PHARYNGITIS	RES	
BP990203	2061	1161	COLD	PHARYNGITIS	RES	
BP981201	2032	6231	COLD LIKE SYMPTOMS	PHARYNGITIS	RES	
BP981201	1215	5044	COLD SYMPTOMS	PHARYNGITIS	RES	
BP981201	1878	2256	COLD SYMPTOMS	PHARYNGITIS	RES	
BP990203	1741	1137	COLD SYMPTOMS (NASAL CONGESTION & DRAINAGE)	PHARYNGITIS	RES	COLD & FLU RELEIF ANTIHISTAMINE

- 5) Explain the variable coding of the investigator verbatim term “blurred vision” and related terms:

PROTOCOL	INO	PNO	ADR	ENGLISH	BODYSYS	COMMENT1
BP981201	1740	19167	BLURRED VISION	ABNORMAL VISION	SS	
BP981201	1944	16292	BLURRED VISION	ABNORMAL VISION	SS	
BP981201	1944	16292	BLURRED VISION	ABNORMAL VISION	SS	
BP981201	2032	6178	BLURRED VISION	ABNORMAL VISION	SS	
BP990203	2061	2136	BLURRED VISION	ABNORMAL VISION	SS	
BP990203	2067	2153	BLURRED VISION	ABNORMAL VISION	SS	
BP960101	1139	6012	BLURRED VISION	AMBLYOPIA	SS	
BP960101	1693	2020	BLURRED VISION	AMBLYOPIA	SS	REPORTED TO DR. MILLER
BP960101	1741	29008	BLURRED VISION	AMBLYOPIA	SS	
BP960102	302	28203	BLURRED VISION	AMBLYOPIA	SS	
BP960102	302	28213	BLURRED VISION	AMBLYOPIA	SS	
BP960102	1214	25206	BLURRED VISION	AMBLYOPIA	SS	
BP960604	1215	7612	BLURRED VISION	AMBLYOPIA	SS	
BP960101	1630	7011	BLURRY EYES	AMBLYOPIA	SS	
BP981201	2048	17118	BLURRY VISION	ABNORMAL VISION	SS	BLURRY VISION PT HAD BEFORE HER ER VISIT. IT WAS NOTED AT HE
BP990203	2060	1080	BLURRY VISION	ABNORMAL VISION	SS	
BP960101	1248	3018	BLURRY VISION	AMBLYOPIA	SS	
BP960101	1630	7009	BLURRY VISION	AMBLYOPIA	SS	
BP990203	2060	1079	BLURRY VISION IN THE A.M.	ABNORMAL VISION	SS	DATE ENDED UNKNOWN, UNABLE TO CONTACT PATIENT.

6) Explain the variability in the coding of the following gastrointestinal adverse events:

PROTOCOL	INO	PNO	ADR	ENGLISH	BODYSYS	COMMENT1
BP960102	302	28207	ACID REFLUX	DYSPEPSIA	DIG	
BP960102	302	28207	ACID REFLUX	DYSPEPSIA	DIG	
BP960102	302	28207	ACID REFLUX	DYSPEPSIA	DIG	
BP981201	2032	6178	ACID REGURGITATION	VOMITING	DIG	SUBJECT REPORTS AE ENDED WITH PREVACID TREATMENT
BP960604	1139	5601	ACID STOMACH	GASTRITIS	DIG	
BP960102	302	28203	GASTRIC UPSET	DYSPEPSIA	DIG	
BP990203	2060	1078	GASTRIC UPSET	DYSPEPSIA	DIG	
BP960102	1139	6209	GASTROINTESTINAL VIRUS	GASTRITIS	DIG	
BP960102	1574	22215	GASTROINTESTINAL VIRUS	GASTRITIS	DIG	
BP960102	131	8201	GI DISCOMFORT	DYSPEPSIA	DIG	
BP960102	1255	24219	GI DISTRESS	DYSPEPSIA	DIG	
BP960102	1721	26209	GI UPSET	GASTROINTESTINAL DISORDER	DIG	
BP981201	1740	19167	GI UPSET	GASTROINTESTINAL DISORDER	DIG	
BP981201	2035	11094	NERVOUS STOMACH	DYSPEPSIA	DIG	
BP960101	1630	7014	STOMACH ACID	GASTRITIS	DIG	

7) Explain the variable coding of adverse events related to numbness:

PROTOCOL	INO	PNO	ADR	ENGLISH	BODYSYS	COMMENT1
BP990203	2067	1052	NUMB LIPS	PARESTHESIA	NER	
BP960102	302	28207	NUMBNESS FROM LOWER BACK-KNEES	HYPESTHESIA	NER	
BP960101	1692	5020	NUMBNESS	PARESTHESIA	NER	
BP960102	1215	21212	NUMBNESS	PARESTHESIA	NER	
BP960102	1574	22208	NUMBNESS +TINGLNG IN BOTH HAND	PARESTHESIA	NER	
BP960102	1723	27204	NUMBNESS AROUND LIPS	PARESTHESIA	NER	
BP990203	2063	2165	NUMBNESS BILAT HANDS	PARESTHESIA	NER	
BP990203	2067	1052	NUMBNESS BOTH HANDS	PARESTHESIA	NER	
BP960604	1215	7616	NUMBNESS IN ARMS AND HANDS	HYPESTHESIA	NER	
BP960102	1627	20205	NUMBNESS IN FACE	HYPESTHESIA	NER	
BP960101	1248	3001	NUMBNESS IN HAND (RT)	HYPESTHESIA	NER	
BP960101	1248	3001	NUMBNESS IN HANDS	HYPESTHESIA	NER	
BP990203	2065	1064	NUMBNESS IN HANDS	HYPESTHESIA	NER	
BP960102	1627	20204	NUMBNESS IN LEGS	HYPESTHESIA	NER	
BP990203	2064	1092	NUMBNESS LEFT ARM	HYPESTHESIA	NER	
BP960102	1708	23218	NUMBNESS OF LEGS AND BUTTOCKS	HYPESTHESIA	NER	
BP981201	2042	21241	NUMBNESS ON LIPS	PARESTHESIA	NER	
BP981201	2032	6173	NUMBNESS RIGHT ARM	HYPESTHESIA	NER	
BP981201	2042	21083	NUMBNESS RIGHT HAND	HYPESTHESIA	NER	
BP960102	1215	21210	NUMBNESS TO ARM	HYPESTHESIA	NER	
BP960102	1215	21204	NUMBNESS-TOP OF THIGH TO KNEE	HYPESTHESIA	NER	NUMBNESS- FROM TOP OF THIGH TO BOTTOM OF KNEE

- 8) Explain the coding of the following two AEs. Should the gastrointestinal hemorrhage have been a serious adverse event, or was the bleeding not a gastrointestinal hemorrhage?

PROTOCOL	INO	PNO	ADR	ENGLISH	BODYSYS	COMMENT1
BP981201	1878	2028	BLEEDING	GASTROINTESTINAL HEMORRHAGE	DIG	PT. WENT TO ER FOR PRESSURE DRESSING PT. SCRATCHED HIS LEG S
BP960604	100	2601	DIVERTICULITIS	PERIODONTAL ABSCESS	DIG	FLAGYL AND CIPRO

Attachment I – Pruritus-related AEs with unclear relationship between investigator verbatim term and COSTART term

Protocol	Inv	Pat	English	ADR	Comment1
BP960101	1248	3008	PRURITUS	ITCHING	PATCH SITES ITCH AFTER BATHING NECK SCAR ITCHES
BP960102	1574	22201	PRURITUS	ITCHING	AT PATCH SITE
BP960102	1574	22202	PRURITUS	ITCHING	AT PATCH SITES
BP960102	1574	22205	PRURITUS	ITCHINESS	AT PATCH SITES
BP960102	1627	20203	PRURITUS	ITCHING	AT PATCHES
BP960102	1627	20209	PRURITUS	ITCHING	ON BACK AT PATCH SITE
BP960102	1708	23210	PRURITUS	ITCHINESS	ITCHINESS AT ANTERIOR THORAX PATCH
BP960102	1723	27208	PRURITUS	ITCHINESS	AT PATCH SITE
BP960102	1723	27221	PRURITUS	ITCHING	UNDER LARGE AND MEDIUM PATCHES
BP960102	1723	27223	PRURITUS	ITCHING	AT PATCH SITES
BP960604	1627	4606	PRURITUS	ITCHING	ITCHINESS IS AT PATCH SITE ONLY DURING LAST 2-3 DAYS OF
BP960101	1215	21006	PRURITUS AT SITE	ITCHING BODY	
BP960101	1630	7027	PRURITUS AT SITE	ITCHINESS ON CHEST	
BP960102	100	4206	PRURITUS AT SITE	ITCHING ALL OVER	
BP960102	131	8206	PRURITUS AT SITE	ITCHY	
BP960102	302	28203	PRURITUS AT SITE	ITCHING OF FACE AND CHEST	
BP960102	1215	21234	PRURITUS AT SITE	ITCHY	
BP960102	1215	21239	PRURITUS AT SITE	NECK AND CHEST ITCH	
BP960102	1708	23218	PRURITUS AT SITE	ITCHY	
BP960604	1803	6604	PRURITUS AT SITE	ITCHING TORSO	
BP981201	100	22315	PRURITUS AT SITE	ITCHINESS	
BP981201	100	22315	PRURITUS AT SITE	ITCHINESS	
BP981201	1215	5039	PRURITUS AT SITE	ITCHINESS BODY	
BP981201	1215	5185	PRURITUS AT SITE	ITCHING BODY	
BP981201	1215	5307	PRURITUS AT SITE	ITCHING	
BP981201	1215	5307	PRURITUS AT SITE	ITCHING RIGHT ARM	
BP981201	1627	23294	PRURITUS AT SITE	ITCHING	
BP981201	1627	23296	PRURITUS AT SITE	ITCHING	
BP981201	1740	19165	PRURITUS AT SITE	GENERALIZED ITCHING	
BP981201	1807	12269	PRURITUS AT SITE	ITCHING	
BP981201	1820	4005	PRURITUS AT SITE	ITCHING	
BP981201	1825	1045	PRURITUS AT SITE	GENERALIZED ITCHING	

NDA 21-306 (000)

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Clinical Review of NDA

Applications for Sponsor – June 10, 2001

Protocol	Inv	Pat	English	ADR	Comment1
BP981201	1825	1047	PRURITUS AT SITE	ITCHING	
BP981201	1825	1052	PRURITUS AT SITE	ITCHING	
BP981201	1825	1052	PRURITUS AT SITE	ITCHING	
BP981201	1825	1207	PRURITUS AT SITE	ITCHING	
BP981201	1825	1207	PRURITUS AT SITE	ITCHING	
BP981201	1825	1209	PRURITUS AT SITE	ITCHING	
BP981201	1825	1211	PRURITUS AT SITE	ITCHING	
BP981201	1825	1211	PRURITUS AT SITE	ITCHING	
BP981201	1825	1212	PRURITUS AT SITE	ITCHING	
BP981201	1825	1212	PRURITUS AT SITE	ITCHING	
BP981201	1825	1212	PRURITUS AT SITE	ITCHING	
BP981201	1878	2028	PRURITUS AT SITE	ITCHING	
BP981201	1878	2255	PRURITUS AT SITE	GENERALIZED BODY ITCHING	
BP981201	1878	2257	PRURITUS AT SITE	ITCHING	
BP981201	1890	8054	PRURITUS AT SITE	UPPER BODY PRURITIS	
BP981201	1890	8054	PRURITUS AT SITE	ITCHING	
BP981201	1944	16141	PRURITUS AT SITE	ITCHING	
BP981201	2032	6174	PRURITUS AT SITE	ITCHINESS	
BP981201	2032	6174	PRURITUS AT SITE	ITCHINESS	
BP981201	2032	6176	PRURITUS AT SITE	ITCHINESS	
BP981201	2034	10149	PRURITUS AT SITE	ITCHES	
BP981201	2034	10149	PRURITUS AT SITE	ITCHES	SEEMS WORSE IN SUN WITH PERSPERATION
BP981201	2034	10152	PRURITUS AT SITE	ITCHING	PT STATES THE ITCHING HAPPENS THE SAME TIME EVERY DAY.. AT
BP981201	2035	11093	PRURITUS AT SITE	ITCHING	
BP981201	2035	11093	PRURITUS AT SITE	ITCHING	
BP981201	2035	11097	PRURITUS AT SITE	ITCHING	
BP981201	2035	11281	PRURITUS AT SITE	ITCHING	PT. WASHED AREA WITH CLEAR WATER ONLY SEEMED TO HELP.
BP981201	2036	13109	PRURITUS AT SITE	LEFT KNEE ITCHY	
BP981201	2036	13109	PRURITUS AT SITE	SLIGHT ITCHING	
BP981201	2036	13112	PRURITUS AT SITE	ITCHING	
BP981201	2039	18128	PRURITUS AT SITE	ITCH	
BP981201	2039	18130	PRURITUS AT SITE	ITCHING IN BODY ARMS & LEGS	
BP981201	2039	18131	PRURITUS AT SITE	FACIAL ITCHINESS	
BP981201	2039	18131	PRURITUS AT SITE	ITCHY ALL OVER BODY	

NDA 21-306 (000)

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Clinical Review of NDA

Applications for Sponsor – June 10, 2001

Protocol	Inv	Pat	English	ADR	Comment1
BP990203	1995	2081	PRURITUS AT SITE	ITCHY	
BP990203	1995	2101	PRURITUS AT SITE	ITCHY	ACCORDING TO PATIENT "FEELS BUMPY"
BP990203	2060	1079	PRURITUS AT SITE	ITCHING	
BP990203	2060	1080	PRURITUS AT SITE	ITCHING	
BP990203	2060	2077	PRURITUS AT SITE	ITCHING	
BP990203	2060	2077	PRURITUS AT SITE	ITCHING	
BP990203	2061	1163	PRURITUS AT SITE	ITCHING LEFT ARM	
BP990203	2067	1153	PRURITUS AT SITE	ITCHING	
BP990203	2068	2055	PRURITUS AT SITE	ITCHING	
BP990203	2068	2055	PRURITUS AT SITE	ITCHING	

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Applications for Sponsor – June 10, 2001

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Subject: *NDA 21-306*

Comments: *Clinical Q.*

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NDA 21-306
 Norspan™
 Clinical Review of NDA
 June 8, 2001

Questions for Sponsor

- 1) Please send Page 3 of Amendment No. 2 for Protocol BP96-0604, dated March 11, 1998. We note that pages 891-893 of the BP96-0604 clinical study report contain pages 1, 2, and 4 of the amendment.
- 2) Please complete the following table of patient-days of exposure in the Phase 2/3 studies. Please note that data for BTDS 5, BTDS 10, and BTDS 20 should be based on actual dose received. (We realize that some of the data, especially for BTDS, is in the application, but we were unable to locate all of the information requested below.)

Study	Patient-Days of Exposure						
	Treatment						
	BTDS 5*	BTDS 10*	BTDS 20*	BTDS (All)	Placebo	Oxy/APAP	HCD/APAP
BP96-0104							
BP96-0101							
BP96-0102							
All Forced-Titration Studies							
BP96-0604							
BP98-1201							
BP99-0203							
All Titration-to-Effect Studies							
BP96-0103							
All Placebo Controlled Studies							
All Controlled Studies							
All Phase 2/3							
*Based on actual dose received							

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NDA 21-306
Norspan™
Clinical Review of NDA
June 1, 2001

Questions for Sponsor (please respond to these issues as soon as possible).

- 1) There appears to be a discrepancy in the two tables presenting subject disposition for the Phase 1 clinical studies in the ISS. The *Clinical Pharmacology Studies* subsection of section 8.13.3.2 of the ISS, as well as Table 8.13.A.2A in the Appendix, note that 21 subjects discontinued from a Phase 1 clinical study. Tables 8.14.1.1.1 and 8.14.1.1.2 also note that 21 subjects discontinued. In Table 8.14.1.1.3, the *All Studies* subheading indicates that 21 subjects discontinued. However, the sum of the patients in the six subgroups below in Table 8.14.1.1.3 totals 24. Specifically, under each of the subheadings of *Interaction Studies*, *Hepatic Impaired*, and *Elderly Hypertensives*, there is one patient who received BTDS 20 who is listed as Discontinued, though the corresponding percentage is 0. These three patients are not accounted for in Table 8.14.1.1.2. Explain this apparent discrepancy.
- 2) In some studies, it was noted that the rates of delivery of the patches were 12.5, 25, and 50 ug/hr. In later studies, it was noted that the rates of delivery were 5, 10, and 20 ug/hr. Did the formulation change, or did the Sponsor discover that the original rates listed were incorrect?

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NDA 21-306 (000)
Norspan™
Clinical and Statistical Review of NDA
April 3, 2001

Questions for Sponsor

- 1) For Study BP96-0604, analyze “Pain on Average” using the same statistical model as was used in Figure 11.1A in the BP96-0604 Study Report, but with no carry forward. Include the results of a repeated measures analyses from Study Day 21 through Study Day 84 (RM21-84). Present the LS mean results in a table and graphs similar to Figure 11.1A.
- 2) For Study BP96-0604, analyze “Pain Right Now” using the same statistical model as was used in Figure 11.1B in the BP96-0604 Study Report, but with no carry forward. Include the results of a repeated measures analyses from Study Day 21 through Study Day 84 (RM21-84). Present the LS mean results in a table and graphs similar to Figure 11.1B.
- 3) For Study BP96-0604, provide the SAS code for the PROC MIXED procedure used for the repeated measures analysis of both “Pain on Average” and “Pain Right Now.”
- 4) For the pooled titration-to-effect studies (BP96-0604 and BP99-0203) in the Integrated Summary of Efficacy, repeat the repeated measures mixed model analyses for “Pain on Average” and “Pain Right Now” including a treatment-by-age interaction term as a potential covariate.

/s/

Sara Shepherd

4/3/01 09:24:51 AM

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Questions for Sponsor

- 1) Were only “treatment-emergent” adverse events included in the adverse events tables listings? If an algorithm for treatment emergence was used, explain the algorithm.
- 2) For the titration-to-effect studies, it appears that adverse event incidence data are presented for all doses combined, while for forced-titration studies the adverse event incidence rates are presented for the assigned dose. It appears that there are no adverse event incidence rates presented by the dose at which the adverse event actually occurred. If such rates are included in the NDA, provide their location. If such rates are not included in the NDA, generate a table of adverse event rates by dose at which the event occurred. Include data from the forced-titration and the titration-to effect studies. The table can be similar in format to Table 8.14.2.2.1.4 in the 4-month safety update. The rows entitled “BTDS 5 mg”, “BTDS 10 mg”, and “BTDS 20 mg” should contain data for AEs that occurred at that dose level. The row “BTDS regimens combined” should be retained. For AEs occurring in the same patient at different dose levels, explain the method used to assign an AE to a given dose level. For AEs whose onset is after the discontinuation of study medication, explain the method of assigning these AEs to a specific dose level. For consistency with the rest of the safety data in the ISS, generate separate tables for the “worst case” of severity and seriousness, as well as for the “as reported” cases.
- 3) Explain how durations of adverse events and days relative to start of study medication were determined. Were all durations of less than 24 hours taken from the “Duration of Event (<24 hr)” field on the Adverse Experiences CRF, and converted to a fraction of a day? Were other durations determined by calculating the difference between two dates? If yes, was the calculation method used the same as the paradigm set forth in the Guidance for Industry “Providing Regulatory Submissions in Electronic Format – NDAs”, Section IV.K, Item 11.6 (General considerations for datasets)? If not, justify the use of an alternative method of calculation.

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NDA 21-306

Purdue Pharma
One Stamford Forum
Stamford, CT 06901-3431

Attention: Lois Hinman, Ph.D.
Senior Director
U. S. Regulatory Affairs

Dear Dr. Hinman:

We received your March 9, 2001 correspondence on March 12, 2001 requesting a face-to-face meeting or teleconference to discuss your responses to the Agency's letter of December 22, 2000 (specifically FDA questions 11-14) regarding the Norspan (buprenorphine transdermal system) NDA. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

- Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
- Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
- Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at <http://www.fda.gov/cder/guidance/2125fn1.htm>.

You did not indicate the type of meeting requested. However, based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C. As indicated to you in my voice mail message of March 22, 2001 and our telephone conversation on March 23, 2001, the meeting is scheduled for:

Date: April 16, 2001
Time: 1:00 p.m. - 2:00 p.m.
Location: Conference Room "L", 3rd Floor Parklawn Building

NDA 21-306

Page 2

CDER participants: Drs. Deborah Leiderman, Michael Klein, Ann-Kathryn Maust, Katherine Bonson, Silvia Calderon, Bob Rappaport, Gerald Dal Pan, Ms. Sara Shepherd and Ms. Corinne P. Moody

If you have any questions, please call me at (301) 827-1999.

Sincerely yours,

{See appended electronic signature page}

Corinne P. Moody
Science Policy Analyst
Controlled Substance Staff, HFD-009
Office of the Center Director
Center for Drug Evaluation and Research

/s/

Corinne Moody
3/29/01 04:12:10 PM

Sent 3-21-01

NDA 21-306 (000)/ IND 50,273 (SN172)
 Norspan™
 Clinical Review of NDA and of IND Safety Report
 March 21, 2001

Questions for Sponsor

- 1) To analyze the occurrences of neutropenia in Phase 1 studies of BTDS in the NDA, provide the following information:
 - a) Create a line listing of all subjects in the Phase 1 studies who had any post-baseline (ie, after start of study treatment) absolute neutrophil count (ANC) less than 2,000/mm³. Include the following information in the listing:

Pro- to- col	Inv	Pat	Treat- ment Group	Dose	Baseline				Lowest ANC Value				Final ANC Value						
					WBC (/mm ³)	Neutro- phil (%)	Band (%)	ANC (/mm ³)	Study Day*	WBC (/mm ³)	Neutro- phil (%)	Band (%)	ANC (/mm ³)	Study Day*	WBC (/mm ³)	Neutro- phil (%)	Band (%)	ANC (/mm ³)	

*If necessary, specify the Study Day relative to first dose of study medication, as well as the duration from removal of last dose of study medication, if applicable.

- b) Was study drug prematurely discontinued because of neutropenia for any subject in Phase 1 studies?
- c) Was specific treatment for neutropenia necessary for any subject in Phase 1 studies?
- d) To analyze pre- and post-baseline ANCs in all subjects in Phase 1 studies, create the following shift table for each treatment group:

		Lowest Post-baseline ANC (/mm ³)				
		≥ 2,000	1,500 - <2,000	1,000 - <1,500	500 - <1,000	<500
Baseline AUC (/mm ³)	≥ 2,000					
	1,500- <2,000					
	1,000- <1,500					
	500- <1,000					
	<500					

- 2) Repeat analyses 1a-1d for the Phase 2/3 studies in the NDA.
- 3) Provide any additional follow-up (eg, results of tests pending in the hematologist's report) for the SAE of neutropenia reported on March 14, 2001 and on March 20, 2001.

Submit paper copies of the responses to Questions 1-3 to IND 50,273.

Submit the responses to Question 1 and 2 to NDA 21-306, in either electronic or paper format. Regardless of the format of the responses, for each of the tables requested in 1a and 2a, also submit the data in a SAS transport file. In the SAS transport file, include visit number and visit date corresponding to the Study Days.

/s/

Sara Shepherd
3/21/01 10:10:45 AM
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NDA 21-306 (000)
Norspan™
Clinical Review of NDA
March 7, 2001

Questions for Sponsor

Study BP96-0604

1. The datasets for the inclusion criteria (INCLUDE) and exclusion (EXCLUDE) criteria for Study BP96-0604, as well as the corresponding DEFINE.PDF files, can not be located. Please indicate their location in the submission, or provide these datasets if they were omitted from the submission
2. How extensively was the “Pain Site” evaluated and documented by the investigator? Were standard criteria used across all investigational sites?
3. How extensively was the “Disease/Condition Causing the Back Pain” evaluated and documented by the investigator? Were standard criteria used across all investigational sites?
4. Provide a table of laboratory values for Study BP96-0604 similar to Table 14.3.4.3 in Study BP99-0203 (ie, include N, Mean, Std. Error, Median, Min, Max for each lab test at Screening, Final Visit, and change from Screening to Final.) If such a table was included for Study BP96-0604 in the submission, provide its location.
5. Based on the inclusion criteria in Study Protocol BP96-0604, it appears that patients could be taking opiates at the time they were screened for the study. However, opiates for back pain were not permissible concomitant medications (Section 5.3.5.4 of the protocol). Were baseline opiate analgesics in patients who were “opiate-exposed” or “relatively opiate naïve” discontinued or “washed out” for a specified period of time before study medication was started? It appears from Data Listing 16.2.11.2 that the opiate was discontinued the day before the VISIT DATE. Does the VISIT DATE in Listing 16.2.11.2 refer to the date of the baseline visit. Where in the study protocol are the plans for discontinuing or otherwise managing baseline analgesics discussed?

CRTs

1. The file CRT/DATASETS/ndapool3/LAB3.xpt is 41,343 KB in size. Divide this file into two files, based on LAB TYPE (ie, chemistry, hematology, etc), so that each file is less than 25,000 KB in size. All lab tests (ie, LAB KEYs) for a specific LAB TYPE should be in the same file. The division of LAB TYPEs between the two files should be done so that the two files are roughly the same size.

/s/

Sara Shepherd
3/13/01 09:59:35 AM
CSO
Faxed to Purdue

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Thursday, February 25, 2010 12:18 PM
To: 'Fanelli, Richard'
Subject: Clinical IR N21306

Hi Rich –

Hope you're enjoying the skiing.
 Below is a clinical IR – we'd like to get a response by tomorrow late afternoon, if possible.

Thanks
 matt

For Studies 3015 and 3024, provide a table for each study, summarizing major protocol violations by type for each treatment arm.

A table could look like:

Violation Type	BTDS 20 N (%)	Placebo N (%)
Did not meet randomization criteria	# (%)	# (%)
Took prohibited medication	# (%)	# (%)
ETC		

Thanks,
 Matt

 Matthew W. Sullivan, M.S.
 Regulatory Project Manager
 Division of Anesthesia, Analgesia
 and Rheumatology Products
 Food and Drug Administration
 Phone 301-796-1245
 Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov



**FAX
TRANSMISSION**

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG
PRODUCTS

5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
Office: 301-827-7410
Fax: 301-480-8682/301-443-7068

To: *Lois Hinman*

Date: *2-22-01*

Fax #: *203-588-6229*

Pages: *3*
(INCLUDING THIS COVER SHEET)

From: *Sara Shepherd*

Subject: *Clinical Question for 21-306*

Comments:

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notify us immediately by telephone and return it to us at the above address.

NDA 21-306 (000)
Norspan™
Clinical Review of NDA
February 22, 2001

Questions for Sponsor

Protocol BP99-0203:

1. What was the intent of the phrase “patients suffering with osteoarthritis pain ***secondary to a flare*** in the knee or hip” (emphasis added) in the protocol objective? How did investigators assess or record the presence of a flare, as the formal entry criteria do not specify a flare, and the CRFs have no place to record the presence of a flare?
2. How many patients were screened for the study? How many patients were screened but did not enter the ibuprofen Run-In Period? How many patients entered the ibuprofen Run-In period but were not randomized?
3. How many patients were enrolled at the time of each protocol amendment? (It appears that Amendment 1 occurred before enrollment began.)
4. It appears that the change of ibuprofen dose during the Run-In Period in Amendment 1 was from 200 mg QID to 400 mg TID. Amendment 2 also changed the dose of ibuprofen during the Run-In Period from 200 mg QID to 400 mg QID. Should not Amendment 2 have changed the dose from 400 mg TID to 400 mg QID?
5. Are the actual Case Report Forms the most recently corrected version? For example, Patient 100-2194 is listed in Data Listing 16.2.1 as having discontinued due to an adverse event related to test medication (itching), and the AE listing (Data Listing 16.2.7.1) indicates that the “TEST MED ACTION TAKEN” was “MED DISCONT”. However, the AE CRF for this patient does not capture the fact that an episode of itching led to study drug discontinuation. Please explain.
6. How were protocol violations defined, apart from the definition in Section 10.2 of the Study report? Were they prospectively defined? Who determined if a protocol deviation constituted a protocol violation?

Study BP96-0604

7. How many patients were screened for this study?
8. Please provide a by-patient listing with the following information for all patients in Study BP96-0604:

NDA 21-306 (000)
Norspan™
Clinical Review of NDA
Question for Sponsor – February 22, 2001

Inv. No.	Pat. No.	Treatment Group	Study Completion	Completed or Reason for Discontinuation	Study Day of			LOCF Value		
					Completion or Discont.	Last Dose	Pain Scores Used in LOCF Analyses		Pain on Average	Pain Right Now
							Actual	Visit		

The “Study Completion” and “Completed or Reason for Discontinuation” should be the same data as are found in Data Listing 16.2.1. The “Study Day of Study Completion or Discont” and the “Study Day of Last Dose” should be the study days corresponding to the appropriate dates in Data Listing 16.2.1. The “LOCF Value – Pain on Average” and the “LOCF Value – Pain Right Now” should correspond to the LOCF values in Data Listing 16.2.6.1.2 and should be the LOCF values used in the primary and secondary analyses. There is no need to put values other than the LOCF values in this listing. The “Study Day of Pain Scores Used in the LOCF Analyses - Actual” should be the study day corresponding to the day the LOCF value was assessed, as noted in Data Listing 16.2.6.1.2. The “Study Day of Pain Scores Used in the LOCF Analyses - Visit” should be the study day corresponding to the Visit when the LOCF value was assessed, as noted in Data Listing 16.2.6.1.2. Please provide both a printed version of this listing as well as a SAS transport file.

General

- The nature and content of many datasets, especially derived data sets, in the CRT folder is not apparent from their names. The “Description of Dataset” in the DEFINE.PDF folder generally is the same as the dataset name, and thus does not help to describe the dataset. Given that many start with “II_”, is there some system for interpreting the names of these datasets? If not, please provide more descriptions of these datasets that clarify the dataset name. In terms of priority, Studies BP99-0203 and BP96-0604, followed by the ISS datasets (including any new datasets submitted with the 120-Day Safety Update), should have the highest priority.

/s/

Sara Shepherd
3/13/01 09:56:19 AM
CSO



**DEPARTMENT OF HEALTH & HUMAN
SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-306

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Lois Hinman, Ph.D.
Sr. Director, US Regulatory Affairs

Dear Dr. Hinman:

Please refer to the teleconference between representatives of your firm and the FDA on December 15, 2000. The purpose of the telecon was to discuss several clinical issues and one chemistry issue. These issues were faxed to your firm on December 14, 2000.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, contact Sara Shepherd, Project Manager, at (301) 827-7430.

Sincerely,

Sara E. Shepherd
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

MEMORANDUM OF TELECON

DATE: December 15, 2000

APPLICATION NUMBER: NDA 21-306

DRUGS: Norspan

BETWEEN: Purdue Pharma

Name: Ms. Kelly Billingham, Sr. Regulatory Associate
Dr. Brian Burke, Director Project Management
Dr. Ron Fitzmartin, Group Executive Director, BCDM
Ms. Alpana Gupta, Group Leader, Statistical Programs, BCDM
Dr. Lois Hinman, Sr. Director, U.S. Regulatory Affairs
Dr. Lynn Kramer, V.P., Medical Research
Dr. Alton Kremer, Executive Medical Director, Medical Research
Dr. Mel Lederman, Medical Director, Scientific Communications
Ms. Catherine Munera, Consultant
Dr. Tony Santopolo, V.P., Regulatory Affairs
Dr. Nelson Sessler, Clinical Research Scientist
Dr. Dan Spyker, Sr. Director, Medical Research

AND

Name: Division of Anesthetic, Critical Care, and Addiction Drug Products
Cynthia McCormick, M.D., Director
Bob Rappaport, M.D., Deputy Director
Gerald Dal Pan, M.D., Medical Reviewer
Tom Papoian, Ph.D., Pharmacology Team Leader
Sara E. Shepherd, Project Manager
Controlled Substance Staff
Ann-Kathryn Yelovich, M.D., Medical Officer,
Katherine Bonson, Ph.D., Pharmacologist
Deborah Leiderman, M.D., Director

SUBJECT: To discuss chemistry, clinical, and abuse liability issues

Chemistry

1. *Are the sites ready for inspection? If not, provide a date when they will be ready for inspection.*

On December 15, 2000, Purdue faxed the location of the sites ready for inspection. This information was located in Attachment 1 to FDA form 356h in the November 3, 2000, NDA submission.

Action: The information submitted was adequate.

Clinical

2. *Safety data and safety analyses in the ISS are presented separately for the two types of dosing regimens, forced titration vs. titration-to-effect. In addition to these tables, safety data should be presented and analyzed for the two dosing regimens combined.*

Purdue stated that the plan for presenting the safety data was presented in the ISS Statistical Analysis Plan submitted to IND 50,273 (#143, April 14, 2000).

3. *The by-patient listings of adverse events in the individual study reports list the stop and start date (ie, calendar date) of the adverse events, with no reference to the study day (ie, day number relative to first day of study drug). From a clinical review point, study day, relative to first day of study drug, is a useful item in a by-patient listing of AEs.*
4. *The by-patient adverse event data listings do not include both the investigator term and the coded term on the same listing. Rather, there is a separate by-patient listing of each adverse event and its coded terms.*
5. *The by-patient adverse event data listings do not include the dose of study medication at the time of the adverse event.*

Purdue stated that responses to questions 2-5 will be submitted as part of the 120-day safety update. However the Division stated that question 2 may be a filing issue and the data are needed prior to the 120-day safety update.

Action: Purdue will compile a single meta table as part of the ISS to answer questions 3 thru 5. They will include a copy for the Controlled Substance Staff. The Division requested that Purdue sort by study and by patient.

6. *No patient profiles have been included in the Case Report Tabulation (CRT) section of the clinical/statistical (CLINSTAT) section of the application.*

Purdue stated that full data sets were submitted to the NDA. This plan was presented to the Division in submission #144 to IND 50,273 on April, 25, 2000. All study reports have patient listings by domain.

Action: The Division will review the need for Patient Profiles.

7. *Is there any table where all studies are pooled for adverse events?*

Purdue stated that they were pooled for exposure, serious adverse events, and hepatic data.

Action: None

8. *Is Purdue adding any new patients?*

Purdue will not add any new patients. The only on-going study is an abuse liability study (9 patients) which will not substantially increase the patient numbers.

9. *Why did Purdue chose 505(b)(1) vs 505(b)(2)?*

Purdue intended the NDA to be 505(b)(1) because they felt they had enough data to justify a (b)(1) vs (b)(2).

10. *What is the status of the reproductive toxicology studies?*

Previous agreements allow these studies to be submitted as a Phase 4 commitment. However the Division urged Purdue to start on the reproductive toxicology studies now and not wait until Phase 4. The carcinogenicity studies can wait until Phase 4. Purdue stated that the protocols were submitted to IND 50,273 (#150) for comment to the Division. The Division stated that the protocols are under review and any comments will be sent to Purdue.

Action: The Division will send comments to Purdue pertaining to submission #150 when the review is complete. ✓

11. *Explain the duration of exposure table and the graph on page 165 of Volume 2.*

Action: Purdue will review the graph and exposure data and provide an explanation of the apparent discrepancy.

12. *Abuse Liability/Scheduling*

The Controlled Substance Staff is reviewing the abuse liability of Norspan separately. The assessment of abuse liability will not be a filing issue. However, Purdue should be aware that the Agency is considering up-scheduling the buprenorphine substance from Schedule V, based on adverse events with the marketed drug product in other countries. Due to this potential change in scheduling, Purdue should develop and submit a risk management plan.

The Controlled Substance Staff will directly contact Purdue concerning abuse liability issues and the location of certain information in the NDA necessary for the review. The Division and Controlled Substance Staff will work together during this review process. The primary project manager (S. Shepherd) will be kept apprised of all communication to ensure documentation and an updated file.

Action: A separate telecon will be scheduled to discuss additional abuse liability issues.

Action: Purdue should begin development of a risk management plan.

/s/

Sara Shepherd
12/22/00 01:11:23 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 20, 2000

To: Lois Hinman, Ph.D.	From: Sara E. Shepherd
Company: Purdue Pharma	Division of Division of Anesthetic, Critical Care, and Addiction Drug Products
Fax number: 203-588-6229	Fax number: 301-480-8682
Phone number: 203-588-7486	Phone number: 301- 827-7430
Subject: Abuse liability issues	

Total no. of pages including cover: 4

Comments:

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NDA 21-306

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Lois Hinman, Ph.D.
Sr. Director, US Regulatory Affairs

Dear Dr. Hinman:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norspan (buprenorphine TDS).

We are reviewing the abuse liability section of your application and have the following information requests. We need your prompt written response to continue our evaluation of your NDA.

Clinical Abuse Liability Issues:

1. Indicate if formal measures of withdrawal or drug-liking were used in any clinical studies.
2. Provide the location of case report forms and narratives for the following patients: patients in appendices 5 and 6 of Abuse Liability Volume 1 (AL V 1); patients who are presented in the Executive Summary of AL V 1, including patients whose numbers are not italicized (e.g., patient from BP 96-0304 who is referred to on p. 76 of AL V 1); patients who showed signs and symptoms of abuse, dependence, or withdrawal involving any substance or signs or symptoms of difficulty tolerating any substance; patients who lost their patches or did not return them; patients who had a history of drug or alcohol abuse or dependence prior to participating in the studies.
3. Clarify what appendices 5 and 6 are and why patients in these appendices were chosen. Examples of some questions are as follows:
 - a. How do appendices 5, 5.1A, and 5.1B relate to each other?
 - b. If appendix 5 includes greater than or equal to 10% of patients with the highest scores for abuse or withdrawal, why does the word "no" appear in the columns for overdose, abuse, and withdrawal in appendix 5?
 - c. What do the titles of appendix 5.1A and 5.1B mean?
 - d. How were the scores in appendix 5.1A and 5.1B generated?
 - e. Why are there comments in appendix 6 that do not appear to be related to overdose, abuse, or withdrawal?

657

- f. Why are there many patient listings with no comments in appendix 6?
4. What were the criteria for inclusion of the case reports summarized in the Executive Summary of AL V 1?
 5. Explain how the Executive Summary in AL V 1 correlates to the appendices. For example, patient 20226 suffered a serious and significant adverse event suggestive of overdose, abuse, or withdrawal (p. 58 of Executive Summary), but is not listed in appendix 5 (which is a listing of greater than or equal to 10 % of patients with the highest total scores for abuse or withdrawal). Provide data including CRFs and narratives for all patients who exhibited signs of overdose alone or of withdrawal.
 6. Explain why only certain patients were included in the overdose summary table (appendix 8 of AL V 2). ✓
 7. Provide data, if collected, from patients following removal of BTDS that assessed withdrawal. ✓
 8. Provide data demonstrating whether there is continued drug absorption following removal and replacement of BTDS, to mimic transfer of BTDS from a patient to another individual. In particular, data should be submitted testing the removal and reapplication of BTDS patches to skin with a secure adhesive tape, such as duct tape.
 9. Provide additional data, if available, investigating whether application of heat to the patch (e.g., through a hot water bottle or heating pad) increases the absorption of buprenorphine from BTDS.
 10. Identify whether discontinuation of BTDS use leads to the development of tolerance, craving and/or withdrawal symptoms that would indicate physical dependence.
 11. Provide a risk management plan that addresses the potential risk for abuse, diversion and overdose of BTDS, given that large amounts of buprenorphine remains in the patch following removal from a patient.

Chemical Extraction Issues:

12. Locate studies that test extraction of buprenorphine from BTDS using other solvents (such as acetone, methanol, ether ethylacetate and ethanol).
13. Locate studies that test whether heating and stirring of the patch or patch pieces for varying amounts of time in each solvent increases the extractability of BTDS.
14. Clarify which BTDS patch will be marketed, since the chemical extraction studies and the clinical abuse liability studies should be conducted on the product intended for marketing.

If you have any questions, call me at (301) 827-7430.

Sincerely,

Sara Shepherd
Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Sara Shepherd
12/22/00 10:47:51 AM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 14, 2000

To: Lois Hinman, Ph.D.	From: Sara E. Shepherd
Company: Purdue Pharma	Division of Division of Anesthetic, Critical Care, and Addiction Drug Products
Fax number: 203-588- 8850 6229	Fax number: 301-480-8682
Phone number: 203-588-7486	Phone number: 301- 827-7430
Subject: Questions for telecon on December 15, 2000	

Total no. of pages including cover: 4

Comments:

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Food and Drug Administration
Rockville MD 20857

NDA 21-306

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Lois Hinman, Ph.D.
Sr. Director, US Regulatory Affairs

Dear Dr. Hinman:

As per our telephone conversation on December 14, 2000, the issues and questions to be discussed during the telecon on December 15, 2000 are listed below.

The abuse liability issues are review issues and will be discussed briefly in the telecon.

Chemistry

1. Are the sites ready for inspection? If not, provide a date when they will be ready for inspection.

Clinical

2. Safety data and safety analyses in the ISS are presented separately for the two types of dosing regimens, forced titration vs. titration-to-effect. In addition to these tables, safety data should be presented and analyzed for the two dosing regimens combined.
3. The by-patient listings of adverse events in the individual study reports list the stop and start date (ie, calendar date) of the adverse events, with no reference to the study day (ie, day number relative to first day of study drug). From a clinical review point, study day, relative to first day of study drug, is a useful item in a by-patient listing of AEs.
4. The by-patient adverse event data listings do not include both the investigator term and the coded term on the same listing. Rather, there is a separate by-patient listing of each adverse event and its coded terms.
5. The by-patient adverse event data listings do not include the dose of study medication at the time of the adverse event.
6. No patient profiles have been included in the Case Report Tabulation (CRT) section of the clinical/statistical (CLNSTAT) section of the application.

If you have any questions, call me at (301) 827-7430.

Sincerely,

Sara Shepherd
Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Sara Shepherd

12/14/00 04:24:25 PM



NDA 21-306

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Lois Hinman, Ph.D.
Sr. Director, US Regulatory Affairs

Dear Dr. Hinman:

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

Name of Drug Product: Norspan (buprenorphine TDS)

Review Priority Classification: Standard (S)

Date of Application: November 3, 2000

Date of Receipt: November 3, 2000

Our Reference Number: NDA 21-306

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 2, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be September 3, 2001, and the secondary user fee goal date will be November 2, 2001.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

NDA 21-306

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7430.

Sincerely,

Sara Shepherd
Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Sara Shepherd
11/14/00 08:59:14 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

PF

IND 50,273

Food and Drug Administration
Rockville MD 20857

Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, Connecticut 06850-3590

MAY 12 1999

Attention: Lois M. Hinman, Ph.D.
Director, U. S. Regulatory Affairs
Drug Regulatory Affairs & Compliance

Dear Dr. Hinman:

Please refer to the telecon between representatives of your firm and FDA on April 13, 1999. The purpose of the telecon was to clarify the reproductive toxicology requirements for an NDA submission for Buprenorphine Transdermal System (BTDS).

As requested, a copy of our minutes of that meeting is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact Nancy Chamberlin, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

IND 50,273

Page 2

cc: Original IND 50,273
HFD-170/Div. Files
HFD-170/CSO Chamberlin
HFD-170 C McCormick
B Rappaport
D Brase
L Jean

Drafted by: N.Chamberlin 5-4-99

Revised: 5-12-99 nc

Initialed by: C. P. Moody 5-10-99

final:

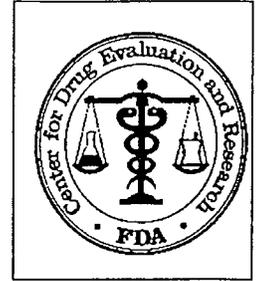
filename: 50273ltr413.doc

CPM/5-11-99

Meeting Minutes for Pharm/tox Telecon

TELCON WITH SPONSOR MINUTES

Meeting Date: April 13, 1999 **Time:** 9:30 -10:30 A.M.
Location: Parklawn Building 9B-45 **Sponsor:** Purdue Pharma L.P.
IND: 50, 273 **Drug:** BTDS



Type of Meeting: Clarification of Pharmtox Requirements for NDA
Meeting Chair: Dou Huey Jean, Ph.D.
External Participant Lead: Lois M. Hinman, Ph.D.
Minutes Recorder: Nancy Chamberlin/ Project Manager

FDA Participants:	Titles:	Offices:
Dou Huey Jean, Ph.D.	Team Leader/Pharmacology	HFD-170
David Brase, Ph.D.	Pharmacology Reviewer	HFD-170
Nancy Chamberlin, Pharm.D.	Project Manager	HFD-170

Purdue Pharma L. P. Participants:	Titles:
Lois M. Hineman, Ph.D.	Director, U.S. Regulatory Affairs
Brian Burke, Ph.D.	Project Manager
Kelly Billingham	Sr. Associate, U.S. Regulatory Affairs
Viny Srinivasan, Ph.D.	Toxicologist
Stan Stadnicki, Ph.D.	Toxicology Consultant

Meeting Objective: The primary objective of this meeting was to clarify for the sponsor the FDA requirements for reproductive toxicity studies for the NDA submission of BTDS .

Background:

FDA informed the sponsor in the December 16, 1998 letter that they would need results of studies of reproductive toxicity (fertility, embryotoxicity, teratogenicity and pre- and post-natal development) and should also state the doses of buprenorphine that were studied as multiples of the Maximum Recommended Human Dose (MRHD) in terms of exposure, i.e., AUC. The firm had planned to use reference literature and FOI information on this topic in the NDA. Also it was the firm's understanding from a 1996 telecon that they would not have to do reproductive studies on this product.

Discussion:

Dr. Jean stated that reproductive studies are needed by the sponsor. She noted that the original NDA studies were not conducted under good laboratory practices (GLP). She requested that the sponsor repeat segment I and III including AUC/ extent of exposure.

The sponsor responded that they have provided literature information and that the transdermal route may not give enough exposure information as compared to what was obtained from the subcutaneous (SC) or intramuscular (IM) routes. They argued that literature information was already known and that Buprenex® was labeled for 1000 times the human dose in animal studies and that it is not teratogenic.

Dr. Jean asked the sponsor if they know what extent of absorption or AUC was in the rats, rabbits by the SC and IM routes. She stated that if they had AUC data in animals, we could do a risk assessment of human exposure.

The sponsor commented that they will do relative exposure prior to their carcinogenicity study. They were still working on the carcinogenicity protocol and have not developed a SC or IM dosing protocol.

Dr. Brase stated that Buprenex's labeling did not provide a basis (mg/kg or mg/m²) for calculations of exposure, so it is not clear what the multiples were based on. It also was mentioned the Buprenex did not have PK data, so we don't have any data for pregnant animals. He asked the sponsor to measure plasma buprenorphine levels in the repro/tox studies and then relate it to those achieved clinically by the highest dose patch.

Dr. Jean stated that the sponsor needs to provide data using good GLPs and that she strongly recommended that they repeat the segment I and III. She expressed a concern about the fertility effects, asked them to look at the effect of the pre- and post- natal development, and to obtain extent of exposure data.

The sponsor wants to continue working on their protocol for carcinogenicity and wanted to discuss whether they could provide the reproductive information as a phase IV commitment. Dr. Chamberlin responded that the people involved in the telecon could not make such a commitment and she recommended that the sponsor fax in a meeting request for further discussion of this issue with Dr. McCormick.

CONCLUSIONS:

The meeting concluded with no agreement on whether the firm would submit the reproductive information to the NDA. It was suggested that the sponsor submit a meeting request to discuss with Dr. McCormick whether the reproductive studies could be conducted as a phase 4 commitment.

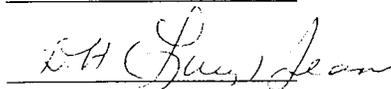
ACTION ITEMS:

- FDA will further discuss this topic with the sponsor.
- FDA will provide the sponsor with a copy of the meeting minutes from this meeting

Minutes Prepared By: N. Chamberlin, Pharm.D.



Minutes Concurred By Chair: D. Jean, Ph.D.



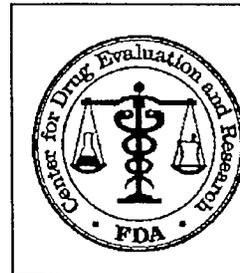
IND 50, 273
Telecon Meeting Minutes April 13, 1999
Page 3

cc: Original IND 50, 273
HFD-170/Div. Files
HFD-170/CSO Chamberlin
HFD-170 C McCormick
 B Rappaport
 L Jean
 D Brase
 C Moody

Drafted by: N.Chamberlin 5-5-99
Revised: 5-7-99nc per David & Lucy, 5-12-99 nc
Initialed: C. P. Moody 5-10-99
Final:
Filed under: #50273Minutes413.DOC
MEETING MINUTES

MEETING MINUTES

Meeting Date: July 14, 1999 **Time:** 10:00a.m. – 11:45 a.m.
Location: Parklawn Building Conference Room "C"
IND: 50,273
Drug: Buprenorphine Transdermal System (BTDS, Norspan® TDS) 5, 10, 20 mg
Sponsor: Purdue Pharma L.P.
Indication: Treatment of chronic pain for up to 7 days
Type of Meeting: Meeting with sponsor to discuss CMC/PK issues prior to NDA filing
Meeting Chair: Bob Rappaport, M.D.
Minutes Recorder: Corinne P. Moody/Chief, Project Management Staff



<u>FDA Attendees: Titles:</u>	<u>Offices:</u>	
Bob Rappaport, M.D.	Deputy Division Director	HFD-170
Albinus D'Sa, Ph.D.	Team Leader/Chemistry	HFD-170
Pat Maturu, Ph.D., M.B.A.	Chemistry Reviewer	HFD-170
Ramana Uppoor, Ph.D.	Team Leader, Pharmacokinetics	HFD-870
Corinne P. Moody	Chief, Project Management Staff	HFD-170

<u>Purdue Pharma L.P.'s representatives:</u>	<u>Titles:</u>
Dr. Brian Burke	Director, Project Management
Dr. Lois Hinman	Director, U.S. Regulatory Affairs
Mr. James Kelly	Associate Director, Regulatory Affairs, CMC
Dr. Philip Palermo	Vice President, Pharmaceutical Analysis
Dr. Bruce Reidenberg	Director, Clinical Pharmacology
Dr. Fred Tonelli	Executive Director, PK/DM
Mr. Ben Oshlack	Vice President, Pharmaceutical Development
Mr. Lino Tavares	Associate Director, Pharmaceutical Development
Dr. Thomas Hille	Pharmacist, Research & Development, Lohmann Therapie-Systeme
Mr. Rudiger Lomb	Manager, Regulatory Affairs Lohmann Therapie-Systeme (LTS)

Meeting Objective: The primary objective of this meeting was to respond to the firm's questions dated June 14, 1999 and advise the sponsor on CMC and pharmacokinetic issues prior to their NDA submission for buprenorphine transdermal system (BTDS). Their proposed indication is the treatment of chronic pain for up to 7 days.

Introduction: Ms. Moody opened the meeting by welcoming the sponsor, and stated that Dr. Bob Rappaport, Deputy Director would chair the meeting due to illness of the Division Director, Dr. Cynthia McCormick. Followed by introductions of all attendees, Dr. Rappaport stated that the November 18, 1998 "pre-NDA" meeting raised a number of concerns regarding their clinical development plan, and suggested that we have another pre-NDA meeting. Per Dr. Hinman, they were planning to submit the NDA in the 2nd quarter of 2000. She commented that they would request another pre-NDA meeting towards the end of this year.

Discussion Points:

Dr. Hinman gave a brief introduction and provided the Agency attendees with copies of their overheads (See attached overheads for details). Dr. Hille (LTS) gave a brief product overview. The discussion focused on the ten questions included in the briefing package as indicated below.

Dr. Hille distributed placebo TDS samples to the attendees and explained the structure and composition of the TDS.

Dr. D'Sa asked the sponsor the following questions:

Q: Of the buprenorphine free base and levulinic acid, what is the ratio in terms of the molar weight?

A: The sponsor responded approximately $\frac{(b)}{(4)}$ moles levulinic acid /buprenorphine base.

Q: Did you use a 1:1 M ratio?

A: See Question 3 on page 4.

Q: Was the composition the same through out for all strengths? Can the same blend be used?

A: Sponsor answered affirmatively to these two questions.

A brief discussion ensued on the total proportionality of the TDS system and the adhesive. The sponsor agreed to send a copy of the video explaining the manufacturing of BTDS to Dr. Maturu's attention prior to submitting the NDA.

SPONSOR'S QUESTIONS:

1. The specifications to be applied for release and stability evaluation of Buprenorphine TDS are presented in the CMC Overview of BTDS (Attachment 1, Table 1.2.5A). The stability specifications are identical to the release specifications with the exception that the stability specifications include quantitation of degradation products which may arise during stability.

The details of the stability testing program are provided in Section 1.2.7 of Attachment 1. The NDA will include 24 month stability data to support the proposed $\frac{(b)}{(4)}$ expiration dating, freeze-thaw temperature cycling evaluations and photostability studies will be performed according to ICH guidelines.

Does FDA have any comments to offer at this time on our proposed specifications for release and stability evaluation?

Dr. Palermo presented the specifications for both release and stability testing for BTDS.

Division response: The attributes, which are tested in the sponsor's specifications, appear acceptable, however, Dr. D'Sa commented that it was premature to make any comments on the specifications. He will need to see the package before making comments. Dr. D'Sa stated that all specifications would be reviewed during the review of the NDA. Dr. Palermo stated that the levels of impurities would be justified in the NDA according to the ICH guidelines. Dr. D'Sa stated that related substances and degradation product testing should be performed at release and during stability studies. Dr. D'Sa also requested that information on in-process testing methods and results as well as an executed batch record be submitted prior to submission of the sponsor's NDA, to aid in the Agency's assessment of the appropriateness of the PPLP specifications.

Dr. Maturu asked the sponsor if there was any overage in the product? Dr. Hille answered that (b) (4) in the manufacture of the product.

There was a brief discussion on how the dissolution method was selected. Drs. Uppoor and D'Sa suggested that information be included on how the 24-hour dissolution test was selected to support the seven-day patch in the NDA. The sponsor stated that the *in vitro* release was being used as a QC tool and that no *in vitro/in vivo* correlation were implied. Drs. Uppoor and D'Sa also requested that the method justification include support for the choice of not less than (b) (4) as the dissolution specification at the last time point instead of (b) (4) release.

2. During the stability program, mass balance is not achieved between a decrease in potency assay and the increase in degradation products (see Attachment 1, Tables 1.2.7A - C, G - 1). We are currently investigating more exhaustive methods of extraction of buprenorphine and potential impurities and plan to submit these data in the NDA.

If extraction studies currently in progress indicate that mass balance is achieved among buprenorphine and the known impurities and no new impurities appear, will these results satisfy the FDA regarding any mass balance considerations?

Dr. Palermo presented a summary of the work in progress to obtain mass balance for the product.

Division response: Dr. D'Sa stated that he could not comment at this time as he needed more information. To answer the question, he needs the following:

- Copies of the analysis and validation of the methods data, to fully assess the data on mass balance presented to date
- Update of the development report (draft was submitted November 1998)
- Cause for loss, e.g. (b) (4) that occurs during manufacture and storage
- Accelerated stability data, which will help clarify the extent of this potential problem

3. During our pre-NDA meeting of November 18, 1998, the FDA requested that PPLP investigate the solid state form of buprenorphine in the patch system. In order to do this, PPLP conducted solid state NMR studies of buprenorphine in the patch. Details of these evaluations

are presented in Attachment 2. Based on the comparison of structural features only the base form was found to exist in the TDS.

We believe these studies adequately address the FDA request. Does the FDA agree?

Dr. Palermo presented the results of the NMR studies that indicated that the form of buprenorphine in the TDS was the free base.

Division response: Dr. D'Sa asked the sponsor if they had made (b) (4). The sponsor answered that they had not successfully made (b) (4). Dr. D'Sa stated that he was not convinced that only buprenorphine was formed in the TDS. Dr. D'Sa indicated that if the (b) (4) does form in the TDS, the product label would have to state as such.

4. A Flux Rate Analysis for the buprenorphine TDS was conducted using three different approaches (i.e., absolute systemic bioavailability, the Wagner-Nelson method for calculating absorption and the residual buprenorphine in the patch). Details of the analyses are presented in Attachment 3. Based on the ranges of buprenorphine delivery observed in the above studies, the recommended release rates for the 5mg, 10mg and 20mg BTDS are 5, 10 and 20 µg/hr respectively. We plan to label the product with this flux ratio.

Does FDA agree with this approach to establishing flux rates?

Dr. Tonelli presented the sponsor's approach and data available in the flux rate determination for BTDS.

Division response: Dr. Uppoor responded that the Agency agrees in general with the sponsor's approach, however, she needed to evaluate the data when the NDA is submitted to see if we agree with the exact values of the flux rate.

Can FDA advise us as to how we may obtain early feedback about the acceptability of the proposed label, which will include flux rate information?

Division response: At this time, we cannot provide feedback on labeling. This is clearly a review issue. Dr. Uppoor stated that this would be a part of the NDA review process.

5. As noted in the process validation overview provided in Attachment 4, IQ, OQ and PO have been completed for the manufacture of buprenorphine TDS using production equipment and three batches (one each produced at low, target and high operating conditions) of each strength at LTS. However, our three consecutive validation batch campaign has not yet been initiated. As buprenorphine is an expensive, controlled substance in short supply and subject to worldwide regulation, PPLP would like to minimize the destruction of such a material by requesting FDA input on the proposed timing for production of the validation batches, relative to submission of the NDA and the PAI. Currently, we plan to produce the validation batches after submission of the NDA and the PAI, but prior to approval. The validation protocols will be available for FDA review at the PAI. All validation batch information would then be available to the FDA prior to product launch.

Does FDA agree with this approach to the timing for preparation of the validation batches for BTDS ?

Mr. Tavares led the discussion on the sponsor's Process Validation Plan. He commented that stability is based on batches manufactured on large-scale equipment. It is the same equipment that will be used to manufacture the commercial lots.

Division response: Yes, in principle, the Agency agrees with the sponsor. Dr. D'Sa stated that the FDA Field office would have to be consulted. The FDA Field inspector conducts validation inspection. Having protocols available at the pre-approval inspection would be acceptable. Dr. D'Sa added that if the firms have not been inspected in a long time (more than two years) or if there were problems with previous inspections, this approach could very well change. No batches should be marketed before completing process validation and obtaining the field's approval.

6. Since it is anticipated that Purdue will have a significant quantity of bulk buprenorphine TDS patches and foil pouches manufactured in advance of the NDA approval (i.e. the validation batches discussed above and in Attachment 4), we are proposing an interim labeling approach until the final labeling is agreed to by FDA. This approach, as described in Attachment 5, involves an interim label text that will be stamped on the TDS's during manufacture. We propose to have the TDS with the interim label text placed in blank pouches that can be over-labeled for sale with label text agreed upon at the time of approval.

Can FDA offer any feedback on the acceptability of this approach?

Mr. Oshlack presented the sponsor's proposals relating to validation batches.

Division response: The Agency has no objections to the use of interim labeling. Per Dr. D'Sa clear identification of the labeling is very important. The pouch should be clearly labeled with an expiration date, based on the date of manufacture, as well as the lot number.

7. NORSPAN is a registered trademark for buprenorphine TDS.

Can FDA advise us if we can obtain early feedback from the FDA Nomenclature Committee on the acceptability of this trademark?

Division response: Ms. Moody informed the sponsor that there is no specific time frame for submitting the proposed proprietary name to the CDER Labeling and Nomenclature Committee, and that it is acceptable to do so prior to submitting the NDA to the Agency. Ms. Moody commented that the Labeling and Nomenclature Committee is currently undergoing reorganization and that she could not guarantee how soon the proposed name would be reviewed by the committee. She added that the submission should be made through the Division of Anesthetic, Critical Care and Addiction Drug Products.

8. 21 CFR314.50(d)(1)(ii)(b) requires that batch production records and associated documentation be submitted for each batch of drug product that is used to conduct a bioavailability or bioequivalence study or used to conduct a primary stability study. Since these records are created and used by LTS in the German Language, translating all of this

documentation would be very time consuming and represent a massive undertaking. We are requesting a waiver of this requirement to allow PPLP to submit an original German language version and a complete English translation for one batch of each strength of drug product. LTS will make available all German language batch records and associated documentation to FDA inspectors upon request at the PAI.

Does FDA agree with this more limited approach to submitting batch record documentation in fulfillment of this regulatory requirement?

Mr. Kelly presented the sponsor's proposals relating to NDA documentation.

Division response: Translation of selected batch records may be acceptable, per Dr. D'Sa. However, the Agency's Office of Compliance will also have to be consulted. If the Agency concurs with this request, the Agency will select the batches to be translated. Dr. D'Sa stated that he needs an update of the lot history since November 1998. The sponsor should submit a list of all the preclinical, clinical, and stability batches, with their request to the Agency to select representative batches for translation. Dr. D'Sa stated that the sponsor needs to submit a Certificate of Analysis for each batch. The sponsor stated that all batches will be translated at the time of the pre-approval inspection, therefore translation should not really be a problem.

9. Our approach to presenting CMC information for the Buprenorphine TDS NDA is outlined in the DRAFT Table of Contents for the CMC Section (Attachment 6). Details of the manufacturing and control of the drug substance will be provided by reference to a Type 11 DMF from the drug substance manufacturer, (b) (4). The NDA will include a brief summary of this information. Full details of the manufacture, control, packaging and labeling of the final dosage form will be included directly in the NDA.

Does FDA agree to the basic outline of this section of the NDA and to our approach for presenting the CMC information?

Division response: The sponsor needs to provide the following in the CMC section of the NDA:

- Two copies of their methods validation
- Environmental assessment (EA) or a request for exemption from submitting the EA
- DMF on all adhesives and packaging components and a letter of authorization (LOA)

10. Purdue will be submitting an electronic NDA for BTDS as the archival copy of the submission.

Will an electronic version of the CMC section be acceptable for review or will a hard copy be required as well?

Division response: Both an electronic version and a hard copy should be submitted. The sponsor must also submit certification that the two submissions are identical.

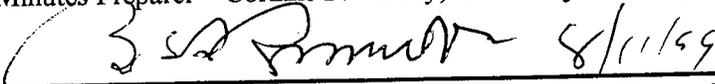
At the conclusion of the meeting, Dr. Hinman summarized the following agreed upon action items.

Action Items:

- The sponsor will send a copy of the video explaining the manufacturing of BTDS to Dr. Maturu's attention prior to submitting the NDA.
- Sponsor agreed to adjust the release specifications to include the test for related impurities and degradation products.
- Sponsor will submit information on in-process testing and results, and executed batch records to the IND, prior to submission of the NDA for BTDS. FDA will review the information, and provide comments if necessary.
- Sponsor will submit a copy of the updated development report as soon as it is available.
- Sponsor will prepare a report on the mass balance studies and submit to the Agency for review and comment.
- Sponsor will submit a copy of the NMR report to the IND with a request for Agency comment on the report.
- Sponsor will gather information available on additional studies carried out in an attempt to (b) (4) of buprenorphine.
- Sponsor will complete and submit a full study report on flux rate determinations to the NDA.
- Sponsor will contact FDA's Foreign Inspection Office to obtain their agreement on the process validation plan.
- Sponsor will use interim labeling – "Buprenorphine TDS" and "5", "10" and "20 mg" designations on the patches prepared from the validation batches.
- Sponsor will submit a request for proprietary name review to HFD-170 for review by the Nomenclature and Labeling Committee.
- Sponsor will update the list of lots used in various studies and submit the list, plus the Certificates of Analyses to the IND. The Agency will comment on which lots and corresponding batch records should be included in the NDA. The sponsor will also prepare a formal request for a waiver (including a statement of the rationale for the request) of the requirement for full batch record translation to HFD-170 and to the compliance branch.
- The sponsor will submit to the IND an updated draft of the Table of Contents for the NDA.
- The Agency will provide the sponsor a copy of the meeting minutes.

The meeting ended at 11:45 a.m.


Meeting Minutes Preparer – Corinne P. Moody, Chief Project Management Staff


Minutes Concurrence – Bob Rappaport, M.D., Meeting Chair/Deputy Division Director

CC: IND 50,273

HFD-170/Division Files

HFD-170/D. Fong/C.P. Moody

HFD-170 C. McCormick

B. Rappaport

A. D'Sa

P. Maturu

HFD-820 S. Koepke

J. Gibbs

HFD-870 R. Uppoor

S. Doddapaneni

Drafted by: cpmoody/08-08-99

Revised: 8/12/99 per R. Uppoor; 8/13/99 per A. D'Sa and B. Rappaport

Initialed by: P. Maturu 8/11/99

Final:

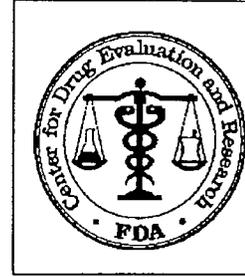
J. Maturu for CPM 8/13/99

FILE NAME: 50273 (PPLP) MM 071499.DOC

DF

PRE-MEETING MINUTES

Meeting Date: July 7, 1999 **Time:** 2:30-3:30 p.m.
Location: 9B-45 Conference room
IND: 50,273
Drug: Buprenorphine Transdermal System (BTDS, Norspan® TDS) 5, 10, 20 mg
Sponsor: Purdue Pharma L.P.
Indication: Treatment of chronic pain for up to 7 days
Type of Meeting: Team Meeting to discuss sponsor meeting on CMC/PK issues
Meeting Chair: Cynthia G. McCormick, M.D.
Minutes Recorder: Debbie Fong/Regulatory Project Manager



FDA Attendees:	Titles:	Offices:
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Bob Rappaport, M.D.	Deputy Division Director	HFD-170
Henry Startzman, M.D.	Medical Officer	HFD-170
Albinus D'Sa, Ph.D.	Team Leader/Chemistry	HFD-170
Pat Maturu, Ph.D., M.B.A.	Chemistry Reviewer	HFD-170
Ramana Uppoor, Ph.D.	Pharmacokinetics Team Leader	HFD-870
Suresh Doddapaneni, Ph.D.	Pharmacokinetics Reviewer	HFD-870
Corinne P. Moody	Chief, Project Management Staff	HFD-170
Debbie Fong, Pharm. D.	Regulatory Project Manager	HFD-170

Purdue Pharma L.P.'s representatives will be:	Titles:
Dr. Brian Burke	Director, Project Management
Dr. Lois Hinman	Director, U.S. Regulatory Affairs
Mr. James Kelly	Associate Director, Regulatory Affairs, CMC
Dr. Philip Palermo	Vice President, Pharmaceutical Analysis
Dr. Bruce Reidenberg	Director, Clinical Pharmacology
Dr. Fred Tonelli	Executive Director, PK/DM
Mr. Ben Oshlack	Vice President, Pharmaceutical Development
Mr. Lino Tavares	Associate Director, Pharmaceutical Development
Dr. Thomas Hille	Pharmacist, Research & Development, Lohmann Therapie-Systeme

Meeting Objective: The primary objective of this meeting was to be able to respond to the firm's questions dated June 14, 1999 and advise the sponsor on CMC and pharmacokinetic issues prior to their NDA submission for buprenorphine transdermal system (BTDS). Their proposed indication is the treatment of chronic pain for up to 7 days.

Introduction: During the pre-NDA meeting held on November 18, 1998, general questions from the sponsor on NDA organization/preparation and the Integrated Summaries of Safety and Efficacy were answered by the Division. Label claims were also discussed, focusing on the inclusion of a quantitative dosage (number of micrograms/TDS) versus a specific release rate. On May 7, 1999, the sponsor requested a meeting to discuss CMC/PK issues prior to their NDA submission for BTDS for the treatment of chronic pain for up to 7 days. The meeting request was formally granted to the sponsor on May 21, 1999. The briefing package dated June 14, 1999 includes several reference documents and questions regarding CMC, labeling, trademark, and CANDA versus hard copy NDA submission issues.

General Discussion: Dr. D'Sa provided background information on the proposed product and inquired about the status of a response from the sponsor to a letter sent by this Division on July 31, 1998. This letter specified requests from the reviewing chemist, Dr. Maturu. Dr. D'Sa and Dr. Maturu felt that the sponsor's response was required to proceed with our face-to-face meeting. Dr. McCormick suggested changing the face-to-face meeting to a teleconference. The Project Managers agreed to contact the sponsor to determine the status of their response to the letter in question, and discuss changing the face-to-face meeting to a teleconference, if appropriate.

Dr. D'Sa reviewed his responses to the CMC-related questions listed below.

FIRM'S QUESTIONS:

1. The specifications to be applied for release and stability evaluation of Buprenorphine TDS are presented in the CMC Overview of BTDS (Attachment 1, Table 1.2.5A). The stability specifications are identical to the release specifications with the exception that the stability specifications include quantitation of degradation products which may arise during stability.

The details of the stability testing program are provided in Section 1.2.7 of Attachment 1. The NDA will include 24 month stability data to support the proposed (b) (4) expiration dating, freeze-thaw temperature cycling evaluations and photostability studies will be performed according to ICH guidelines.

Does FDA have any comments to offer at this time on our proposed specifications for release and stability evaluation?

Division response: Related substances and degradation product testing should be performed at release and during stability studies.

The sponsor's specifications are acceptable, however the specifications will have to be set based on data for clinical lots. At this time, this data is not available. Therefore, it is premature for this Division to comment. The sponsor needs to provide the following:

- Executive batch record
- Lot history (linkage table)
- Certificate of analysis
- In-process testing and results

(b) (4)

2. During the stability program, mass balance is not achieved between a decrease in potency assay and the increase in degradation products (see Attachment 1, Tables 1.2.7A - C, G - I). We are currently investigating more exhaustive methods of extraction of buprenorphine and potential impurities and plan to submit these data in the NDA.

If extraction studies currently in progress indicate that mass balance is achieved among buprenorphine and the known impurities and no new impurities appear, will these results satisfy the FDA regarding any mass balance considerations?

Division response: This is a review issue. To answer the question, we need more information on the following:

- Methods of analysis and validation of the methods data, e.g. were the appropriate extraction solvents used?
 - Cause for loss, e.g. polymerization/dimerization that occurs during manufacture and storage.
 - Accelerated stability data, which will help clarify the extent of this potential problem
3. During our pre-NDA meeting of November 18, 1998, the FDA requested that PPLP investigate the solid state form of buprenorphine in the patch system. In order to do this, PPLP conducted solid state NMR studies of buprenorphine in the patch. Details of these evaluations are presented in Attachment 2. Based on the comparison of structural features only the base form was found to exist in the TDS.

We believe these studies adequately address the FDA request. Does the FDA agree?

Division response: No, this Division does not find these studies satisfactory. The ratio of levulinic acid used is ^{(b) (4)} in this formulation. The test samples were composed of an equimolar ratio (1:1), which is not representative of the proposed formulation. We suggest that the sponsor actually make the ^{(b) (4)} of buprenorphine, then demonstrate that it is not formed in the product, via ^{(b) (4)}

4. A Flux Rate Analysis for the buprenorphine TDS was conducted using three different approaches (i.e., absolute systemic bioavailability, the Wagner-Nelson method for calculating absorption and the residual buprenorphine in the patch). Details of the analyses are presented in Attachment 3. Based on the ranges of buprenorphine delivery observed in the above studies, the recommended release rates for the 5mg, 10mg and 20mg BTDS are 5, 10 and 20 µg/hr respectively. We plan to label the product with this flux ratio.

Does FDA agree with this approach to establishing flux rates?

Division response: Dr. D'Sa pointed out that the labeled flux rate differs from the observed results.

Dr. Doddapaneni explained that flux rate provides a more accurate estimate of absorption. The three different approaches proposed are acceptable. Usually, a crossover study with the

intravenous formulation and the patch is conducted. However, PPLP presents combined data from different studies, which may be acceptable if the same formulation was used and similar populations were studied. If the studies were not comparable, then the sponsor may not be able to label the product as 5, 10 and 20 µg/hour. Then, the sponsor will either need to reformulate the patch or conduct another study if they wish to use the above specified flux rates.

Can FDA advise us as to how we may obtain early feedback about the acceptability of the proposed label, which will include flux rate information?

Division response and discussion: At this time, we cannot provide feedback on labeling. This is clearly a review issue. Dr. Upoor asked Dr. D'Sa if the nomenclature committee normally considers flux rate in their reviews. Dr. D'Sa explained that labeling total dose is also required. It was pointed out that flux rate is most important for clinical purposes.

5. As noted in the process validation overview provided in Attachment 4, IQ, OQ and PO have been completed for the manufacture of buprenorphine TDS using production equipment and three batches (one each produced at low, target and high operating conditions) of each strength at LTS. However, our three consecutive validation batch campaign has not yet been initiated. As buprenorphine is an expensive, controlled substance in short supply and subject to worldwide regulation, PPLP would like to minimize the destruction of such a material by requesting FDA input on the proposed timing for production of the validation batches, relative to submission of the NDA and the PAI. Currently, we plan to produce the validation batches after submission of the NDA and the PAI, but prior to approval. The validation protocols will be available for FDA review at the PAI. All validation batch information would then be available to the FDA prior to product launch.

Does FDA agree with this approach to the timing for preparation of the validation batches for BTDS?

Division response: Yes, in principle, we agree with the sponsor. It was noted that validation would be done prior to marketing the product. At the prior-approval inspection, the validation protocol would be ready for inspection.

The sponsor appears to have made several scale-up attempts, and this Division's review will be expedited if the sponsor submits the following:

- Executive batch record
 - Scale-up report
 - Protocol for changing controls (Change control protocol)
 - In-process testing
6. Since it is anticipated that Purdue will have a significant quantity of bulk buprenorphine TDS patches and foil pouches manufactured in advance of the NDA approval (i.e. the validation batches discussed above and in Attachment 4), we are proposing an interim labeling approach until the final labeling is agreed to by FDA. This approach, as described in Attachment 5, involves an interim label text that will be stamped on the TDS's during manufacture. We

propose to have the TDS with the interim label text placed in blank pouches that can be over-labeled for sale with label text agreed upon at the time of approval.

Can FDA offer any feedback on the acceptability of this approach?

Division response: We have no objections to the use of interim labeling. However, the sponsor should include flux rate and the date of manufacture on the label. The date of manufacture should be [REDACTED] (b) (4). The date of labeling should not be listed as the date of manufacture.

7. NORSPAN is a registered trademark for buprenorphine TDS.

Can FDA advise us if we can obtain early feedback from the FDA Nomenclature Committee on the acceptability of this trademark?

Division response: We will send a consult to the Nomenclature Committee.

8. 21 CFR314.50(d)(1)(ii)(b) requires that batch production records and associated documentation be submitted for each batch of drug product that is used to conduct a bioavailability or bioequivalence study or used to conduct a primary stability study. Since these records are created and used by LTS in the German Language, translating all of this documentation would be very time consuming and represent a massive undertaking. We are requesting a waiver of this requirement to allow PPLP to submit an original German language version and a complete English translation for one batch of each strength of drug product. LTS will make available all German language batch records and associated documentation to FDA inspectors upon request at the PAI.

Does FDA agree with this more limited approach to submitting batch record documentation in fulfillment of this regulatory requirement?

Division response: Batch record documentation for clinical and stability batches is mostly a regulation in place due to generic submissions.

The sponsor should provide a lot history of all batches manufactured, including certificates of analysis and where the lots were used. We will choose three lots on which executive batch records will be needed, which can then be translated.

9. Our approach to presenting CMC information for the Buprenorphine TDS NDA is outlined in the DRAFT Table of Contents for the CMC Section (Attachment 6). Details of the manufacturing and control of the drug substance will be provided by reference to a Type 11 DMF from the drug substance manufacturer, [REDACTED] (b) (4). The NDA will include a brief summary of this information. Full details of the manufacture, control, packaging and labeling of the final dosage form will be included directly in the NDA.

Does FDA agree to the basic outline of this section of the NDA and to our approach for presenting the CMC information?

Division response: The sponsor needs to provide the following in the CMC section of the NDA:

- Two copies of their methods validation
- Environmental assessment (EA) or a request for exemption from submitting the EA
- DMF on all adhesives and packaging components

Dr. Doddapaneni pointed out that the sponsor's dissolution specifications indicate (b) (4), release at the end of a 24-hour period. This release is too fast and not what we expect in vivo. We must determine if this is the best approach, or the sponsor needs to reconsider their specification. This is a review issue.

10. Purdue will be submitting an electronic NDA for BTDS as the archival copy of the submission.

Will an electronic version of the CMC section be acceptable for review or will a hard copy be required as well?

Division response: Both an electronic version and a hard copy should be submitted, since some of the reviewers have limited experience reviewing electronic submissions. The sponsor must also submit certification that the two submissions are identical.

Action Items:

- The Project Managers will contact the sponsor to determine the status of their response to this Division's letter dated July 31, 1998, specifying requests from the chemistry reviewer, Dr. Maturu. The Project Managers will discuss changing the face-to-face meeting to a teleconference with the sponsor, if appropriate. The face-to-face meeting with the sponsor is scheduled for July 14, 1999 from 10:00 to 11:30 a.m. in Parklawn Conference Room C. If it is switched to a teleconference, we will request that the teleconference take place at the same date and time.
- We will issue a consult to the Nomenclature Committee regarding the acceptability of NORSPAN as a registered trademark.

CC: IND 50,273

HFD-170/Division Files

HFD-170/D. Fong/~~C.P. Moody~~

HFD-170 C. McCormick

B. Rappaport

A. D'Sa

P. Maturu

~~C. Moody~~

HFD-870 R. Uppoor

S. Doddapaneni

Reviewed:

Drafted by: D. Fong 7/12/99

Revised: 7/13/99 per A. D'Sa; 8/2/99 per R. Uppoor; 8/5/99 per B. Rappaport

Initialed by: P. Maturu 7/13/99; S. Doddapaneni 8/5/99; C. P. Moody 8/12/99; C. McCormick 8/13/99

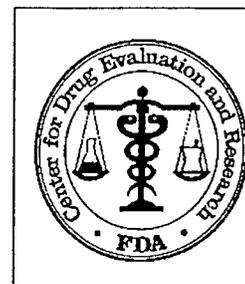
Final:

Handwritten signatures and initials: a large signature, a smaller signature, the initials 'CPM', and the date '8/24/99'.

FILE NAME: 50273(PPLP)PREMTG070799.DOC

TELCON WITH SPONSOR MINUTES

Meeting Date: May 5, 1999 **Time:** 3:30 -4:30 P.M.
Location: Parklawn Building 9B-45 **Sponsor:** Purdue Pharma L.P.
IND: 50, 273 **Drug:** BTDS



Type of Meeting: Clarification of Pharmtox Requirements for NDA
Meeting Chair: Cynthia G. McCormick, M.D.
External Participant Lead: Lois M. Hinman, Ph.D.
Minutes Recorder: Nancy Chamberlin/ Project Manager

FDA Participants:	Titles:	Offices:
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD-170
Sharon Hertz, M.D.	Medical Reviewer	HFD-170
Henry Startzman, M.D.	Medical Reviewer	
Dou Huey Jean, Ph.D.	Team Leader/Pharmacology	HFD-170
David Brase, Ph.D.	Pharmacology Reviewer	HFD-170
Nancy Chamberlin, Pharm.D.	Project Manager	HFD-170

Purdue Pharma L. P. Participants:	Titles:
Lois M. Hinman, Ph.D.	Director, U.S. Regulatory Affairs
Brian Burke, Ph.D.	Project Manager
Viny Srinivasan, Ph.D.	Toxicologist
Stan Stadnicki, Ph.D.	Toxicology Consultant

Meeting Objective: The primary objective of this meeting was to clarify for the sponsor the FDA requirements for reproductive toxicity for the NDA submission of BTDS.

Background:

FDA informed the sponsor in the December 16, 1998 letter that they would need results of studies of reproductive toxicity (fertility, embryotoxicity, teratogenicity) and should also state the doses of buprenorphine that were studied as multiples of the Maximum Recommended Human Dose (MRHD) in terms of exposure, i.e., in terms of AUC. The firm had planned to use reference literature and Freedom of Information (FOI) information on this topic in the NDA. Also it was the firm's understanding from a 1996 telecon that they would not have to do reproductive studies on this product.

Discussion:

Dr. McCormick led the discussion. Due to prior understandings and timing of the NDA submission, she clarified which pharm/tox submission would have to be submitted with the NDA (e.g., in the 1st quarter of 2000) and which could be submitted as phase 4 commitments.

1. Carcinogenicity-

The sponsor is working on the protocol for carcinogenicity such as obtaining drug plasma levels in rodents. Dr. McCormick confirmed that this would be a phase IV commitment and that we would have to make a disclaimer in the labeling on the absence of knowledge.

2. Mutagenicity package will be provided in the NDA-

Dr. Jean suggested that the mutagenicity package be submitted ahead of time to the IND, if possible. The sponsor answered affirmatively.

3. Reproductive Toxicity Studies-

Dr. Jean stated that reproductive studies are needed by the sponsor. She noted that the original NDA studies were not conducted under Good Laboratory Practices (GLPs). She requested that the sponsor repeat segment I and III, providing AUC and extent of exposure using the current ICH and GLP standards, and agreed that these could be done as a phase 4 commitment. Dr. McCormick agreed that the reproductive segment I and III studies could be submitted as phase 4 commitments and that we would have to work together on the labeling. ✓

CONCLUSIONS:

The meeting concluded with agreement on submitting the mutagenicity information to the IND and that the data from the carcinogenicity and segment I and III reproductive studies could be submitted as phase 4 commitments.

ACTION ITEMS:

- FDA CDER/CAC will review the carcinogenicity protocols when submitted by the sponsor after they provide the data.
- FDA will provide the sponsor with a copy of the meeting minutes from this meeting.

Minutes Prepared By: N. Chamberlin, Pharm.D.

Nancy Chamberlin

Minutes Concurred By Chair: Cynthia G. McCormick, M.D.

Cynthia G. McCormick MD



DEPARTMENT OF HEALTH & HUMAN SERVICES

DF

IND 50,273

Food and Drug Administration
Rockville MD 20857

Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, Connecticut 06850-3590

DEC 16 1998

Attention: Lois M. Hinman, Ph.D.
Director, Regulatory Affairs

Dear Dr. Hinman:

Please refer to the meeting between representatives of your firm and FDA on November 18, 1998. The purpose of the pre-NDA meeting was to discuss the clinical development plan for Buprenorphine Transdermal System (BTDS).

As requested, a copy of our minutes of that meeting is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes. In addition, for your information we are providing you with the following pharmacology comments that were not discussed at the meeting:

1. Until Phase IV carcinogenicity studies are completed, the label should state that "Because carcinogenicity studies have not been performed with NORSPAN TDS, the carcinogenic potential of NORSPAN TDS remains unknown."
2. The label should contain results of your mutagenicity (genotoxicity) studies.
3. Results of studies of reproductive toxicity (fertility, embryotoxicity, teratogenicity) should also state the doses of buprenorphine that were studied as multiples of the MRHD in terms of exposure, i.e., in terms of AUC.

If you have any questions, contact Nancy Chamberlin, Project Manager, at (301) 827-7410.

Sincerely,

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

IND 50,273

Page 2

cc: Original IND 50,273

HFD-170/Div. Files

HFD-170/CSO Chamberlin

HFD-170 C McCormick

B Rappaport

M Scheinbaum

P Maturu

D Brase

L Jean

A Dsa

C Moody

T Permutt

M Klein

HFD-870 /S Doddapaneni

R Uppoor

Drafted by: N.Chamberlin /November 18, 1998

Revised: 12-14-98nc, 12-15-98nc

Initialed by:

final:

filename: 50273ltr1118.doc

Chamberlin 12-15 + 16/98

Meeting Minutes for Pre-NDA meeting

MEETING MINUTES

Division of Anesthetic, Critical Care, and Addiction Drug Products (DACCADP), HFD-170

Date: November 18, 1998 9:30-11:00 **Place:** Parklawn 3rd floor conference room M

Drug: Buprenorphine Transdermal System (BTDS) IND 50,273

Sponsor: Purdue Pharma L.P.

Type of Meeting: pre-NDA Meeting

Meeting Chair: Cynthia McCormick, MD

External Participant Lead: Lois Hinman, Ph.D.

Minutes Recorder: Nancy Chamberlin, Pharm.D

FDA Participants:	Titles:	Offices:
Cynthia McCormick, MD	Director, DACCADP	HFD-170
Bob A. Rappaport, MD	Deputy Director, DACCADP	HFD-170
Monte Scheinbaum, MD	Medical Reviewer	HFD-170
David Brase, Ph.D.	Pharmacology Reviewer	HFD-170
Anwar Goheer, Ph.D.	Acting Team Leader/Pharmacology	HFD-170
Venkata Ramana Uppoor, Ph.D.	Team Leader, Pharmacokinetics	HFD-870
Albinus D'Sa, Ph.D.	Team Leader, Chemistry	HFD-170
Pat Maturu, Ph.D.	Chemistry Reviewer	HFD-170
Tony Chite	Project Manager	HFD-170
Nancy Chamberlin, Pharm.D.	Project Manager	HFD-170

Participants from Purdue Pharma L.P.:

Claudia Bohnert, Ph.D.	Clinical Research
Brian Burke, Ph.D.	Project Management
Ronald Fitzmartin, Ph.D.	Team Leader
Ronald Hargreaves, Ph.D.	CMC, Regulatory Affairs
Lois Hinman, Ph.D.	Regulatory Affairs
Serge Karpow, Pharm.D.	Clinical Research
Jeffery Lazar, M.D., Ph.D.	Clinical Pharmacology
Catherine Munera, Ph.D.	Biostatistics and Clinical Data Management
Philip Palermo, Ph.D.	Pharmaceutical Analysis
Robert Reder, M.D.	Clinical Research
Stanley Stadnicki, Ph.D.	Pharmacology/Toxicology

Meeting Objective: The primary objective of this meeting is to gain a common understanding of the development plan for Norspan TDS™ (Buprenorphine Transdermal System BTDS), and for the FDA to convey to the Sponsor any suggestions and requirements for this product's development prior to submitting an NDA.

Introduction: The firm presented an overview of their clinical program. The firm conducted 12 PK studies in normal and special populations. The firm provided 4 studies in their submission that they had planned to use for efficacy claims. They have safety exposure data in 750 patients for at least 2 to 3 months and 300 of these for over 1 year. The adverse events were common to other opiates, and oxycodone/acetaminophen. The skin site reactions were similar to the other products.

Their intention would be to market an “up to 7 days” BTDS product for chronic pain.

Discussions Points: Discussion was held on the following questions

Firm’s Questions:

1. PPLP would like to confirm the adequacy of the clinical program, as outlined in the October 5th package, for filing an NDA for BTDS for the treatment of pain.

Division’s Response:

- It appeared that only 1 study (604) was solid for an efficacy claim. The post-op study would not be appropriate for supporting a chronic indication. It is unknown whether the lack of efficacy found in the other studies was due to studying the product in the wrong population or due to a problem with study design.
- The Agency strongly urged the firm to do another efficacy study in a different model, i.e., cancer pain, pediatric population, adolescent cancer patients, and HIV positive patients.
- The Agency encouraged the firm to do a study in the malignant pain patients, as they are potential users of chronic pain medications. Discussion was held on whether the time to onset in cancer patients might be different than in the non-malignant group. They should consider using a similar design to Study 604 in malignant and non-malignant pain.
- The firm mentioned the possibility of using their ongoing long-term safety study to perform a withdrawal based efficacy study. Dr. McCormick stated that it would be problematic to interpret. However, if the firm is interested in pursuing this study, they will submit a protocol for the Division to review prior to use.

- It was suggested that the firm could use rescue medications to see at what concentration/dosage antagonist properties develop.
 - A brief discussion was held on the importance of primary efficacy variables such as VAS, PPI pain scores and the amount of rescue medications used. It was suggested that the firm look at both factors with equal weights. FDA statisticians could be consulted on how to assess the variables together.
 - The Division mentioned the firm should consider looking at pediatric cancer pain at this time or as a possible phase IV commitment.
2. PPLP would like to confirm that the basic organization of the NDA as presented in the draft NDA Table of contents in the June 4th package is acceptable.

Division's Response:

The format is good and appropriate. However, the long-term safety data needs to be located in the ISS not in the ISE.

3. PPLP would like to confirm that the plan for analyzing and presenting safety data in the Integrated Summary of Safety in the June 4th package is acceptable.

Division's Response:

- Safety database is probably adequate. However, we don't know what the exposures are at different doses.
- We would like to know the percentage of safety database at the highest doses, especially for those patients receiving the drug for 1 year or longer.

4. PPLP would like to confirm that the plan for analyzing and presenting efficacy data in the Integrated Summary of Efficacy in the June 4th package is acceptable.

Division's Response:

The firm needs to do an additional efficacy study. The format proposed for the ISE is acceptable, however.

5. PPLP would like to discuss FDA's request for Phase 4-carcinogenicity study on BTDS in light of prior agreements and discussions between PPLP and the Agency in terms of the toxicology program.

The firm committed that it was difficult to do an oral study with buprenorphine due to the high first pass effect and they don't know the pharmacokinetics of skin painting.

Division's Response:

The following steps were agreed upon with the firm-

- The firm will pursue the feasibility studies to determine appropriate blood levels.
 - They will submit the data to the FDA, who will take it to the carcinogenicity committee to give some guidance as to what action plan to take. (The turn around time is about 45 days from sponsor's submission date.)
 - Then the FDA will discuss with the firm if they should conduct a full study or what the next step will be.
 - In addition, the FDA pharmacologist would like to know whether buprenorphine is metabolized by skin.
6. PPLP proposes to state the total amount of buprenorphine in the TDS as the quantitative "label claim," (i.e., xx mcg/TDS) rather than as a specific release rate and would like to confirm that this is acceptable.

Division's Response:

- Labeling based on total buprenorphine is generally allowed only if an insignificant amount is left in the patch after use. Generally release rate is preferred and is dependent on data of how much is remaining in the patch. The sponsor stated that this can be problematic since release rate from buprenorphine TDS is first order and release rate changes with number of days it is used (e.g. 5 days vs. 7 days).
- Labeling is data driven based on information that the firm provides. The firm needs to look at linearity. Discussion was held on the possibility that they may want to consider using both release rate and total amount in labeling.
- Need to discuss this further with the firm's packaging group and obtain FDA comments on the labeling. It could be a NDA review issue.

Additional FDA Comments:

Chemistry Issue:

- Discussion was held on whether the product (b) (4)

- Batch records were in German. The firm agreed to submit their English version to the NDA, and if needed sooner they would have them translated.

Bioavailability Related Questions-

- The drug appears to produce steady state concentrations in 3 days. It will be up to the firm to determine if they have adequate data to provide multiple dose information from their 3-day and 7-day patch data, and the PK data from their current phase III trials. This justification needs to be submitted in the NDA.
- If the firm does not have enough data, they may either conduct another multiple dose study or could obtain plasma samples in their next phase III clinical study to obtain steady state pharmacokinetics.

CSET:

- Abuse liability. Propose a schedule, e.g., schedule V. The firm must submit a report justifying whether it should remain as schedule V.

Electronic Submission :

- Must follow the Center's policy for Electronic Submissions.

ACTION ITEMS:

- **The firm will take the information discussed in this meeting under advisement and attempt to address the FDA concerns.**
- **It was agreed that the firm's toxicology group and FDA's toxicology group would have to discuss further what would be required for carcinogenicity testing.**

- It was agreed that the firm should submit protocols for the Agency to pre-review and that they would meet again to discuss study designs, if necessary.
- Firm needs another efficacy trial to strengthen their NDA submission.
- Firm needs to review their PK data to see if they have sufficient data or whether they would have to conduct a multiple dose study.
- Labeling needs to be discussed further. The firm needs to talk to their packaging group and obtain FDA comments on the labeling strength. Also the firm needs to have discussion with FDA chemistry reviewers on the name if it is a (b) (4)
- FDA will provide the sponsor with a copy of the meeting minutes.

Minutes Prepared By: N. Chamberlin, Pharm.D.

Minutes Concurred By Chair: C. McCormick, M.D.

N. Chamberlin 12-16-98

Cynthia McCormick 12-16-98

Meeting Recorder: Nancy Chamberlin, Pharm.D, HFD-170
Drafted: NC 11/17/98,
Revised: 11/25/98 nc, 12-14-98nc, 12-15-98nc,12-16-98nc
Filed under: # 1118SPMTG.DOC

DF
JUN 30 1998

MEMORANDUM OF TELECON

IND/NDA #: 50,273

DRUG NAME: Buprenorphine Transdermal System

DATE/TIME OF TELECON: June 30, 1998/ 12:45 p.m./ Room 13-57

SPONSOR: Purdue Pharma

NOTES TAKEN BY: Tony Chite

INITIATED BY SPONSOR OR FDA: Sponsor

IN ATTENDANCE/ FDA: Cynthia McCormick, Bob Rappaport, Monte Scheinbaum, Albinus D'Sa, David Brase, Tom Permutt, Suresh Doddapaneni, Corinne Moody, Tony Chite

IN ATTENDANCE/ SPONSOR: Ron Fitzmartin, Ron Hargreaves

PURPOSE: To discuss electronic filing of the NDA and the needs of the statistician. To make reference to the DAMOS demonstration of June 24, 1998.

DISCUSSION:

When asked by the sponsor for an opinion of DAMOS, the agency stated that the DAMOS system seems workable.

The agency asked the sponsor if the CANDAs that was to be submitted in the fall was ready to be sent. The agency does not want the sponsor to redo what they have already done.

The DAMOS based submission had been suggested by the sponsor so the agency could become familiar with the model used in Europe.

The sponsor was asked if the implementing of DAMOS would put them behind in their submission and the sponsor replied that it would not. If the agency does not want to use DAMOS, the sponsor would not submit in this format.

The sponsor responded "no" to the agency's question if there was an added expense or extra work to the sponsor to submit the NDA in the DAMOS format. Either one seems workable, so if it is more expensive the agency suggested using the less expensive.

The sponsor suggested that it create something with DAMOS in addition to following the guidance. The sponsor is looking forward to implementing it in September. The model presented was HTML browser, front end.

The sponsor stated it would need to refine the system and inform the agency as to how they are progressing.

It was reiterated that the agency does not want to cause any extra work or expense for the sponsor by selecting a particular format.

IND 50,273

Page 2

cc:

original IND 50,273

HFD 170/ Division File

HFD 170/ T Chite