

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022496Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22496

SUPPL #

HFD # 170

Trade Name Exparel

Generic Name Bupivacaine Liposome Injectable Suspension

Applicant Name Pacira Pharmaceutical, Inc.

Approval Date, If Known October 28, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(2)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

3 years

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# 016964	Marcaine Hydrochloride
NDA# 018304	Sensorcaine
NDA# 022046	Bupivacaine Hydrochloride
NDA# 018692	Marcaine

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:

There were two clinical investigations submitted by the Applicant that were essential to the approval of this product:

Study SKY0402-C-317 was a multicenter, randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of 106 mg of EXPAREL in 193 patients undergoing bunionectomy.

Study SKY0402-C-316 was a multicenter, randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of 266 mg of EXPAREL in 189 patients undergoing hemorrhoidectomy.

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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"):

There were two "new" clinical investigations submitted by the Applicant that were essential to the approval of this product (the investigations are also listed in 2(c):

Study SKY0402-C-317 was a multicenter, randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of 106 mg of EXPAREL in 193 patients undergoing bunionectomy.

Study SKY0402-C-316 was a multicenter, randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of 266 mg of EXPAREL in 189 patients undergoing hemorrhoidectomy.

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 # 069198	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>

! Explain:

Investigation #2

IND # 06198

YES

!
!
! NO
! Explain:

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

Investigation #1

YES

Explain:

!
!
! NO
! Explain:

Investigation #2

YES

Explain:

!
!
! NO
! 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: Sharon Turner-Rinehardt
Title: Senior Regulatory Health Project Manager
Date: October 24, 2011

Name of Office/Division Director signing form:
Title:

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

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

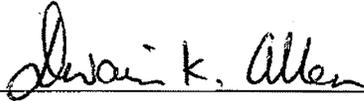
/s/

SHARON M TURNER RINEHARDT
10/28/2011

BOB A RAPPAPORT
10/28/2011

3. DEBARMENT CERTIFICATION

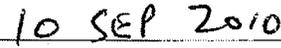
Pacira Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this New Drug Application (NDA).



Dwain K. Allen

Director, Regulatory Affairs

Pacira Pharmaceuticals, Inc.



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022496 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Exparel Established/Proper Name: Bupivacaine Liposome Injectable Suspension Dosage Form: Injection		Applicant: Pacira Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Sharon Turner-Rinehardt		Division: DAAAP
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>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): Marcaine, NDA 016964</p> <p>Provide a brief explanation of how this product is different from the listed drug. This product provides for a new dosage form and indication.</p> <p>If no listed drug, explain. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><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 checked="" 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>October 28, 2011</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input checked="" type="checkbox"/> None

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

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics²</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

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

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	Included, October 30, 2011
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval, October 28, 2011
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. 	October 28, 2011
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	March 2, 2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" 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 	
<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 	October 28, 2011
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	Acceptable, February 8, 2011 February 8, 2011
<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 June 16, 2011 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC September 27, 2011 <input type="checkbox"/> SEALD <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>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	December 10, 2011 <input type="checkbox"/> Not a (b)(2) September 27, 2011 <input type="checkbox"/> Not a (b)(2) October 26, 2011
<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>October 5, 2011</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters (except action letters), emails, faxes, telecons)</i>	October 27 and December 10, 2011, January 4, 14, and 20, March 10, and 25, April 21, May 6, 9 and 17, June 2, 3, 13, 20 and 23, August 2, 9, and 18, September 2, 7, 21 (2), and 23, October 3 and 4, 2011
❖ Internal memoranda, telecons, etc.	June 9 and September 22, 2011
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg February 16, 2010
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg January 11, 2006
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None October 28, 2011
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None October 9, 2011
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None 4
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	N/A
• Clinical review(s) <i>(indicate date for each review)</i>	September 23 and October 7, 2011 Filing: December 8, 2010
• 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>	Clinical Review, September 23, 2011
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable

⁵ Filing reviews should be filed with the discipline reviews.

❖ 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>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested June 1, 2011
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 September 23, 2011/Filing: December 10, 2010
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 September 19, 2011/Filing: December 7, 2010
❖ 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) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 27, 2011
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 23, 2011/ Filing: November 4, 2010
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None August 12 and September 28 and October 20, 2011/Filing: November 24, 2010 Biopharm: June 1 and August 5, 2011
❖ Microbiology Reviews		<input type="checkbox"/> Not needed September 28, 2011/ Filing: November 8, 2010
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input type="checkbox"/> None June 8, 2011
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		September 28, 2011 (clinical review)
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input 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>		Date completed: September 23, 2011 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input 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.

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

/s/

SHARON M TURNER RINEHARDT
10/30/2011



NDA 022496

NDA ACKNOWLEDGMENT

Pacira Pharmaceuticals, Inc.
10450 Science Center Drive
San Diego, CA 92121

Attention: Dwain K. Allen
Director, Regulatory Affairs

Dear Mr. Allen:

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

Name of Drug Product: SKY0402 (bupivacaine extended-release liposome injection)

Date of Application: September 28, 2010

Date of Receipt: September 28, 2010

Our Reference Number: NDA 022496

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 27, 2010 in accordance with 21 CFR 314.101(a).

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

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

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

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

If you have any questions, call Tanya Clayton, Senior Regulatory Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

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

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

/s/

TANYA D CLAYTON
10/27/2010

From: [Turner-Rinehardt, Sharon](#)
To: ["Dwain Allen";](#)
Subject: NDA 22496 Exparel: Informtion Request
Date: Thursday, October 13, 2011 3:40:53 PM

Dear Dwain,

We have the following information request.

Regarding the temperature indicators on the carton and container labels, conduct the following studies as outlined or provide the data, if available.

A. Effect of heat:

Test material: Drug product stored in its secondary packaging

Monitoring: Measurement of temperature on the secondary packaging and inside the vial

Conditions: Place the product in an environmental chamber at 25^o C including devices to measure the temperature on the carton and in the vial. Increase the temperature to 45^o C

and hold the temperature at that value for up to eight hours.

Observation: Record the temperatures on the carton and in the vial. Record the time and temperature when the indicator on the package turns red. Measure the PSD at appropriate time points.

B. Effect of freezing:

Test material: Drug product stored in its secondary packaging

Monitoring: Measurement of temperature on the outside of the vial.

Conditions: Place the product in an environmental chamber or a cooling bath at 25^o C including a device to measure the temperature in the vial.

Decrease the temperature to -15^o C

and hold the temperature at that value for up to eight hours.

Observation: Record the temperatures in the vial. Record the time and temperature when the indicator on the vial turns white. Measure the % free bupivacaine and the visual appearance of the vial at appropriate time points.

I ask that you provide this information as soon as possible. Any questions regarding this request, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Senior Regulatory Health Project Manager

Division of Anesthesia, Analgesia and Addiction Products

Phone: (301) 796-2254

Fax: (301) 796-9713

Email: sharon.turner-rinehardt@fda.hhs.gov

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

/s/

SHARON M TURNER RINEHARDT
10/20/2011

From: [Turner-Rinehardt, Sharon](#)
To: ["Dwain Allen";](#)
Subject: NDA 22496 Exparel: Information Request Regarding Patent Certification
Date: Tuesday, October 04, 2011 6:28:32 PM

Dear Dwain,

We are unable to ascertain what patent certification (Paragraph II, "no relevant patents" or something else) Pacira intended to cite in the NDA submission. Provide the exact patent certification that was intended for this NDA. If it was intended to be a "no relevant patents" statement, then you must resubmit using the exact language provided under 21CFR 314.50(i)(1)(ii). I ask that you provide this information by noon (EST) Thursday, October 6, 2011.

Regards,
Sharon

Sharon Turner-Rinehardt

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Addiction Products
Phone: (301) 796-2254
Fax: (301) 796-9713
Email: sharon.turner-rinehardt@fda.hhs.gov

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

/s/

SHARON M TURNER RINEHARDT
10/04/2011

From: [Turner-Rinehardt, Sharon](#)
To: ["Dwain Allen";](#)
Subject: NDA 22496: Carton and Container Label Revisions
Date: Monday, October 03, 2011 6:48:05 PM

Dear Dwain,
We have the following requests regarding the carton and container labels submitted on September 6, 2011.

1. Remove the phrase [REDACTED] (b) (4)
[REDACTED] from the carton labels.

2. Explain the difference between the instructions on the vial label:

“Do not Use if Center is Red.”

and the instruction in the package insert

[REDACTED] (b) (4)
[REDACTED] The freeze indicator turns from green to white when exposed to freezing temperatures. [REDACTED] (b) (4)
[REDACTED]

3. Provide the data to support the effect of the temperature on whichever temperature indicator is to be used.

4. Specify which of the four “panels” provided for the carton label is visible from which aspect i.e. which is the top and which are on the sides.

5. Explain why the vial label has a “Peel” tab. Provide instructions in the Package insert to describe what is done with the label after it is peeled off.

I ask that you provide a response to this request by 3pm (EST) Friday, October 7, 2011. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt
Senior Regulatory Health Project Manager

Division of Anesthesia, Analgesia and Addiction Products

Phone: (301) 796-2254

Fax: (301) 796-9713

Email: sharon.turner-rinehardt@fda.hhs.gov

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

/s/

SHARON M TURNER RINEHARDT
10/04/2011

From: [Turner-Rinehardt, Sharon](#)
To: ["Dwain Allen";](#)
Subject: NDA 22496: DRAFT FDA Edited Label
Date: Friday, September 30, 2011 6:53:42 PM
Attachments: [DRAFT FDA EDITED LABEL_093011.pdf](#)

Dear Dwain,

Please find attached the DRAFT FDA edited label for Exparel. Please note that section 14 is not included in this draft. We will provide the edits for this section at a later date. Please also note, that there may be additional edits to the sections provided this draft. I ask that you provide your concurrence or objections with justification to our edits by noon (EST) Friday, October 7. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Addiction Products
Phone: (301) 796-2254
Fax: (301) 796-9713
Email: sharon.turner-rinehardt@fda.hhs.gov

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

/s/

SHARON M TURNER RINEHARDT
09/30/2011

From: [Turner-Rinehardt, Sharon](#)
To: ["Dwain Allen";](#)
Subject: NDA 22496 Exparel: Information Request
Date: Friday, September 23, 2011 11:48:40 AM

Dear Dwain,

We have the following request for information.

1. Confirm whether all the plasma bupivacaine levels were measured at the same laboratory.
2. Confirm whether the specimens that had high levels (>750 mcg/L) were retested and if so, specify whether the results were different on re-evaluation. Also, provide information as to whether

it is possible to determine if those specimens contained Exparel liposomes.
3. Clarify whether you tested or could test for bupivacaine levels in blood samples with small quantities, consistent with possible systemic exposures, of Exparel added.

Also, Exparel should be added to whole blood prior to centrifugation. Specify if that technique was used in the original determinations.

I ask that you provide a response as soon as possible.

Regards,
Sharon

Sharon Turner-Rinehardt

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Addiction Products
Phone: (301) 796-2254
Fax: (301) 796-9713
Email: sharon.turner-rinehardt@fda.hhs.gov

ATTACHMENT

Summarized below is Pacira's response to FDA's Information Request communicated via email on September 23, 2011, by Sharon Turner-Rinehardt, Senior Regulatory Health Project Manager (DAAAP):

NOTE: FDA's IR is in **bold** font; Pacira's response follows in regular font.

FDA Question 1: Confirm whether all the plasma bupivacaine levels were measured at the same laboratory.

Pacira Response:

For all clinical studies that included a drug pharmacokinetic component, plasma bupivacaine levels were assayed by the same laboratory: [REDACTED] (b) (4) which utilized a validated LC-MS/MS bioanalytical method (reference is made to the original NDA 22-496, Sequence 0000, Section 2.7.1.1.2, Summary of Biopharmaceutic Studies and Associated Analytical Methods). Regarding the nonclinical GLP studies, one of two laboratories was used: [REDACTED] (b) (4) [REDACTED] Both laboratories also used validated methods (reference is made to the original NDA 22-496, Sequence 0000, Section. 4.2.2.1, Analytical Methods and Validation Reports).

FDA Question 2: Confirm whether the specimens that had high levels (>750 mcg/L) were retested and if so, specify whether the results were different on re-evaluation. Also, provide information as to whether it is possible to determine if those specimens contained Exparel liposomes.

Pacira's response:

The upper limit of the bupivacaine calibration curve is 500 mcg/L. All samples which initially gave a result above this concentration were reanalyzed after dilution with control matrix so that the response was within the range of the bupivacaine calibration curve. An incurred sample reanalysis (ISR) for studies (b) (4) and 316 (the studies that included a vast majority of the samples >750 mcg/L) was also performed and this included 9 samples that had high plasma levels (>750 mcg/L). All of these 9 retested samples gave results that were within 20% of the original value. All ISR was performed on the same plasma sample aliquot that had been used for the initial analysis.

With respect to FDA's second question (i.e. if specimens contained liposomes), it is highly unlikely that plasma samples received by the test lab contained intact EXPAREL multivesicular liposomal particles. Freezing of plasma samples (during shipping and storage) will result in disruption of liposome and release of encapsulated bupivacaine, as was described in Section 3.2.P.8.3 of the NDA.

In addition, the LC-MS/MS bioanalytical test method mixes plasma samples with an organic solvent (reference is made to the original application, Sequence 0000, Section 2.7.1.1.2), which dissolves/break down liposomal membrane, to extract all bupivacaine from the plasma sample. Therefore, any liposome that possibly survives freezing would be destroyed by the extraction procedure.

Bupivacaine analysis is therefore a measurement of the entire bupivacaine content in plasma, regardless of whether this represents unencapsulated bupivacaine or bupivacaine encapsulated in EXPAREL liposomes.

FDA Question 3: Clarify whether you tested or could test for bupivacaine levels in blood samples with small quantities, consistent with possible systemic exposures, of Exparel added. Also, Exparel should be added to whole blood prior to centrifugation. Specify if that technique was used in the original determinations.

Pacira's Response:

Although spike and recovery of EXPAREL in whole blood has not been performed, we believe the assay is adequate in determining total bupivacaine content in the blood sample for the reasons outlined below.

The density of EXPAREL liposomal particles is lower than the density of plasma (1.007 vs. 1.025 g/cm³, respectively), and after centrifugation will end up on the surface of the plasma layer; in-house feasibility studies have demonstrated this phenomenon. Therefore, if intact liposomal particles are present in whole blood, centrifugation to obtain plasma will result in all EXPAREL particles being captured in the plasma fraction. During shipping and storage of frozen samples, most particles present will be ruptured by freezing and any remaining particles will be destroyed by the solvent extraction procedure described above.

Thus, whether EXPAREL particles are present or not in the whole blood, procedures used for plasma preparation, shipping, storage, and solvent extraction will result in accurate measurement of total bupivacaine content (encapsulated and unencapsulated) in the whole blood.

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

/s/

SHARON M TURNER RINEHARDT
09/26/2011

From: [Turner-Rinehardt, Sharon](#)
To: ["Dwain Allen";](#)
Subject: NDA 22496 Exparel: Information Request
Date: Wednesday, September 21, 2011 9:49:44 AM

Dear Dwain,
We have the following request for information.

Indicate where in the NDA application the following information can be found

1. The rationale that findings from the pivotal studies conducted abroad can be extrapolated to the US population.

 (b) (4)

I ask that you provide a response by 10 am (EST) tomorrow, Thursday, September 22, 2011 or sooner. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Addiction Products
Phone: (301) 796-2254
Fax: (301) 796-9713
Email: sharon.turner-rinehardt@fda.hhs.gov

ATTACHMENT

On September 21, 2011, an FDA information request was received by Pacira via an email from Ms. Sharon Turner-Rinehardt, Sr. Regulatory Health Project Manager, that requested the following information:

FDA Question 1: The rationale that findings from the pivotal studies conducted abroad can be extrapolated to the US population.

Pacira Response:

The two pivotal clinical studies are Study No. SKY0402-C-317 (conducted in the United States and Study No. SKY0402-C-316 (conducted ex-United States).

SKY0402-C-317 (Bunionectomy) was a Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind study to evaluate the efficacy and safety of intraoperative administration of SKY0402 compared to placebo conducted in the United States.

SKY0402-C-316 (Hemorrhoidectomy) was a Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind study to evaluate the efficacy and safety of SKY0402 compared to placebo.

The rationale that findings from the pivotal studies conducted abroad can be extrapolated to the US population is based on several considerations. These include: 1) one of the two pivotal studies was conducted exclusively in the United States, 2) in the second pivotal study, conducted ex-US, all enrolled subjects were White/Not Hispanic or Latino, 3) SKY0402 is intended for local administration into the surgical wound; therefore studies of the effect of food on bioavailability were considered not applicable, 4) SKY0402 is intended for single-dose-administration, and 5) subgroup analysis conducted on ethnicity and race in the two pivotal studies SKY0402-C-317 and SKY0402-C-316 did not find any clinically significant differences in either efficacy or safety.

Studies have been conducted in the US, Australia, United Kingdom, Belgium, the Netherlands, Czech Republic, the Republic of Georgia, Serbia, and Poland. As the demographics in these countries are reasonably similar, other than the expected decreased ethnic diversity outside the US, it is not expected that the non-US studies differ in a clinically meaningful way from the US studies.

These data are discussed in various sections of the NDA. Please see below excerpts that are copied from the NDA:

2.5 Clinical Overview

2.5.1.5 Timing of Submission

There are no studies currently ongoing and no new studies are planned to be initiated in 2010. Studies have been conducted in the US, Australia, United Kingdom, Belgium, the

Netherlands, Czech Republic, the Republic of Georgia, Serbia, and Poland. As the demographics in these countries are reasonably similar other than the expected decreased ethnic diversity outside the US, it is not expected that the non-US studies differ in a clinically meaningful way from the US studies.

2.5.2 Overview of Biopharmaceutics

SKY0402 is only intended for local administration into the surgical wound; therefore studies of the effect of food on bioavailability are not applicable.

2.5.3 Overview of Clinical Pharmacology

It should be noted that Pacira discussed with the Agency that a hepatic and renal impairment study would not be required since SKY0402 is intended for single-dose administration. This was discussed in a (second) pre-IND meeting on January 11, 2006. Subsequently, Pacira did conduct a hepatic impairment study using SKY0402 (see Study SKY0402-C-110).

2.5.6.2 SKY0402 Safety and Efficacy Summary

Pacira has conducted a study in the special population of subjects with moderate hepatic impairment, and found that dose adjustment is not required in this population.

2.5.4.3 Efficacy Results

A pooled analysis of the primary efficacy endpoint, AUC of NRS-R pain intensity scores, combined the data from the two pivotal studies (SKY0402-C-316 and SKY0402-C-317) using the wWOCF+LOCF imputation method and included all randomized subjects who received study drug (Intent-to-Treat population). The primary efficacy endpoint was also summarized for five subpopulations (age, gender, ethnicity, race, and American Society of Anesthesiology [ASA] class) for the two Phase 3, placebo-controlled studies (SKY0402-C-316 and SKY0402-C-317) combined and for all studies combined.

The secondary efficacy measure of time to first use of supplemental opioid medication use was pooled across nine studies: SKY0402-C-316, SKY0402-C-317, SIMPLE Hemorrhoidectomy 312, SKY0402-C-209, SKY0402-C-207, SKY0402-C-201, (b) (4)

(b) (4) . (b) (4) For the pooled analysis, all SKY0402 doses were combined and compared to bupivacaine HCl and to placebo (for more information, see ISE Appendix 6.2, ISE SAP).

The pivotal hemorrhoidectomy study (SKY0402-C-316) was conducted outside the US. It is common in the US to perform a palliative hemorrhoidectomy procedure (such as banding) prior to attempting a curative one (such as a Milligan-Morgan repair). The banding procedure, however, may be performed on an outpatient basis and cause less pain than curative procedures; this could result in a decreased ability to differentiate active drug from comparator and potentially could impact data collection. Patients in the US who fail palliative therapy will often proceed to a curative surgery where the standards of care are similar in or out of the US despite slight variations in technique or instrumentation. Therefore, it is not expected that the US and

the ex-US populations differ in a clinically meaningful way from each other as patients who would receive SKY0402 after approval.

2.5.4.3.2.3 Subgroup Analyses of Combined Studies

Based on combined data from the pivotal Phase 3 studies SKY0402-C-316 and SKY0402-C-317, the primary efficacy endpoint evaluated by subpopulation for any differences in efficacy results by age, gender, ethnicity, race, or ASA class showed the following:

- Efficacy by Age: The mean AUC of NRS-R pain intensity scores from time 0 to 24 and 72 hours were generally lower in both SKY0402 and placebo groups with increasing age: the lowest scores were in subjects >65 years, followed by the 40-<65 year old group, and the highest AUCs were recorded in the <40 year age group. Since pain scores varied by age for both the SK0402 and placebo groups, and since the scores in both groups were lower in the older age groups, it is unlikely that there is a relationship between AUC of NRS-R pain intensities for SKY0402 and age.
- Efficacy by Gender: The AUC of NRS-R pain intensity scores were higher in males than females for SKY0402-treated and placebo subjects. Higher pain intensity scores were recorded in females receiving placebo and with lower scores following SKY0402, this suggests that females may have had greater pain relief with SKY0402 than males. However, these differences are not likely to be clinically relevant.
- Efficacy by Ethnicity: There were no Hispanic or Latino subjects in the 300 mg SKY0402 group, but for the SKY0402 120 mg dose group, Hispanic or Latino subjects had slightly higher AUC of NRS-R pain intensity scores for time 0 to 24 and 72 hours than non-Hispanic groups; these findings suggest no significant differences in response to SKY0402 by ethnicity.
- Efficacy by Race: There were no non-Caucasians in the 300 mg SKY0402 group, but for the 120 mg SKY0402 dose group, non-Caucasians appeared to have lower AUC of NRS-R pain intensity scores from time 0 to 24 and 72 hours than Caucasian groups. For placebo groups, lower AUC of NRS-R pain intensity scores from time 0 to 24 and 72 hours were reported in Caucasians than non-Caucasians; these findings suggest no significant differences in response to SKY0402 by race.
- Efficacy by ASA Class: There were no ASA Class 3-4 subjects in the 120 mg SKY0402 dose group, two subjects in the 300 mg SKY0402 dose group, and three subjects in the placebo group. Consequently, there were too few subjects to draw conclusions on efficacy by ASA class in the pivotal studies. For the SKY0402 All Doses group, the mean AUC of NRS-R of pain intensity scores from 0 to 24 hours for ASA Class 1-2 subjects was 113.0 and for ASA Class 3-4 subjects was 92.4, and for time 0 to 72 hours, values were 337.6 and 285.1, respectively. For the pooled bupivacaine HCl dose group, the mean AUC of NRS-R of pain intensity scores from 0 to 24 hours for ASA Class 1-2 subjects was 149.8 and for ASA Class 3-4 subjects was 109.2, and for time 0 to 72 hours, values were 436.8 and 344.2, respectively. While some ASA class group differences were observed in these studies, the differences are unlikely to be clinically relevant.

Taken together, the results indicate that dosing modifications are not necessary for the patient subgroups analyzed.

2.5.5.9 Subgroup Analyses (All Wound Infiltration Studies Pool)

The TEAEs were analyzed by age, gender, race, ethnicity, and ASA class (ISS Section 5.2.6). Across the SKY0402, bupivacaine HCl, and placebo groups, the incidence of TEAEs was generally higher in older subjects (≥ 65 years) and in subjects with pre-existing comorbidities (i.e., ASA Class 3-4 subjects). The incidence of TEAEs was higher among females than males. The observed differences in these subgroups were not deemed to be clinically meaningful. Most of the subjects were Caucasian and Non-Hispanic/Latino. Overall, the numbers of subjects in the race and ethnic groups other than Caucasian and Non-Hispanic/Latino are too small to draw meaningful conclusions. However, there does not appear to be any meaningful differences in tolerability based on race and ethnicity.

Please note that further details are provided in 2.7.3 Summary of Clinical Efficacy and 2.7.4 Summary of Clinical Safety and the ISS as referenced above.

1 PAGE HAS BEEN WITHHELD IN FULL AS b4 (CCI/TS) IMMEDIATELY
FOLLOWING THIS PAGE

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

/s/

SHARON M TURNER RINEHARDT
09/26/2011

From: [Turner-Rinehardt, Sharon](#)
To: ["Dwain Allen";](#)
Subject: NDA 22496 Exparel: Information Request
Date: Wednesday, September 21, 2011 9:49:44 AM

Dear Dwain,
We have the following request for information.

Indicate where in the NDA application the following information can be found

1. The rationale that findings from the pivotal studies conducted abroad can be extrapolated to the US population.

(b) (4)

I ask that you provide a response by 10 am (EST) tomorrow, Thursday, September 22, 2011 or sooner. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Addiction Products
Phone: (301) 796-2254
Fax: (301) 796-9713
Email: sharon.turner-rinehardt@fda.hhs.gov

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

/s/

SHARON M TURNER RINEHARDT
09/21/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Wednesday, September 21, 2011 8:58 AM
To: 'Dwain Allen'
Subject: RE: Information request for NDA 22496-September 21, 2011

Dear Dwain,

Please refer to amendment dated September 2, 2011 for NDA 22496. We request the following to continue evaluation of your application.

Provide the data to support the stability of the [REDACTED] (b) (4)
[REDACTED] in the revised Master Batch Record submitted in the
September 2, 2011 amendment.

Provide the testing that is performed to ensure the quality of this [REDACTED] (b) (4)

[REDACTED] (b) (4)

We request a response as soon as possible to complete the review. Do not hesitate to contact me if there are any questions.

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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

/s/

SWATI A PATWARDHAN
09/21/2011

MEMORANDUM OF TELECON

DATE: September 16, 2011

APPLICATION NUMBER: NDA 22496

BETWEEN:

Name: Mark Walters, Sr. V.P., Technical Operations,
Vladimir Kharitonov, Ph.D., V.P. Product Development & Tech. Transfer
Peter Ying, Ph.D., Sr. Manager, Quality Control
Gary Patou, M.D., Chief Medical Officer
Glen Knott, Sr. Associate, Regulatory Affairs
Dwain Allen, Director, Regulatory Affairs

AND

Name: **FDA**

Prasad Peri, Branch Chief, Br. VIII, ONDQA
Art Shaw, CMC reviewer, ONDQA
Swati Patwardhan, Regulatory Project Manager-quality, ONDQA

SUBJECT: Update on [REDACTED] (b) (4) facility.

This is a memo to file regarding telephone conversation on September 16, 2011, with Sponsor to discuss recent inspection findings of [REDACTED] (b) (4)

Pacira was notified that [REDACTED] (b) (4) was recently inspected and the inspection findings can impact approvability of NDA 22496. Pacira stated that they have been aware of the problems at [REDACTED] (b) (4) and therefore, they have chosen [REDACTED] (b) (4). The Agency was concerned about the batches that were tested by [REDACTED] (b) (4). Per Pacira, all batches manufactured since January 2010 had been manufactured using [REDACTED] (U) (4)

Pacira stated that they will submit an amendment to withdraw the [REDACTED] (b) (4) and update responsibilities for [REDACTED] (b) (4). The [REDACTED] (b) (4) was included in the original submission for performing compendial testing of incoming raw materials (drug substance and excipients).

Swati Patwardhan
Regulatory Project Manager-Quality

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

/s/

SWATI A PATWARDHAN
09/22/2011



NDA 022496

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Pacira Pharmaceuticals, Inc.
10450 Science Center Dr.
San Diego, CA 92121

Attention: Dwain Allen
Director, Regulatory Affairs

Dear Mr. Allen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exparel (bupivacaine extended-release liposome injection).

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Sharon Turner-Rinehardt, Sr. Regulatory Project Manager, at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

SARA E STRADLEY
09/07/2011
on behalf of Parinda Jani

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Friday, September 02, 2011 12:40 PM
To: 'Dwain Allen'
Subject: NDA 22496 IR-9-2-2011

Dear Dwain,
We are reviewing NDA 22496 and have following additional request:

- We recommend that you change the acceptance criterion for (b) (4) to NMT (b) (4) which is the Limit of Quantitation
- Please refer to the 5th bullet in the Word document provided prior to the T-con on August 29, 2011. You refer to "acceptable product performance in clinical trials filed in the NDA were conducted using product that fell outside of the FDA proposed specifications." Please provide the specific batches that were used in these clinical trials

Please acknowledge the receipt.

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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

/s/

SWATI A PATWARDHAN
09/02/2011



NDA 22496

DISCIPLINE REVIEW LETTER

Pacira Pharmaceuticals, Inc.
Attention: Dwain K. Allen
Director, Regulatory Affairs
10450 Science Center Dr.
San Diego, CA 92121

Dear Mr. Allen:

Please refer to your September 28, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exparel™ (bupivacaine) Extended-release liposome injection, 150mg/10mL; 300mg/mL.

We also refer to your submissions dated July 22, 2011.

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

A. Drug Substance

[Redacted] (b) (4)

2. Regarding Method 053-10005 [Redacted] (b) (4)
 - a. Provide a chromatogram showing the results of testing bupivacaine spiked with [Redacted] (b) (4)
 - b. Provide the results of testing for [Redacted] (b) (4) in batches of bupivacaine from [Redacted] (b) (4)

B. Drug Product

1. The strength of the drug product should be expressed as 13.3 mg/mL bupivacaine. All specifications, tests, etc. should conform to this expression of strength.
2. Provide a “batch formula”, including the materials used as processing aids.

3. Regarding the Pharmaceutical Development:

c. Provide the data to justify the (b) (4) conditions for the measurement of the (b) (4)

d. Provide the data to support the following statements in 3.2.P.2.2.3.4:

(b) (4)

e. (b) (4)

f. Explain how (b) (4)

g. Specify the strength of the Kenalog[®] used for the drug-drug interaction studies.

4. Regarding the manufacturing facilities:

a. Explain whether Pacira's facility in San Diego is dedicated to the manufacturing of Exparel[™] or whether DepoDur[®] is manufactured using the same facility.

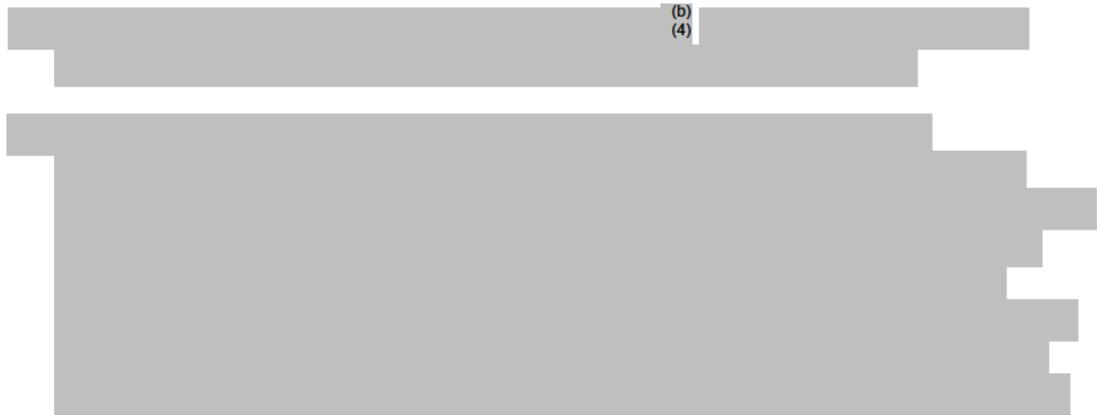
b. Specify where the stability testing is performed.

c. Specify which tests of the drug substance are performed by which testing site.

5. Regarding the manufacturing procedure:

(b) (4)

(b)
(4)



6. Regarding Method 005-01070 (Appearance, Identity and Purity of DPPG Raw Material):
 - a. Provide the source of the standards.
 - b. Provide a copy of a sample chromatogram.
 - c. Include a system Suitability Test in the description of the test method.
7. Regarding the Specifications
 - a. Regarding the % free bupivacaine: The acceptance criterion of “NMT (b)(4)” on stability is not supported by the data or your own analysis. We recommend an acceptance criterion of NMT (b)(4) on stability.
 - b. Regarding the (b)(4) content: The acceptance criterion of “NMT (b)(4)” on stability is not supported by the data or your own analysis. We recommend an acceptance criterion of NMT (b)(4)
 - c. Regarding the pH: Amend the acceptance criteria to reflect the results of the batch data and stability analysis, which show that the pH varies between 6.3 and 7. Alternatively, provide data to demonstrate that the drug product is stable when the pH is in the range from 5.0 to 8.5.
 - d. Include the (b)(4) in the specifications, since a change in the (b)(4) can affect the calculation of the % free bupivacaine. Provide a methods validation report for this test.
8. Regarding the Analytical Procedures
 - a. Regarding Method 005-01002 (Appearance): Include instructions in the appearance test to suspend the particles before viewing.
 - b. Regarding Method 053-40011:
 - i. Identity: Include directions for assessing and reporting the Identity.

- ii. % Free bupivacaine: Provide a justification for including S (% supernatant volume) in the calculation for % free bupivacaine.
 - iii. Total bupivacaine and % free bupivacaine: Amend the calculation procedure to report the content as bupivacaine base.
 - c. Regarding Method 053-40008 (In vitro release assay):
 - i. Provide the procedure used to qualify new lots or grades of BSA for use in the assay.
 - ii. Provide data to justify the statement that “*Sample tubes can be stored in 2–8°C for up to three days before preparation for HPLC analysis.*”
9. Regarding the Batch Analysis: Provide a response to our request for information (e-mail dated August 9, 2011) concerning the discrepancies between the data for in vitro release in the Certificates of Analysis and the Batch Analysis for batches 04-2502 and 05-2502.
10. Regarding the Methods Validation:
 - a. Regarding Method 053-40008 (In vitro release assay):
 - i. Explain why the data for the instrument-to-instrument precision and the data for the day-to day precision for the in vitro release assay are exactly the same.
 - ii. Explain why the test method is so sensitive (b) (4).
 - iii. Provide more specific instructions in the test method to ensure that a calibrated pipetter capable of delivering 1.80 mL exactly, be used for the procedure.
 - b. Regarding Method 053-40013 (b) (4) Provide the peak area percentages of the new compounds observed in the forced degradation studies used in the validation of the assay for (b) (4) Describe any attempts that have been made to identify these compounds.
 - c. Regarding Method 053-00012 (Bupivacaine Related Substances): Provide the calculations for estimating the LOQs and LODs.
 - d. Regarding Method 053-40011 (% Free bupivacaine): Provide a measurement of recovery by spiking bupivacaine into samples of Exparel™ and then centrifuging the spiked sample and measuring the bupivacaine in the supernatant.
11. Regarding the Stability:

- a. Provide data to demonstrate that batches of drug product manufactured at the newly-constructed facility will maintain sterility and absence of endotoxin during storage under the labeled conditions.
- b. We note that the data in the Zuidam and Crommelin paper (Journal of Pharmaceutical Sciences 84 (no. 9): 1113 – 1119, 1995) show that the hydrolysis rate for DPPG is 17 times the hydrolysis rate for (b) (4). Therefore it is possible that DPPG is degrading and may be detectable. Provide data from stability studies showing the release of (b) (4).
- c. Amend the post-approval stability protocol to include testing for (b) (4) (b) (4).
- d. The data in Section P.8.3.4.3 do not support the statement in the labeling that samples may be stored for up to one month at 25°C. The data indicate that the longer the samples were stored at 5°C before storage at room temperature, the greater the increase in (b) (4) is observed.
- e. Specify whether the vials that were “frozen” in the experiments reported in Section P.8.3.5.4 that showed deterioration of the liposomes also showed signs of loss of container/closure integrity. If the contents of vials can be frozen (with concomitant loss in liposome integrity) without loss of container/closure integrity then it will be difficult to determine whether the vials have been frozen. This means that there is no support for the following statement on Page 29 of Section P.8.3 (b) (4)
- f. Provide the details of the vibration testing. ASTM D4169 contains many different types of testing and the phrase “vibration table” is not included in the document.

C. DMF (b) (4) and DMF (b) (4) are deficient. The holders have been notified.

We have determined that the identified deficiencies preclude discussion of labeling changes and/or postmarketing requirements/commitments at this time.

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 Swati Patwardhan, Regulatory Project Manager-Quality, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

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

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

/s/

ALI H AL HAKIM
08/18/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Tuesday, August 09, 2011 10:45 AM
To: 'Dwain Allen'
Cc: Turner-Rinehardt, Sharon
Subject: RE: Information request for NDA 22496

Hi Dwain,

We request clarification for following:

Please explain the following discrepancies between the values for the in vitro release assay.

Lot		4h	24h	48h	72h
04-2502	Value in Batch Analysis Summary Table	(b) (4)			
	Value in COA				
05-2502	Value in Batch Analysis Summary Table				
	Value in COA				

We note this discrepancy in the above two batches. Could you also check other batches to ensure that this discrepancy is limited to these 2 batches only.

Let me know if you have any questions.

Thank you

Swati Patwardhan
 Regulatory Health Project Manager for Quality
 Office of New Drug Quality Assessment (ONDQA)
 Center of New Drug Evaluation and Research
 Phone: 301-796-4085
 Fax: 301-796-9748

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

/s/

SWATI A PATWARDHAN
08/09/2011



NDA 022496

DISCIPLINE REVIEW LETTER

Pacira Pharmaceuticals, Inc.
10450 Science Center Dr.
San Diego, CA 92121

Attention: Dwain Allen
Director, Regulatory Affairs

Dear Mr. Allen:

Please refer to your New Drug Application (NDA) dated and received September 28, 2010, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Exparel (bupivacaine extended-release liposome injection).

The Division of Medication Errors Prevention and Analysis (DMEPA), of the Office of Surveillance and Epidemiology (OSE) have completed their review of your proposed carton and container labeling, and have identified the following deficiencies.

1. CONTAINER LABELING

- a. Revise the dosage form to “Bupivacaine Liposome Extended-Release Injectable Suspension” where it appears in labels since this product is a suspension that requires multiple inversions to re-suspend the particles prior to withdrawal from the vial.
- b. Revise the expression of the strength including deleting ‘Bupivacaine’ and increasing the prominence of the total mg per total volume:
1.3%
133 mg/10 mL
(13.3 mg/mL)

1.3%
266 mg/20 mL
(13.3 mg/mL)
- c. Revise the route of administration warning statement to read as follows: “For Infiltration ONLY. Not for administration by any other route of administration”

- d. Revise the labels of the 133 mg/10 mL versus 266 mg/20 mL sizes to provide added differentiation between the strengths. Currently, the two sizes are differentiated with colors that look similar (green versus blue). Added differentiation is needed to help distinguish the two different total drug contents during drug selection, preparation and administration, and to minimize the risk of wrong strength selection during the drug use process. Revise the colors so they are not so similar, and add the selected colors to other elements of the labels to emphasize the differentiation between the two strengths, 133 mg/10 mL versus 266 mg/20 mL.
- e. Consider revising the NDC numbers for the two proposed sizes. The two NDC numbers for this product [REDACTED] (b) (4) [REDACTED] Postmarketing experience has demonstrated that wrong strength medication errors have occurred with products assigned the same middle portion of the NDC number.

2. CARTON LABELING

- a. Refer to comments 1a, b, c, d, and e.
- b. Remove the strength statement that reads [REDACTED] (b) (4) [REDACTED]

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 Sharon Turner-Rinehardt, Senior Regulatory Health Project Manager, at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

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

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

/s/

SARA E STRADLEY
08/02/2011

From: [Turner-Rinehardt, Sharon](#)
To: ["Dwain Allen";](#)
Subject: NDA 22496 EXPAREL: Information Request
Date: Thursday, June 23, 2011 4:03:39 PM

Dear Dwain,
We have the following information request.

Provide the media fill protocol(s) used to simulate the following six unit operations involved in the ^{(b) (4)} manufacturing of the drug product at the commercial batch scale using the upgraded processing equipment, piping, vessels and process control automation:



Also include the most recent media fill requalifications simulating the



I ask that you provide a response to this information request by 1pm (EST), Monday, June 27, 2011. Any questions regarding this request, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt
Senior Regulatory Health Project Manager

Division of Anesthesia, Analgesia and Addiction Products

Phone: (301) 796-2254

Fax: (301) 796-9713

Email: sharon.turner-rinehardt@fda.hhs.gov

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

/s/

SHARON M TURNER RINEHARDT
06/23/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Monday, June 20, 2011 10:57 AM
To: 'Dwain Allen'
Subject: RE: IR for NDA 22496 6-20-2011

Dear Dwain,

Please refer to your email dated June 15, 2011 requesting clarification on the two issues.

- For issue related to the sampling in the in vitro release assay, we request additional information as follows:

Provide

1. The exact sampling plan, incorporating the proposals in the e-mail dated June 13, 2011 and the e-mail dated June 15, 2011.
2. Measures that will be taken to minimize bacterial growth during the (b) (4) incubation.
3. The proposal for the time points.
4. Plan to perform the tests on existing batches to provide acceptable data.

You can submit the proposal via e-mail, which we would review and provide a feedback, before a formal amendment is submitted.

- For issue related to USAN for bupivacaine. We would like to clarify that requesting USAN is the responsibility of the NDA applicant. (b) (4)

Please refer to 21 CFR 299.4.

Please acknowledge the receipt.

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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

/s/

SWATI A PATWARDHAN
06/20/2011



NDA 022496

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Pacira Pharmaceuticals, Inc.
10450 Science Center Dr.
San Diego, CA 92121

Attention: Dwain Allen
Director, Regulatory Affairs

Dear Mr. Allen:

Please refer to your New Drug Application (NDA) submitted and received September 28, 2010, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Exparel (bupivacaine extended-release liposome injection).

On May 25, 2011, we received your May 25, 2011, solicited 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 October 28, 2011.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 30, 2011.

If you have any questions, call Sharon Turner-Rinehardt, Senior Regulatory Health Project Manager, at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

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

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

/s/

SARA E STRADLEY
06/13/2011

MEMORANDUM OF TELECON

DATE: June 9, 2011

APPLICATION NUMBER: NDA 22496

BETWEEN:

Name: **FDA**

Patrick Marroum, Biopharmaceutics Lead-ONDQA
Angelica Dorantes, Team Leader-Biopharmaceutics-ONDQA
John Duan, Biopharmaceutics reviewer-ONDQA
Danae Christodoulou, CMC Lead, ONDQA
Art Shaw, CMC reviewer, ONDQA
Swati Patwardhan, Regulatory Project Manager-quality, ONDQA

AND

Name: **Pacira**

Mark Walters, Sr. V.P., Technical Operations,
Vladimir Kharitonov, Ph.D., V.P. Product Development & Tech. Transfer
Peter Ying, Ph.D., Sr. Manager, Quality Control
Glen Knott, Sr. Associate, Regulatory Affairs
Dwain Allen, Director, Regulatory Affairs

SUBJECT: In Vitro Release testing program for NDA 22-496

This Memo to file documents the teleconference between the Agency and Pacira held on June 9, 2011, to discuss the adequacy of their proposed approach for the setting of the in vitro release specifications of their liposomal product submitted under NDA 22-496. A set of questions were provided prior to the T-con, which are included as an attachment at the end of this Memo.

Reference is made to the IR (information request) Letter sent on June 3, 2011, requesting additional in vitro drug release information. Reference is also made to Pacira's response via an eMail correspondence dated June 6, 2011. In this eMail Pacira mentions that their understanding was that they had already responded adequately to the Agency's previous requests in their Amendment to the NDA dated February 24, 2011. In our e-mail dated June 7, 2011, we informed Pacira that we had reviewed the February 24, 2011 amendment and that our responses in the June 3, IR letter were based on that submission. In an e-mail dated June 7, 2011, Pacira requested a teleconference to seek some clarification related to the comments included in the IR

1 PAGE HAS BEEN WITHHELD IN FULL AS b4 (CCI/TS)
IMMEDIATELY FOLLOWING THIS PAGE

release test be submitted, in which the recommendations made in this teleconference and in the previously submitted IR Letter dated June 3, 2011, be considered.

Swati Patwardhan
Regulatory Project Manager-Quality, ONDQA

Patrick Marroum
Biopharmaceutics Lead-ONDQA

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

/s/

SWATI A PATWARDHAN
06/20/2011

PATRICK J MARROUM
06/20/2011



NDA 22-496

INFORMATION REQUEST

Pacira Pharmaceuticals, Inc.
Attention: Dwain K. Allen
Director, Regulatory Affairs
10450 Science Center Dr.
San Diego, CA 92121

Dear Mr. Allen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exparel™ (bupivacaine) Extended-release liposome injection, 150mg/10mL; 300mg/mL.

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

1. As stated in previous comments, [REDACTED] (b) (4)
2. [REDACTED] (b) (4)
3. [REDACTED] (b) (4)
4. [REDACTED] (b) (4)

5. The in vitro release acceptance criteria at 4, 24 and 48 hours are recommended as follows while the criterion for the last time point will be determined after the sampling time is extended to 96 hours.

4 hours:  (b) (4)
24 hours: 
48 hours: 

We request a response no later than June 15, 2011.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager-Quality, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

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

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
06/03/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Thursday, June 02, 2011 9:53 AM
To: 'Dwain Allen'
Cc: Turner-Rinehardt, Sharon
Subject: RE: Information request for NDA 22496-6/2/2011

Dear Dwain,

Could you specify how many vials are taken for testing for each assay or point to where this information can be found in the NDA.

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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

/s/

SWATI A PATWARDHAN
06/02/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Tuesday, May 17, 2011 10:50 AM
To: 'Dwain Allen'
Subject: RE: Information request for NDA 22496

Dear Dwain,

- We refer to the amendment dated May 13, 2011:
Please let us know when do you expect to submit an Executed Batch Record for the preparation of the Bulk Suspension for at least one batch using the new facility and Master Batch Record
- Provide data to demonstrate that the amount of (b) (4) in Exparel® is present at a level which will yield NMT (b) (4).
If these studies show that (b) (4) is present above this level, add a test and acceptance criterion for (b) (4) as part of the specifications and commit to monitoring (b) (4) on stability. Alternatively perform appropriate testing to show that (b) (4) is not genotoxic.

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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

/s/

SWATI A PATWARDHAN
05/17/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Monday, May 09, 2011 4:57 PM
To: 'Dwain Allen'
Subject: RE: NDA 22-496-IR

Hi Dwain,

In section 3.2.P.4 you have provided specifications for the DEPC, DPPG and (b) (4). All of these included references to test procedures provided by the DMF holders. You have included brief descriptions of these test procedures in their NDA.

Please clarify if you are performing the tests provided by the DMF holders as part of your receipt of the excipients or are you relying on your own Identity and Purity tests along with COAs from the suppliers.

If the test are performed as described by the DMF holders, then we suggest that you communicate with the DMF holders concerning comments we sent to the DMF holders regarding their test procedures so that Pacira can update the procedures in their NDA.

(b) (4) - DMF Holder was sent an Deficiency letter on February 25, 2011

(b) (4) -DMF Holder was sent an Deficiency letter on February 25, 2011

(b) (4) -DMF Holder was sent an Deficiency letter on February 25, 2011

(b) (4) -DMF Holder was sent an Deficiency letter on April 28, 2011

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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

/s/

SWATI A PATWARDHAN
05/09/2011

From: [Turner-Rinehardt, Sharon](#)
To: ["Dwain Allen";](#)
Subject: NDA 22496 EXPAREL: Information Request
Date: Friday, May 06, 2011 6:11:27 PM

Dear Dwain,
Provide a copy of an Executed batch Record (EBR) using the Master Batch Record (MBR) already provided in section 3.2.P.3.3. The version of the EBR already provided in 3.2.R is for an older, smaller process and does not match the MBR provided in 3.2.P.3.3. I ask that you provide this information by Tuesday, May 10, 2011. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22 Room 3193
Silver Spring, MD 20993-0002
Phone: (301) 796-2254
Fax: (301) 796-9713
Email: sharon.turner-rinehardt@fda.hhs.gov

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

/s/

SHARON M TURNER RINEHARDT
05/06/2011

From: [Turner-Rinehardt, Sharon](#)
To: ["Dwain Allen";](#)
Subject: NDA 22496 EXPAREL: Information Request
Date: Thursday, April 21, 2011 4:35:22 PM

Dear Dwain,
We have the following information request.

Provide the protocol and summary report, with associated data, for the

 (b) (4)

I ask that you provide this information by 1 pm (EST) April 28, 2011 or sooner.
Any questions regarding this request, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Addiction Products
Phone: (301) 796-2254
Fax: (301) 796-9713
Email: sharon.turner-rinehardt@fda.hhs.gov

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

/s/

SHARON M TURNER RINEHARDT
04/21/2011



NDA 22-496

**METHODS VALIDATION
MATERIALS RECEIVED**

Pacira Pharmaceuticals, Inc.
Attention: Dwain K. Allen
Director, Regulatory Affairs
10450 Science Ctr. Dr.
San Diego, CA 92121

Dear Mr. Dwain K. Allen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exparel (bupivacaine liposomal extended release) Injection, 150 mg/10 mL and 300 mg/20 mL and to our 3/31/2011 letter requesting sample materials for methods validation testing.

We acknowledge receipt on 4/12/2011 of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

JAMES F ALLGIRE
04/12/2011



NDA 22496

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Pacira Pharmaceuticals, Inc.
Attention: Dwain K. Allen
Director, Regulatory Affairs
10450 Science Ctr. Dr.
San Diego, CA 92121

Dear Mr. Dwain K. Allen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exparel (bupivacaine liposomal extended release) Injection, 150 mg/10 mL and 300 mg/20 mL.

We will be performing methods validation studies on Exparel (bupivacaine liposomal extended release) Injection, as described in NDA 22496.

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



Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis

Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

JAMES F ALLGIRE
03/31/2011

From: [Turner-Rinehardt, Sharon](#)
To: ["Dwain Allen";](#)
Subject: NDA 22496 EXPAREL: Information Request
Date: Friday, March 25, 2011 3:22:30 PM

Dear Dwain,
We have the following information requests.

1. Provide a description of how the investigators remained blinded in study SKY0402-C-316 and 317 during administration of the study drug. The syringes were to have been covered with finger cots to prevent the investigators from seeing the contents (i.e., study drug); however, they were also to have been able to discern the presence of blood in the syringe during attempts at aspiration.
2. Provide a sample of Exparel in a clear container.
3. Provide a list of all subjects who had plasma bupivacaine levels that were 750 ng/mL or higher and a copy of their CRFs.
4. Perform an analysis of the safety database (i.e., all clinical studies) identifying those subjects who had any sign or symptom of either neurotoxicity or cardiotoxicity following administration of study drug. Create a table of the results providing the following information in separate columns:

Subject ID
Study Number
Study Drug
Dose
Adverse event
Time to onset following study drug administration
Plasma bupivacaine level at (or closest to) the time of onset - if available
Intervention(s)
Time to resolution (from time of onset)
Outcome

I ask that you provide a response by noon (EST), Friday, April 1, 2011. If you have any questions regarding this request, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Senior Regulatory Health Project Manager

Division of Anesthesia, Analgesia and Addiction Products

Phone: (301) 796-2254

Fax: (301) 796-9713

Email: sharon.turner-rinehardt@fda.hhs.gov

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

/s/

SHARON M TURNER RINEHARDT
03/25/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Thursday, March 10, 2011 3:45 PM
To: 'Dwain Allen'
Cc: Turner-Rinehardt, Sharon
Subject: RE: DMF correspondence for NDA 22-496

Hi Dwain,

While reviewing DMFs in support of your NDA application 22496, following DMF holders were contacted to provide additional information request to complete the review of those respected DMFs

MF #	DMF holder	Subject	Communication type	Comm. Date
				(b) (4)

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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

/s/

SWATI A PATWARDHAN
03/10/2011



NDA 022496

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Pacira Pharmaceuticals, Inc
10450 Science Center Drive
San Diego, California 92121

ATTENTION: Dwain K. Allen
Director, Regulatory Affairs

Dear Mr. Allen:

Please refer to your New Drug Application (NDA) dated September 28, 2010, received September 28, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bupivacaine Extended-release Liposome Injection, 150 mg/mL and 300 mg/mL.

We also refer to your November 12, 2010 correspondence, received November 12, 2010, requesting reconsideration of your proposed proprietary name, Exparel. We have completed our review of the proposed proprietary name, Exparel and have concluded that it is acceptable.

The proposed proprietary name, Exparel, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your November 12, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Abolade (Bola) Adeolu, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4264. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Sharon Turner-Rinehardt at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
02/08/2011

From: [Turner-Rinehardt, Sharon](#)
To: ["dwaina@pacira.com"](mailto:dwaina@pacira.com);
Subject: NDA 22496 SKY0402 Bupivacaine: Information Request
Date: Thursday, January 20, 2011 10:57:24 AM
Attachments: [IR N22496_012011.pdf](#)

Dear Dwain,

As Tanya Clayton may have mentioned, I am your new project manager for this NDA. My contact information is under my signature.

Also, I have the following information requests. Please see the attached document for the first information request and below for the second one. I ask that you respond by 2 pm (EST) Tuesday, January 25, 2011.

Request 2:

For Study SKY0402-C-317 (bunionectomy), we have been unable to locate a dataset containing the raw pain intensity score for each patient at each assessed time point. Such a dataset was located for Study SKY0404-C-316. The dataset was named "NRSR.xpt". If the dataset was submitted, provide the location and name of the dataset within the submission. If it was not included, submit the dataset for Study SKY0402-C-317 using the same format as that of the dataset submitted for Study SKY0402-C-316.

If you have any questions regarding this request, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt
**Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22 Room 3193
Silver Spring, MD 20993-0002
Phone: (301) 796-2254
Fax: (301) 796-9713
Email: sharon.turner-rinehardt@fda.hhs.gov**

NDA 22496
Information Request
January 20, 2011

The Certificate of Analysis for bupivacaine obtained from (b) (4) has an acceptance criterion of NMT (b) (4) for the process impurity (b) (4) (b) (4)

Based on the proposed maximum dose of (b) (4) bupivacaine per day this would represent an unacceptable maximum intake of (b) (4) which is (b) (4) the permissible amount for genotoxic impurities set at 1.5 mcg/day [FDA CDER Draft Guidance for Industry - Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (Dec. 2008)].

You may address this issue in any of the following ways:

1. Reduce the maximum amount of (b) (4) permitted in the finished drug product from (b) (4) to a level equal to or below the recommended threshold of (b) (4). Three ways to accomplish this are to:
 - a. Add a test for (b) (4) with an acceptance criterion of NMT (b) (4) in the specification for the drug product. Include a methods validation report to show that the assay is capable of quantifying (b) (4) at this level.
 - b. Provide data to show that the manufacturing process for the drug product is capable of reducing the amount of (b) (4) to (b) (4). Include a methods validation report to show that the assay is capable of quantifying (b) (4) at this level.
 - c. Set an acceptance criterion for (b) (4) in the bupivacaine drug substance of NMT (b) (4).
2. Provide evidence from nonclinical testing which demonstrates that (b) (4) is not carcinogenic.

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

/s/

SHARON M TURNER RINEHARDT
01/20/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Friday, January 14, 2011 10:34 AM
To: 'dwaina@pacira.com'
Cc: Turner-Rinehardt, Sharon
Subject: Re: IR for NDA 22-496 1-14-2011

Dear Mr. Allen,

We have the following comments about your proposed in vitro release method and the acceptance criteria related to your NDA application 22-496 Bupivacaine liposome injection.



- **The last time point should be chosen representing the time at which release or until a plateau if there is incomplete release.** (b) (4)

Please acknowledge the receipt and let me know if you have any questions.

Swati Patwardhan, MS
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Phone (301)796-4085
Fax (301)796-9748

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

/s/

SWATI A PATWARDHAN
01/14/2011

From: [Clayton, Tanya](#)
To: [Dwain Allen;](#)
cc: [Clayton, Tanya;](#)
Subject: Information Request -NDA 22496
Date: Tuesday, January 04, 2011 11:55:14 AM
Attachments: [ClinPharm Table.doc](#)

Hello Dwain,

I hope you had a great holiday! The review team is requesting the following information:

For QT Studies SKY0402-C-105 and SKY0402-C-107 submit the following information.

- Complete the attached ClinPharm table.
- Update variable EGDTC up to seconds for raw triplicate ECG data.
- ECG analysis dataset which is the average of the triplicates at each time point.
- Give us QTcP slope, QTcl slope of each subject (alpha in report) for different models in dataset(s) also, please indicate which model/alpha is chosen for QTcl, QTcP calculation in ECG dataset.
- Submit all related ECG waveforms to the ECG warehouse at www.ecgwarehouse.com.

Please submit the requested items ASAP.

Kind Regards,
Tanya D. Clayton
Senior Regulatory Health Project Manager
Food and Drug Administration
Division of Anesthesia and Analgesia Products
(301) 796-0871 Phone
Tanya.Clayton@fda.hhs.gov

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

/s/

TANYA D CLAYTON
01/04/2011



NDA 022496

FILING COMMUNICATION

Pacira Pharmaceuticals, Inc.
10450 Science Center Drive
San Diego, CA 92121

Attention: Dwain K. Allen
Director, Regulatory Affairs

Dear Mr. Allen:

Please refer to your New Drug Application (NDA) dated September 28, 2010, received September 28, 2010 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for SKY0402 (bupivacaine extended-release liposome injection).

We also refer to your submissions dated October 21, November 8, 12, 18 and 23, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 28, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team, and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 5, 2011.

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

1. You did not provide a justification for having different acceptance criteria for the percent free bupivacaine on stability (b) (4) compared with at release (b) (4)
2. In the label, you have not provided an adequate bridge to the reproductive toxicology data of the bupivacaine reference drug Marcaine®. It is not clear how the safety margins described for bupivacaine in Marcaine can be applied to your drug product used at the maximum recommended human dose.

3. You have not provided complete (b) (4) data for your proposed commercial process.
4. You have not provided comparability data for the drug product, nor a comparability protocol, to assess the alternate drug substance supplier, (b) (4) and the alternate lipid supplier, (b) (4).
5. You have not monitored or reported (b) (4) content in your drug product batches at release.
6. You have not monitored leachables in your drug product.
7. We note the discrepancy between quantitative composition per mL, where the drug substance weight is expressed as “anhydrous bupivacaine hydrochloride salt equivalent” versus the batch formula, where the drug substance weight is expressed as bupivacaine free base equivalent.
8. The total viable count listed for (b) (4) were listed as (b) (4) (page 28 Section 3.2.A.1). However, you have not related the acceptance criteria to the (b) (4).
9. For the media fill data in Table 31, page 62, Section 3.2.A.1, you did not provide the reason for rejection of the vials.
10. You did not provide the validation study that supports (b) (4)
(b) (4)
11. (b) (4)
(b) (4)
(b) (4)
12. You did not provide in vitro release profiles between (b) (4) batches.

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

To address the potential review issues listed above, we request that you submit the following information:

1. Provide a justification for having different acceptance criteria for the percent free bupivacaine on stability (b) (4) compared with at release (b) (4)
2. Provide an adequate scientific bridge to allow meaningful use of the reproductive toxicology data contained in the bupivacaine reference drug Marcaine® in your proposed label.
3. As agreed with the Division during the teleconference of November 23, 2010, submit complete process validation data for your proposed commercial process in February 2011, after completion of modifications in your manufacturing equipment for the (b) (4) production scale.
4. Withdraw the alternate drug substance site, (b) (4) and the alternate lipid supplier, (b) (4). These suppliers will not be reviewed as alternate suppliers during this review cycle, and may be submitted in a post-approval supplement as per the SUPAC-MR requirements for a site-transfer.
5. Revise the phrase “expressed as anhydrous bupivacaine HCl equivalent” to “expressed as anhydrous bupivacaine free base equivalent” in the unit quantitative composition of your drug product, Module 3, Section 3.2.P.1, Table 1.
6. Provide the (b) (4) content in your drug product, in batches produced at the (b) (4) at release. Monitor and report (b) (4) content in your production scale batches and establish a specification, or justify to the contrary, as appropriate.
7. Provide leachables levels in your NDA batches, e.g., rubber oligomers, (b) (4) or other identified extractables in your extraction studies. The safety of leachable levels observed should be supported by a toxicological evaluation, taking into account the potential that such impurities may be known or suspected highly reactive and/or genotoxic compounds. Depending on the identity of the leachables, their levels, and the quality of toxicologic support, further nonclinical studies to support safety qualification may be necessary.
8. Relate the acceptance criteria for the (b) (4) to the volume of (b) (4).

9. Provide the reason for rejection of the vials and information on any rejected vials integral or cosmetic rejects.
10. Provide the validation study that supports [REDACTED] (b) (4)
[REDACTED]
11. Provide revised specifications for the in vitro release test.
12. Provide in vitro release profiles between [REDACTED] (b) (4) batches.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Anesthesia and Analgesia Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

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

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

If you have any questions, call Tanya Clayton, Senior Regulatory Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

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

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

/s/

RIGOBERTO A ROCA on behalf of BOB A RAPPAPORT
12/10/2010



IND 069198

MEETING MINUTES

Pacira Pharmaceuticals, Inc.
10450 Science Center Drive
San Diego, CA 92121

Attention: Dwain Allen
Director Regulatory Affairs

Dear Mr. Allen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SKY0402 (bupivacaine extended-release liposome injection.)

We also refer to the meeting between representatives of your firm and the FDA on February 16, 2010. The purpose of the meeting was to provide feedback on your preparations for submitting a New Drug Application (NDA) for your product.

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 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES



Meeting Date: February 16, 2010
Time: 1:30 PM EST
Location: Teleconference
Application: IND 069198
Regulatory Status: Active IND
Products: SKY0402 (bupivacaine extended-release liposome injection)
Proposed Indication: Post-operative pain management
Sponsor: Pacira Pharmaceuticals, Inc.
Type of Meeting: Type B, pre-NDA
Meeting Chair: Bindi Nikhar, M.D., Anesthesia Team Leader
 Division of Anesthesia and Analgesia Products (DAAP)
Minutes Recorder: Kimberly Compton, Project Manager, DAAP

Industry Representatives	Title
Dwain Allen	Director, Regulatory Affairs, Pacira Pharmaceuticals (Pacira)
Gary Patou, M.D.	Chief Medical Officer (Pacira)
Erol Onel, M.D.	Senior Director, Medical Affairs (Pacira)
Mark Walters	Senior Vice President, Technical Operations & Business Development (Pacira)
Vladimir Kharitonov, Ph.D.	Executive Director, Product Development & Technology Transfer (Pacira)
	(b) (4)
FDA	Title
Rigoberto Roca, M.D.	Deputy Director, DAAP
Bindi Nikhar, M.D.	Medical Team Leader, DAAP
Arthur Simone, M.D., Ph.D.	Medical Officer, DAAP
Gary Bond, Ph.D.	Pharmacology/Toxicology Reviewer, DAAP
Adam Wasserman, Ph.D.	Supervisory Pharmacologist, DAAP
Dionne Price, Ph.D.	Statistical Team leader, Division of Biometrics II (DBII)
David Petullo, Ph.D.	Statistical Reviewer, DBII
Nina Ni, Ph.D.	Chemistry Reviewer, Office of New Drug Quality Assessment (ONDQA)
Danae Christodoulou, Ph.D.	Pharmaceutical Assessment Lead (PAL), ONDQA
David Lee, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Susan Leibenhaut, M.D.,	Division of Scientific Investigations (DSI)
Tejashri Purohit-Sheth, M.D.	DSI Team Leader
Marty Pollock, R.Ph.	Safety Evaluator, Office of Surveillance and Epidemiology (OSE)
Kim Compton	Senior Regulatory Project Manager, DAAP

Background:

On February 10, 2010, (prior to the February 16 meeting) the Agency forwarded to the firm the Agency's comments and responses to the questions posed by the sponsor in their January 7, 2010, meeting package.

The firm indicated they would like to discuss Questions 2, 11, 14, and 15 and provide clarifications for questions 1, 4, 6, and 12 as well as Chemistry Comments 1, 5, and 7.

Presented below are the Agency's comments and responses to questions in the background meeting package. The sponsor's questions are listed in *italics*, with Agency responses and comments in **bold**. The firm's replies follow the response to which they pertain in *italic* text, and discussion that took place at the meeting is captured in normal text following the question to which it pertains.

Meeting:

Chemistry Questions

Question 14

Is Pacira's basic approach to (b) (4) k batches prior to filling as a single finished product lot acceptable to the FDA? Please see Attachment 8 for further information.

FDA Response

This is acceptable with the following caveats:

- a. **Propose acceptance criteria of all critical in-process controls (IPCs), e.g.,**
(b) (4)
- b. **Propose and justify a range for bupivacaine concentration and acceptable** (b) (4)
- c. **At least one registration batch that is manufactured by** (b) (4)
(b) (4) **batches needs to be filed in the NDA as a bridging study for the proposed changes in manufacturing scale-up, with a minimum of 6-month long term and accelerated stability data; this should be submitted in addition to the primary stability batches.**
- d. **Use two individual** (b) (4) **batches with the extreme limits of the proposed bupivacaine liposomal concentrations** (b) (4).

Discussion

See Question 15

Question 15

Assuming Pacira adequately addresses the points originally requested by the Agency for the larger scale, is the approach proposed by Pacira for the (b) (4) scale acceptable to the Agency? Please see Attachment 8 for further information.

FDA Response

See response to Question 14.

Discussion of Questions 14 and 15

The sponsor stated that agreement on the scale-up plan had been reached at the End-of-Phase 2 (EOP2) meeting and noted that both the clinical and NDA registration (stability) batches are produced from the same (b) (4) batch. After scale-up the sponsor will submit data from the (b) (4) batches to the NDA. The sponsor plans to test and (b) (4), only after the scale-up criteria are met.

The Agency stated that if the sponsor is not changing anything in manufacturing from the (b) (4) to the (b) (4) batches, then the proposal is acceptable since it is less than 2.5 X scale-up. However, if the bupivacaine concentration results have wide variability in the batches (b) (4), then the sponsor will have difficulty controlling the bupivacaine concentration and other critical physicochemical attributes of the liposome, which is concerning to the Division.

The sponsor stated that page 18 of the background package provided acceptance criteria for total bupivacaine concentration (b) (4) (b) (4), noting that they are targeting to overshoot a bit at manufacturing (b) (4) at final release.

The sponsor stated that they do not have stability data from any development batches of the larger scale yet, only at the (b) (4) scale, noting they will be using the same containers for the larger scale as those for the (b) (4) scale.

The Division stated that they were uncomfortable with this approach since no pooled batches were used in the clinical trials and noted that data from (b) (4) pooled batches is very limited. The Division stated that the sponsor will need to provide something more representative, not necessarily (b) (4) but larger than (b) (4) of the final plan in the NDA, including some data on pooled batches and a bridging stability study. The NDA will not be acceptable without this information.

The sponsor stated that they cannot manufacture at the (b) (4) scale yet, but can have that data for the Prior Approval Inspection. They inquired if they could submit the NDA with 3 months accelerated (room temperature) and 3 months normal (refrigerated), (b) (4) stability data and provide the 6-month data during the NDA review, on three batches.

The Division stated that it is likely this will be acceptable, but noted that it would require internal discussion and the Division will include a Post-Meeting note in the meeting minutes.

*****Post-Meeting Note-**

After internal discussion, the proposal to submit 3-month stability data on three NDA batches at the (b) (4) scale is acceptable. The 6-month data may be amended during NDA review.

Additional Chemistry Comments

- 1. Express the drug substance as anhydrous free base in the drug product.**
- 2. Propose limits for bacterial endotoxins for all excipients.**

3. **Justify the proposed limit of free bupivacaine in drug product based on the observed levels on release and stability data.**
4. **Provide a particle size distribution profile as “Report Result” in the specifications.**
5. **Provide additional in vitro release data between time 0 and 24 hours (every 6 hours) and include in the drug release specification.**
6. **Propose specifications for [REDACTED] (b) (4)ed impurities/degradants in the drug product.**
7. **Provide stability data of unloaded liposomes (placebo), as per FDA draft Guidance on liposome drug products.**
8. **Provide a detailed pharmaceutical development report, including a justification for the selection of critical process controls that impact critical quality attributes and specifications in the NDA.**
9. **Refer to ICH Q8, ICH Q9, and ICH Q10 documents for additional guidance.**
10. **Provide data on physicochemical compatibility of bupivacaine with other co-administered drugs or implants. Include data on particulates, bupivacaine, assay and impurities/degradants.**
11. **Provide a specification for osmolality for the drug product.**
12. **Provide a list of all manufacturing and testing facilities, in alphabetical order, statement about their cGMP status and whether they are ready for inspections at the time of NDA submission. For all manufacturing sites, provide a contact name, telephone number, facsimile number and email address. Clearly specify the responsibilities of each facility, and which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.**

Discussion

The Division noted that some of the data showed greater than (b) (4) release of bupivacaine at 24 hours and consequently, the Division is interested in gaining a better understanding of the release profile of the product. The sponsor stated that they have 4-hour release data for some product and will provide that in the NDA.

The Division stated that it is acceptable to express the product as the bupivacaine HCl equivalent, but the Agency is moving away from including salts in the established names, if the strength is expressed as the free base.

The sponsor stated that they have good stability data for the loaded liposome and proposes to not provide data on the placebo (unloaded) liposomes. The Division stated that the sponsor should provide a rationale to support this position in their NDA.

Non-clinical Toxicology Questions

Question 1

Based on feedback from the Agency, Pacira has conducted the specified nonclinical studies (pharmacokinetic studies in rat, guinea pig, mini pig, rabbit and dog; and several toxicology studies including single dose studies in rat, rabbit and dog via multiple routes of administration, 28 day repeat-dose studies in rabbit and dog, and local tolerance studies) in support of a file-able NDA. Pacira plans to also provide a detailed literature review of bupivacaine pharmacology, pharmacokinetic, and toxicology.

Does the Agency concur that a review of the literature on the nonclinical pharmacology, pharmacokinetics, and toxicology in addition to the pharmacokinetic and toxicology studies referenced above is acceptable for fulfilling the requirements of the Nonclinical Pharmacology and Toxicology Sections of the NDA?

Please see Attachment 2 for summary information.

FDA Response



Note that determination of the appropriateness of a 505(b)(2) submission and resolution of the juvenile testing issue(s) in Question 2 will be necessary for successful filing of the NDA.

Discussion

There was no further discussion on this point.

Question 2

Pacira plans to conduct a juvenile toxicology study in rats to support dosing in a pediatric age group less than 12 years of age and to conduct this in parallel with the proposed adolescent human trial. Does the Agency concur with this juvenile toxicology plan and timing?

Please see Attachment 2 and Attachment 7 for summary information.

FDA Response

While the plan appears supported, submit to the IND a detailed scientific justification that the acute-rat and repeat-dose 28-day dog studies are sufficient to support the safety of the proposed adolescent clinical trial. Otherwise, you will need to conduct a 28-day

rat study similar to the 28-day dog study prior to initiation of the adolescent clinical trial. Juvenile animal toxicology testing to support pediatric studies < 12 years old should be submitted prior to any clinical trials in this population.

Discussion

The Division stated that in accordance with the February 2006 FDA Guidance for Industry titled "Nonclinical Safety Evaluation of Pediatric Drug Products", the sponsor's proposal to conduct one non-clinical (rodent) juvenile animal study to support clinical studies in patients less than 12 years old is acceptable at this point, but noted that if data from other studies were to indicate safety concerns in juveniles, or demonstrate that the rat is not the best model, the sponsor may need to conduct non-clinical studies in a second species.

Clinical Pharmacology and Clinical Questions

Question 3

Pacira conducted two studies evaluating the ECG effects of increasing doses of EXPAREL in normal volunteers with multiple ECGs obtained at plasma bupivacaine concentrations up to 647 ng/mL up to a supratherapeutic dose of 750mg. Results from these two studies, nonclinical and additional cardiac safety data from several clinical studies can be found in Attachment 3. Does the Agency concur that Pacira has satisfactorily investigated the cardiac safety of EXPAREL and that no further studies are necessary?

FDA Response

Provided the thorough QTc studies were appropriately designed and executed and cover the highest systemic exposures likely with the to-be-labeled dosing recommendations, the issue of QTc-related effects of the drug product have been addressed.

Whether Exparel is associated with other cardiac function abnormalities will be determined by the hemodynamic and ECG assessments conducted in the clinical trials. Your analysis of these data should include an assessment of any changes from baseline that were observed following dosing, particularly at T_{max}, for the various surgical procedures, routes of administration, and more vulnerable patient populations (e.g., the elderly, those with underlying cardiovascular disease, ASA-PS 3 and 4).

It is noted that systemic exposures greater than 1 mcg/mL were observed following (b) (4). As cardiac toxicity can occur at lower levels in some patients, an analysis of the hemodynamic and ECG findings at and near T_{max} will be critical to support a dosing regimen. Insufficient data in this regard would be considered a major deficiency in the characterization of the risk profile for Exparel.

Discussion

There was no further discussion on this point.

Question 4

The time to onset of the analgesia following infiltration by DepoBupivacaine was evaluated in an initial study (SKY0402-C-106) undertaken by Pacira; results of that were confirmed and expanded upon by a subsequent study (SKY0402-C-109). Results of the trials revealed that the time to onset for EXPAREL was under 2 minutes, and that the time necessary to achieve a 30% reduction in pain was under five minutes. A summary of these two studies can be found in Attachment 3. Does the Agency concur that the data to be included in the NDA adequately addresses the time to onset of analgesia question?

FDA Response

The recommendation by us that the onset and duration of analgesia be assessed following actual skin incision, as opposed to needle prick, was intended to mean that these data were to be captured following actual clinical, i.e., post-surgical, use. The information in trial SKY0402-C-109 will be useful, however, when combined with data from your other trials where such data were collected.

In the NDA submission, any observed differences in onset or duration based on the surgical-procedure or dosing should be identified for possible inclusion in the label if the product is approved.

Discussion

The Division stated that it is important for the clinician to know the expected time of onset of analgesia for the drug in order to determine whether the treatment was adequate, or whether an alternative therapy needs to be considered.

In addition, it is important to clarify the doses used for the various surgical procedures so the safety of that dose and its systemic exposure may be evaluated.

Question 5

Reference is made to the Agency's letter, dated November 3, 2009, regarding Pacira's Clinical Protocol

[Redacted]

[Redacted]

FDA Response

[Redacted]

(b) (4)



Discussion

There was no further discussion on this point.

Question 6

Reference is also made to the Agency's letter, dated July 2, 2009, regarding Pacira's Clinical Protocol

(b) (4)



FDA Response

(b) (4)



Question 7

Does the Agency agree that the EXPAREL safety database, which exceeds 1000 patients and volunteers in 21 clinical trials and at doses up to 750 mg by injection as a single dose, constitutes an acceptable NDA safety database? EXPAREL has demonstrated an adverse event profile similar to bupivacaine HCl solution in multiple clinical trials. Please see Attachment 3 for further information.

FDA Response

It is not clear from your submission what dose(s) you are proposing for approval. This limits our ability to address this issue, but the following guidance should be useful.

The clinical development program must include a sufficient number of Exparel exposures to characterize the risk profile of the product. This includes safety assessments in the more vulnerable patient populations likely to receive the product if it were approved (e.g., the elderly and sicker patients) and for the surgical procedures following which the drug is likely to be administered. In addition, there should be a sufficient number of exposures at the highest to-be-labeled dose to allow an adequate characterization of risk at this end of the dosing spectrum. These exposures should be with the to-be-marketed formulation.

Discussion

There was no further discussion on this point.

Question 8

Does the Agency concur that the two Phase 3 studies that evaluated the efficacy of EXPAREL in representative models of both orthopedic, bunionectomy (SKY0402-C-317) and general surgical, hemorrhoidectomy (SKY0402-C-316) are two adequate and well controlled double blind randomized placebo-controlled trials that support the efficacy claim for single-dose administration by local infiltration into the surgical wound prior to closure to provide postoperative analgesia? (Both of these trials met their primary endpoints with statistically significant reductions in the AUCs of the NRS scores through 36 and 72 hours respectively and showed statistically significant reductions in opioid use.) Please see Attachment 3 for further study information and Attachment 9 for the proposed Package Insert.

FDA Response

A formal review of the pivotal trials will be conducted at the time of the NDA submission. The trials appear to be appropriately designed to compare Exparel against placebo for the two procedures studied. However, there are several issues that should be addressed and submitted together with the NDA submission:

- a. An evidence-based rationale is required to support the claim that bunionectomy is a model for orthopedic procedures and hemorrhoidectomy is a model for general surgical procedures.
- b. Labeling will require the specification of a dose to be used for each procedure as well as adjustments to the dose, if needed, for specific patient populations, e.g., sicker or elderly patients.
- c. If there is a difference in requirements for various surgical procedures, then doses need to be specified for each procedure.
- d. The label should also reflect differences, where they exist, between onset and duration of analgesia based on patient population, surgical procedure, and route administration.
- e. Comparisons to bupivacaine, for claims and labeling purposes, require a rationale for comparing volume doses instead of milligram doses.



Discussion

There was no further discussion on this point.

Question 9

Does the Agency concur that Pacira has conducted an adequate number of clinical studies

(b) (4)

Please see

Attachment 3 for further information.

FDA Response

(b) (4)



Discussion

There was no further discussion on this point.

Statistics Questions

Question 10

Are the Statistical Analysis Plans, as outlined, for both the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) adequate to support review of clinical safety and efficacy data? Please see Attachment 5 and Attachment 6 for further information.

FDA Response

ISS: See response to Question 11.

ISE: The main purpose of the ISE statistical analysis plan is to explain how the results of the individual studies support the claims being made. While your plan is generally acceptable, we have the following comments.

1. **The full analysis set (FAS) should not depend on post-treatment pain assessments. Any patient randomized and treated with study drug should be included in the FAS.**
2. **Include a comparison of results for relevant subpopulations across all studies.**
3. **Include and discuss the results of all controlled trials.**
4. **Consult the Guidance document for additional information concerning the ISE: Guidance for Industry: Integrated Summary of Effectiveness**
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf>

Discussion

There was no further discussion on this point.

Question 11

There are 21 studies in our SKY0402 program. Eleven of these studies were performed in a non-surgical setting, one was performed in a surgical setting as an ankle nerve block, and one was performed in a surgical setting but was stopped after only three subjects were enrolled and therefore will not be combined with other studies in the ISS. A total of 10 studies will be pooled in the ISS. These will include all Phase 2 and 3 studies conducted in subjects administered SKY0402 by the wound infiltration route who have undergone orthopedic, general, and plastic and reconstructive surgeries.

Since the two pivotal studies (SKY0402-C-316 and SKY0402-C-317) are placebo controlled and the supportive studies are active controlled multimodality studies (concomitant APAP and/or ketorolac are included in each treatment arm), and since different doses were used in the pivotal and supportive studies, the pivotal and supportive studies will not be pooled in the ISE. Since the two pivotal studies are in different surgeries, used different doses, and the primary efficacy endpoint was different, the two pivotal studies will not be pooled in the ISE. The results from the orthopedic surgery studies will be shown in separate tables from the general surgery studies (b) (4)

In terms of the format of SAS datasets we propose to provide the following:

- 1. SDTM datasets (with define files and electronic annotated CRFs) for all studies that will be pooled in the ISS and/or included in the ISE*
- 2. ADAM datasets (with define files) for the two primary efficacy studies (SKY0402-C-316 and SKY0402-C-317)*
- 3. Pooled SDTM and ADAM datasets (with define files) for the ISS and ISE*
- 4. Non-CDISC formatted (1999 guidance compliant) SAS datasets (with define.pdf files) for 10 of the studies that will not be pooled in the ISS.*

Is the approach to datasets to be included in the NDA as proposed by Pacira acceptable?

FDA Response

This approach is not acceptable.

The ISS needs to include all human safety data generated during development. This (b) (4)

The database should be organized to allow separation of subjects based on demographics, treatment, dose, surgical procedure (if any), adverse events, safety assessments (e.g., vital signs, serum bupivacaine levels) and other pertinent factors that are important in evaluation of safety for an injectable local anesthetic.

You should conduct evaluations of safety based on the subsets you suggest; however, you are obligated to evaluate safety based on an integrated database.

Reference to the following guidance, may provide you with useful information regarding the analyses you conduct and the manner in which you present your integration of safety data.

Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072275.pdf>

(b) (4)

Discussion

The sponsor proposed excluding studies 203 and 211 from the pooled data sets to be submitted to the NDA because they are from nerve block studies and not similar to the indication proposed in the NDA. The Division stated that in order to comprehensively assess the safety profile of the product, it is important to pool adverse event data obtained from all clinical studies performed using the product, irrespective of various routes of administration that the sponsor chose to explore while conducting their clinical studies. Data from specific studies may be teased out later as part of the safety analysis. If the sponsor is aware of differences in the adverse event (AE) profile for 203 and 211 and can provide a rationale for why those concerns would not apply to the rest of the dataset, the Division can take that into account as it performs its own analyses.

The Division noted that in an NDA review, it is important to look at the data for a product both globally and in more focused fashions since doses and patient populations may vary from study to study; however, all exposure information is important and needs to be considered as part of the safety analysis. The Division directed the sponsor to create one large data file for all Phase 2 and 3 studies (including 203 and 211) designed so data can be broken out per study and by other demographic variables as well. The sponsor may also provide an analysis excluding the data from studies 203 and 211, if they feel it is warranted.

The sponsor agreed to provide the database as requested.

The sponsor stated that they plan to pool PK data from all studies that have PK data in CDISC format with a side-by-side comparison for PK data not in CDISC format (which is mostly the Phase 1 study data) as they are not converted to CDISC format. The firm noted that it would be logistically difficult to convert these Phase 1 PK data to CDISC format as they are from a number of different studies with different dosing levels and very disparate data.

The Division observed that several of the Phase 1 studies for this development program may have potentially important safety information, and the data from those would be needed in comparable formats so it can be easily reviewed and evaluated with the other data. The sponsor proposed providing SDTM files of the individual (not pooled) Phase 1 studies so the Agency will be able to manipulate the data. The Division stated that it will be important to look to see if any patients in the Phase 1 studies had exposures comparable to those expected in actual clinical use because that will provide important safety information that needs to be evaluated. The sponsor stated that the product has a different PK profile in healthy volunteers with intact skin, than when applied to wounds.

The Division summarized by stating that all of the safety data is considered when analyzing the risks associated with a particular product. Including the Phase 1 data as part of the pooled

datasets will be important for this product. The Division understands that Phase 1 data are not always the most relevant in the overall evaluation of safety, but they do provide important safety/exposure information for this product. If a legitimate argument can be made for weighing some data less or disregarding it all together, two analyses can be performed: one with all data included and one with only the most relevant data included.

The Division directed the sponsor to examine their Phase 1 trials to determine in which ones exposure levels are relevant to the proposed labeled use of the product, and those data should be pooled along with the rest of the safety data. The sponsor indicated that they understood this request.

Pediatric Development Questions

Question 12

Pacira believes that the proposed pediatric development program, with a stepwise approach to different age groups, designed based upon FDA feedback, dated 27 December 2007 is appropriate and adequate to characterize the product in the pediatric adolescent population and that no additional toxicology studies are needed to initiate the proposed pediatric adolescent study in 12-18 year olds. Pacira proposes to begin this study as a 3b commitment pending Agency review of the forthcoming adolescent protocol, which will be submitted by the end of the first quarter of 2010. Please see Attachment 7 for further details, including the pediatric plan and the draft version of the pediatric adolescent protocol synopsis. Does the Agency concur?

FDA Response

Studies in the pediatric population should not begin until, at a minimum, you have completed your assessment of safety and efficacy and identified an appropriate dosing regimen in the adult population.

It is appropriate to evaluate the safety and efficacy in adolescents prior to studying other age groups within the pediatric patient population.

It is also likely that additional toxicology studies will not be necessary to support studies in this age group; however, you should make the argument for proceeding without them in your submission of the protocol.

Discussion

The sponsor indicated that they would submit a pediatric plan with their NDA.

Question 13

Pacira proposes to commence the first pediatric clinical trial in adolescent subjects 12 to 18 years old as a Phase 3b commitment, and then (after the toxicology study mentioned in Question 2 above is completed [Section 9.1 of this document]) to address the additional planned studies in children 6 to <12 years old and then in younger children >2 to <6 years old, as Phase 4 commitments. Please see Attachment 7 for further information, including the pediatric plan and draft versions of both pediatric protocol synopses (i.e., children 6 to <12 years old, and younger children >2 to <6 years old). Does the Agency concur with this approach?

FDA Response

See the response to Question 12 also.

While pediatric trials will be required if Exparel is approved for adults, the timing of these trials (pre- or post-approval) is somewhat flexible. You may submit a request for a deferral of your pediatric program. With either approach, trials should not begin until you have completed your assessment of adults.

In addition, you have not included pediatric patients ages 2 years old and under in your program. It is expected that all pediatric age groups are likely to require post-op pain control; the choice of analgesic treatment would be dependent upon age, surgical procedure, clinical condition of the patient, etc. If Exparel were to be approved, it is possible that in clinical practice it will be used in these younger age groups. You are required to address the < 2 years age group in your pediatric clinical development program, unless there are compelling safety or efficacy reasons why the product would not be applicable to this age group. If you think that this youngest age group needs to be excluded from your clinical program, you may apply for a waiver, including a rationale for the waiver with your request. This request would need to be submitted with your NDA.

Discussion

There was no further discussion on this point.

Regulatory and Risk Management Questions

Question 16

Pacira proposes that all of the risks associated with EXPAREL described above can be addressed through a technology approach (enhanced packaging and temperature indicators) and communication plan of expanded labeling instructions in the Package Insert and that no medication guide, distribution controls, or evaluation plan exceeding normal pharmacovigilance practices are required. Does the Agency agree with Pacira's risk management technology and labeling approach in dealing with identified risk factors for EXPAREL?

FDA Response

A complete review of the full risk evaluation plan after the NDA is submitted will be necessary to determine whether your proposed approach is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA. In addition, the adequacy of the storage conditions proposed and the use of custom vials to prevent liposome membrane breakdown due to thermal and physical stress will be evaluated by the Agency during NDA review.

Discussion

There was no further discussion on this point.

Question 17

Pacira believes it has conducted all the studies, CMC, preclinical and clinical sufficient for a complete assessment of EXPAREL in an NDA review. Does the Agency concur?

FDA Response

See responses to previous questions.

Discussion

There was no further discussion on this point.

505(b)(2) Comments

We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-voll.pdf>)).

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

Division of Scientific Investigations (DSI) Comments

Broadly, DSI has two types of requests for data to be submitted to the NDA; one type addresses the site selection process and the other type addresses the clinical data submitted in the NDA that will be used for the inspection as background materials.

1. Request for general study-related information as well as specific clinical investigator information
 - a. Include the following information in tabular format in the original NDA for each of the completed Phase 3 clinical trials:
 - 1.) Site number
 - 2.) Principle investigator

3.) Location: city, state, country, to include contact information (phone, fax, email)

b. Include the following information in tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:

1.) Number of subjects screened for each site, by site

2.) Number of subjects randomized for each site, by site

3.) Number of subjects treated who prematurely discontinued for each site, by site

c. Include the following information in tabular format in the NDA for each of the completed Phase 3 clinical trials:

1.) Name, address and contact information of all CROs used in the conduct of the clinical trials

2.) The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies

3.) The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g., monitoring master files, drug accountability files, SAE files, etc.)

2. Request for Site Level Data

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

3. Request for Individual Patient Data Listings format

a. For each site in the pivotal clinical trials that will be inspected provide the name of primary investigator, accurate address and phone number, e-mail contact

b. For each pivotal trial provide sample blank CRF and case report data tabulations for the site with coding key

c. For each pivotal trial provide site-specific individual subject data (“line”) listings from the datasets

1.) Line listings for each site listing the subject/number screened and reason for subjects who did not meet eligibility requirements

- 2.) **Line listings by site and subject of treatment assignment (randomization)**
- 3.) **Line listings by site and subject of drop-outs and discontinued subjects with date and reason**
- 4.) **Line listings by site of evaluable subjects/ non-evaluable subjects and reason not evaluable**
- 5.) **Line listings by site and subject of AEs, SAEs, deaths and dates**
- 6.) **Line listings by site and subject of protocol violations and/or deviations reported in the NDA, description of the deviation/violation**
- 7.) **Line listings by site and subject of the primary and secondary endpoint efficacy parameters or events. Provide all the data listings that comprised the area under the curve for the NRS scores for the primary endpoint.**
- 8.) **Line listings by site and by subject of rescue or concomitant medications (as appropriate to the pivotal clinical trials.)**
- 9.) **Line listings by site and by subject of liver function tests and HgA₁C**

Discussion

There was no further discussion on this point.

The sponsor summarized their understanding of the meeting as follows (includes action items)

1. The sponsor understands that their scaling plan to increase the batch size [REDACTED] ^{(b) (4)} is acceptable.
2. If the sponsor plans to include pooling of batches in the NDA, they will provide 3 months of room temperature and 3 months of accelerated data with the NDA and 6 months of data during the review cycle. The Division will discuss this proposal internally and include a Post-Meeting Note in the meeting minutes. (See Post-Meeting Note under discussion of Questions 14 and 15 above.)
3. The sponsor will pool all safety data from the Phase 2 and 3 studies and provide SDTM data on all Phase 1 studies and pool those Phase 1 studies that (based on dosing and exposure levels) have relevance to the rest of the pooled data.
4. The sponsor understands that if they were to provide appropriate justification that it is the best model, a single juvenile rodent study may be adequate to support clinical studies in patients less than 12 years old.
5. The sponsor plans to provide in the NDA 4-hour in vitro release data for lots already manufactured. The Division clarified that the sponsor should include a specification for the 4-hour in vitro release time point.

6. The sponsor understands that their proposal to express the strength of their product in equivalents to the HCl salt form of bupivacaine is acceptable, but acknowledges that the Agency is moving away from including salts in the established name of products.
7. The sponsor will provide, in the NDA, a rationale for why data on unloaded (placebo) liposomes is not needed.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-69198

GI-1

PACIRA
PHARMACEUTICA
LS INC

BUPIVACAINE S-R
ENCAPSULATED

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

/s/

KIMBERLY A COMPTON
03/22/2010



IND 69, 198

Skye Pharma Inc.
10450 Science Center Drive
San Diego, CA 92121

Attention: Paula C. Adams, Ph.D.
Director, Regulatory Affairs

Dear Dr. Adams:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SKY0402.

We also refer to the meeting between representatives of your firm and the FDA on January 12, 2006. The purpose of the meeting was to discuss issues related to your preparations for reactivating your IND and preparing to proceed with phase 3 studies with your SKY0402 product.

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 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R. Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: January 11, 2006

Location: White Oak Building 22, Conference Room 1419

Sponsor: SkyePharma, Inc.

IND: 69, 198

Drug Name: SKY0402

Proposed Indication: Post-operative pain management

Type of Meeting: Type B, Pre-IND (2nd) Meeting

Meeting Chair: Sharon Hertz, M. D.

Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Minutes Recorder: Kimberly Compton, Regulatory Project Manager, DAARP

Industry-SkyePharma, Inc. Representatives	Title
Gordon L. Schooley, Ph.D.	Chief Scientific Officer
Richard E. Jones, Ph.D.	Sr. VP, Research & Development
Garen Manvelian, M.D.	Sr. Director, Clinical & Medical Affairs
Neda Rashti	Director, Clinical Operations
Brigitte Richard, Ph.D.	Director, Toxicology
Paula Adams, Ph.D.	Director, Regulatory Affairs
Ann Marie Choquette	Regulatory Affairs Associate
Mark Walters	VP, Commercial Development (Project Manager for SKY0402)
(b) (4)	(b) (4)
FDA Representatives	Title
Bob Rappaport, M.D.	Director, DAARP
Sharon Hertz, M.D.	Deputy Director, DAARP
Lex Schultheis, M.D., Ph.D.	Medical Officer, DAARP
Adam Wasserman, Ph.D.	Pharmacology/Toxicology Reviewer, DAARP
Dan Mellon, Ph.D.	Supervisor, Pharmacology Toxicology, DAARP
Srikanth Nallani, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer, DAARP
Ravi Harapanhalli, Ph.D.	Chief, Branch V, Office of New Drug Quality Assurance (ONDQA)
Danae Christodoulou, Ph.D.	Chemist, Branch V, ONDQA
Dionne Price, Ph.D.	Statistics Reviewer
Tom Permutt, Ph.D.	Team Leader, Statistics
Kim Compton	Regulatory Project Manager

Meeting Objective:

The purpose of the meeting was to provide responses to the sponsor's questions from their December 9, 2005, meeting package regarding their preparations for reactivating their IND and preparing to proceed with phase 3 studies with the SKY0402 product.

Background:

The sponsor's questions are listed in *italics* with the FDA responses presented at the meeting following. Pertinent discussion that took place at the meeting regarding a specific question will follow the question and FDA response. The questions are presented in the order in which they were discussed at the meeting.

On January 10, 2006 (prior to the January 11, 2006 meeting) the Agency forwarded to the sponsor the Agency responses to the questions.

Discussion:

Opening Remarks

(b) (4)

Question 1

Are the projected CMC information and plans for NDA-enabling studies described in this briefing package adequate to support an NDA?

FDA Response

In general yes, but additional issues need to be addressed for use of the liposome:

- Stability of the liposome formulation under the conditions of use, namely the expected (b) (4)
- Physico-chemical compatibility of the liposome with currently used prosthetics including hernia mesh (b) (4) should be assessed including possible dose dumping due to compromised structure of liposomes.
- Compatibility of liposomes with all drugs that may be potentially co-administered with this drug should be assessed including possible dose dumping due to compromised structure of liposomes.

Discussion of Question 1

(b) (4)

Question 2

For Phase 3 clinical trial materials and registration batches, SkyePharma proposes to apply specifications on a set of key product attributes. To support the scale-up process and demonstrate lot-to-lot consistency, it is SkyePharma's intent to monitor and characterize several additional product attributes, but not to apply those as clinical or commercial product specifications. From the Agency's viewpoint, is this adequate to support an NDA?

FDA Response

- The specifications are considered a subset of the detailed product characterization studies. The strategy is acceptable but the critical product quality attributes and final (commercial) product specifications are subject to review.
- Provide a detailed pharmaceutical development report including justification for the selection of critical process controls that impact critical quality attributes and specifications in the NDA.
- Scientific basis for the process scale up should be provided including a list of equipment and their principles of operations, and critical process parameters that are preserved throughout the process scale-up.

Discussion of Question 2

The sponsor stated that they have completed studies with two types of hernia repair mesh and their product and they have observed no interactions. The sponsor does not expect to see any interactions with (b)(4), but will look for them prior to NDA submission.

Dr. Harapanhalli stated that the Division is interested in any possibility of dose-dumping or other interactions and agreed that such information could be included with the NDA submission.

The sponsor clarified for Dr. Wasserman that direct study of the mesh strength with exposure to the drug product was conducted *in vitro*. Mesh used in *in vivo* nonclinical studies was for the assessment of the potential interaction between SKY0402 and the mesh on adverse events and wound healing only and to date, no significant events have been observed.

Question 3

SkyePharma will be using an approximately (b)(4) process for manufacture of Phase 3 clinical supplies and registration-enabling stability lots. To meet the forecasted commercial demand for SKY0402, SkyePharma plans to implement a (b)(4) for commercial production, using a process and equipment essentially identical (except for size) to that used for the (b)(4). Assuming that (b)(4) material passes all product specifications and the (b)(4), manufacturing process is fully validated, SkyePharma intends to introduce this material into commercial production with no further nonclinical or clinical studies beyond those described in this briefing document. From the Agency's viewpoint, is this acceptable?

FDA Response

This is acceptable with the following caveats:

- A clear rationale for process scale-up should be provided including how critical process parameters are identified and are preserved during the scale-up.
- The three registration batches that are filed in the NDA and become part of the primary stability study should be of pilot scale (b)(4) batches
- A commitment to place first three consecutive (b)(4) batches on post-approval stability should be provided.

In addition:

- Microbial product quality should be considered during process development, scale up, commercialization and process validations.
- Provide the master batch record for the (b)(4) commercial batch in the NDA
- Provide parameters of the (b)(4) scale-up in the pharmaceutical development report in the NDA.

Discussion of Question 3

Dr. Harapanhalli indicated that formulations such as liposomal products are very sensitive to process scale-up and that a scientific basis for the scale-up will be the overriding factor in assessing the CMC bridging of the pilot and commercial scales.

Question 4

Are the proposed stability studies (on (b)(4) material, with support from smaller, early pilot-scale lots, outlined in this briefing package) adequate to support an NDA?

FDA Response

Yes, see responses to Question 3. In addition:

- Include inverted and upright vial configurations for the registration batches.
- Provide stability information on temperature cycling to simulate conditions of use for the drug product.
- Provide a description and relevance of prior manufacturing knowledge from similar processes described in your related NDAs, e.g. DepoPur.

There was no additional discussion on this question beyond the information presented in the slide.

Question 5

The briefing package summarizes the results of all nonclinical studies, including those agreed in Agency discussions in early 2005. Toxicology studies to support the (b) (4) and the results will be submitted before any clinical studies via this route are initiated. Does the Agency agree that the nonclinical studies performed to date are adequate and sufficient to support the Phase 3 program and subsequent NDA filing for all routes of administration in the proposed indication?

FDA Response

Although the nonclinical studies conducted with SKY0402 up to this date appear to be appropriately designed and satisfy the recommendations for nonclinical evaluation of test article in 2 species for each route intended for clinical study, at this time the Division cannot agree that the data to be provided is sufficient for either support of Phase 3 studies or NDA filing. Support of the completed nonclinical studies for the Phase 3 program will be determined upon review.

- Repeat-dose toxicity studies of 1-month duration in an appropriate nonclinical model will be required for each route in support of the NDA. These repeat-dose studies may be of a modified type (i.e. non-daily dosing).
- Tests of liposomal stability under various forces and conditions will be necessary to assess the potential risk of unintentional release of encapsulated bupivacaine (b) (4) as well as other routes. The required information related to the stability and performance of liposomal release of bupivacaine will be under the following conditions:
 - Under various (b) (4).
 - With alterations in pH and any other characteristics of the local environment which may be expected to be seen during and following surgery.
 - After exposure to corticosteroids, other local anesthetics, and other compounds likely to be administered to the site during the duration of SKY0402 exposure.

Discussion of Question 5

The sponsor stated that they would like to submit an audited draft report at the time of IND reactivation and then the final report three months later, then proceed with their Phase 3 study. Dr. Wasserman stated that if the submitted data were supportive of the proposed Phase 3 clinical trials then such a plan would be acceptable to the Division.

The sponsor stated that their nonclinical (b) (4) is in progress with an expected completion time in February or March, prior to the projected start of the clinical (b) (4) studies.

The sponsor inquired if a study in a second species would be required since this is not a novel drug. Dr. Wasserman stated that while the Division is familiar with the drug, the delivery system is novel with an extended period of activity and the unique nature of the drug product. Therefore, in order to satisfy ICH guidelines, a study in a second species will be required. Dr.

Wasserman stated that if the sponsor proposed and could adequately justify the most appropriate species in which to conduct these one-month studies for a particular route then this may be acceptable. The sponsor indicated that they would submit such a justification and proposal for review.

Dr. Mellon clarified that for their (b) (4) studies, the sponsor may examine two non-rodent models due to the inherent difficulty in completing (b) (4) studies in a rodent model.

In addition, the Division noted that the sponsor should submit any information they can locate regarding how various (b) (4) that occur in the clinical setting compare with those that are generated in animal models to assist in the interpretation of the nonclinical study results.

Regarding exposure of the product to corticosteroids and other local anesthetics, the sponsor stated that they have completed *in vitro* tests and have determined that there are interactions depending on the volumes and concentrations of products used. The interactions have been fairly significant with the local anesthetics, and of some significance with the corticosteroids. The sponsor stated that they therefore plan to advise that other local anesthetics or corticosteroids not be co-administered in the clinical studies of SKY0402. The sponsor will continue to attempt to characterize the potential interactions between SKY0402 and other products and have the data available for the NDA. Dr. Mellon stated that such information will be required for the label of the product. Dr. Wasserman stated that different body spaces might make identification of a time-of-interaction window difficult. The sponsor indicated that they would study that factor as well.

In terms of the potential for interaction of SKY0402 with blood products, the sponsor stated that they have not looked for any reaction between SKY0402 and clotting or inflammatory factors. Dr. Schultheis pointed out that there can be bleeding (b) (4) post operatively; so the effect of clotting blood on bupivacaine release should be examined. The sponsor stated that there is some loss of bupivacaine to the exterior of the liposome in interaction studies already completed. The sponsor stated that they have examined the drug release rate *in vitro* over three days.

Dr. Mellon raised the issue that the animal models used to study the effects of SKY0402 have been completed with healthy tissues and asked if the sponsor would address the effects of potential physiological conditions on the drug product, such as differences in local pH that are typically noted in inflamed tissue. The sponsor stated they studied that situation and the product appears not to be significantly affected.

Question 6

SkyePharma intends to develop this product for post-operative analgesia and not for peri-operative analgesia/anesthesia. Further, we do not intend to develop SKY0402 for intrathecal administration, since the prolonged duration of action produced by this formulation with this route of administration is not a useful clinical application. In the Phase 3 program, (b) (4)

(b) (4)) with the possible exception noted above for the (b) (4)
route. (b) (4)

. Does the Agency agree that the Phase 3 program, with one pivotal study in each proposed route of administration, will support the general use of SKY0402 for post-operative pain management in the various routes investigated?

FDA Response

- One pivotal trial, such as that proposed for inguinal herniorrhaphy, may be acceptable for an indication of postoperative analgesia by the route of wound infiltration. The spectrum of patient age and concomitant disease included in the trial should be representative of the patient population who will be exposed in practice.

- (b) (4)

- (b) (4)

- (b) (4)

Discussion of Question 6

The sponsor stated that they are planning to use ASA categories I, II, and III in their Phase 3 studies and have only limited exclusion criteria, so they estimate that approximately 25% of their participants will be over 65 years old. This plan is acceptable to the Division.

The sponsor inquired if one clinical trial to evaluate (b) (4) administration would be sufficient for approval since unencapsulated bupivacaine is widely used that way in clinical practice. Dr. Hertz stated that the Division has significant concerns regarding the (b) (4) route of administration. Since (b) (4) administration is not an approved route for the unencapsulated product; two pivotal trials will be required for approval of the encapsulated formulation. It will be acceptable to support safety data with open-label studies, but two pivotal (efficacy) trials will be required to approve the product for (b) (4) administration. Dr. Hertz stated that if the sponsor chose not to pursue approval of the (b) (4) route, the labeling would be carefully worded to discourage use of the product by this route.

Dr. Rappaport stated that for a 505(b)(2) submission, some info can be taken from the reference listed drug, but specific studies with the new product are often needed.

(b) (4)



Question 7

As noted above and in Section 11 of this briefing package, the Phase 3 development program will include three studies with a dose-ranging (stage 1)/comparative pivotal (stage 2) Phase 3 study design. In stage 1 of the studies, two or three doses will each be tested in approximately 12 subjects (in a dose-escalation fashion, if the doses have not been previously tested in that route of administration), and a dose will be subsequently chosen for use in stage 2 of the study. An interim analysis will be performed on the primary endpoint after about 1/2 of the initially estimated patients are enrolled in stage 2 to investigate the variability and re-estimate the final sample size. Additional details regarding the statistical analysis plans are provided in the protocol synopses located in

Section 11.5 of this briefing package. Does the Agency agree that this is an acceptable study design?

FDA Response

- The proposed study design is acceptable.
- The proposed sample size re-estimation is acceptable.

There was no additional discussion on this question beyond the information presented in the slide.

Question 8

As noted briefly above, the proposed model for wound infiltration is hernia repair, and enrollment in this trial will be limited to males only. Therefore, for the infiltration route of administration, no data would be available in female patients. However, females will be well represented in the overall SKY0402 clinical program, since they will be enrolled in all of the other proposed clinical trials (b) (4) routes). Does the Agency agree that this is acceptable to support a label in both males and females?

FDA Response

Yes in this setting as female patients will be enrolled in other studies, and the reference listed product does not limit use to female patients.

There was no additional discussion on this question beyond the information presented in the slide.

Question 9

For the Phase 3 studies where patients are discharged home on the day of surgery, patients will receive standardized postoperative medication consisting of acetaminophen, when needed, for mild or moderate pain. When pain is uncontrollable with acetaminophen, opioids (e.g., oxycodone) will be available for use as needed. For the Phase 3 studies where patients are hospitalized for an extended period of time, IV PCA with an opioid will be available for use as needed. Does the Agency agree that these post-operative medication regimens are acceptable for the Phase 3 studies?

FDA Response

Yes

There was no additional discussion on this question beyond the information presented in the slide.

- We will also examine the pain intensity curves over time.

Discussion of Question 10

The Division indicated that total opioid use over a period of time can be an acceptable endpoint for a trial where it would be unusual for patients to do without options for rescue medication in the post-operative period. The Division will also need to see a favorable risk-benefit profile for this product in that the reduction in opioid consumption would have to be clinically meaningful to justify the additional risk that may be associated with the use of encapsulated bupivacaine. Dr. Rappaport stated that an appropriate responder analysis can be performed to help evaluate whether an observed reduction in opioid use is clinically relevant.

*****POST-MEETING NOTE:**

The sponsor could also compare the cumulative opioid requirements based on a predefined meaningful difference.

The sponsor found the Agency's response acceptable, but is endeavoring to create one unified development plan for their product. Therefore, the route they choose to pursue will depend on advice received from the (b) (4) regulatory agencies.

Dr. Hertz stated that in the course of the trials, the Division would like to have an understanding of the onset and duration of effect relative to the unencapsulated product. The sponsor indicated that efficacy of the product in the early postoperative period will be masked by the offset of general anesthesia, but they will obtain some data on this issue. The sponsor agreed to gather data on analgesic effect in the recovery room when the product is administered in the operating room.

Question 11

For the Phase 3 studies, SkyePharma intends to utilize a single dose of commercially available unencapsulated bupivacaine (bupivacaine HCl solution, e.g., Sensorcaine® or Marcaine®) at clinically relevant doses as an active control with the intention to (b) (4) SKY0402. SkyePharma does not intend to utilize placebo in the Phase 3 studies. Does the Agency concur?

FDA Response

The treatment effect of the bupivacaine dose selected for your control will have to be carefully defined or trials that appear “successful” may only indicate (b) (4) (b) (4).

Discussion of Question 11

(b) (4)

Question 12

SkyePharma does not intend to use a continuous infusion of unencapsulated bupivacaine as a control (b) (4) for any of the Phase 3 studies. Does the Agency concur?

FDA Response

Yes

There was no additional discussion on this question beyond the information presented in the slide.

Question 13

Based on the above considerations, we believe that exposure in approximately 500 patients/subjects will be adequate to demonstrate the safety of SKY0402. Does the Agency concur?

FDA Response

No, we do not concur as there are several unique potential safety concerns with this product:

- Bupivacaine is not approved for [REDACTED] (b) (4)
- There may be a risk of liposomal disruption [REDACTED] (b) (4), thereby exposing patients to higher levels of bupivacaine than with other routes of administration.

- [REDACTED] (b) (4)

Discussion of Question 13

Dr. Schultheis stated that if the sponsor were to choose not to pursue the [REDACTED] (b) (4) of administration, 400 patients would be sufficient for the infiltration route, [REDACTED] (b) (4) [REDACTED] (b) (4) about 500 patients would be sufficient. Dr. Hertz stated that patient exposure data from open label studies is acceptable as safety data only.

Question 14

Since SKY0402 is intended for single-dose administration only, hepatic and renal impairment is unlikely to impact the safety and efficacy of SKY0402. Further justification of this position, based on available SKY0402 pharmacokinetic data and literature review is presented in Appendix 1. Does the Agency concur?

FDA Response

It may not be necessary to study the effect of hepatic and renal impairment on PK of SKY0402. However, propose how you intend to administer the product to these subjects in the proposed Phase 3 studies and also in the product label.

Discussion of Question 14

The sponsor stated that since they are not planning to propose any dose adjustments for patients with renal or hepatic impairment, they will not exclude these type of patients from their studies.

Question 15

SkyePharma does not intend to perform a clinical study to specifically evaluate the impact of SKY0402 on the QT/QTc interval, since the effects of bupivacaine on QT/QTc interval are well characterized in the literature. [Detailed justification, based on current SkyePharma clinical data (Phase 1 and 2) and a literature review, is provided in Appendix 2.] Since cardiotoxicity of bupivacaine is linked with high plasma concentrations, instead of a thorough QT/QTc study (as outlined in ICH E14, "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Non-Antiarrhythmic Drugs"), SkyePharma proposes ECG characterization through evaluation of Holter monitor data to be evaluated in conjunction with PK data through 96 hours following perineural (b)(4) dosing in stage 1 of each Phase 3 study. The data will provide a comparison among multiple SKY0402 doses and commercially-available bupivacaine HCl solution in approximately 100 subjects. Does the Agency agree with this approach?

FDA Response

- A thorough QT study may not be required if PK data demonstrates exposure with maximum doses of SKY0402 are within the range considered safe with unencapsulated bupivacaine.
- However, all trial patients should be monitored continuously by EKG because preliminary PK data indicates that peak blood levels of bupivacaine following administration of SKY0402 can achieve a level that is 70% of minimum reported level associated with QT prolongation (1 mcg/mL).

Discussion of Question 15

Dr. Schultheis stated that the Division is looking for assurance that blood levels of the product will not reach levels known to cause QT segment prolongation. He indicated that the data the sponsor has generated with certain doses thus far may address this. Dr. Hertz stated that if preliminary data indicated that the proposed dose results in a blood level that is close to the threshold associated with QT prolongation, a Holter analysis will not be sufficient. In this setting, patients will need to be observed clinically with real-time assessment of their EKG until blood levels are expected to be well below the threshold associated with QT prolongation. She invited the sponsor to submit a justification for the level of EKG monitoring they propose to use. The sponsor stated that they have some data on this topic and their plan is that once the data is available from Stage 1, the sponsor will determine if it is acceptable to proceed without monitoring each patient.

Question 16

Since it would be impossible to differentiate between laboratory abnormalities due to the actual surgical procedure or due to drug administration, SkyePharma intends to perform exploratory routine laboratory testing in stage 1 only of all of the Phase 3 studies. Does the Agency concur?

FDA Response

Laboratory testing should be performed for variables associated with previously identified abnormalities such as those found on CBC in preclinical studies.

Discussion of Question 16

The sponsor stated they have observed no trends of concern so far in laboratory parameters. Dr. Hertz requested that the sponsor submit the available information with a justification to convince the Division that outlined laboratory testing was not needed.

Question 17

SkyePharma intends to request a deferral of studies in the pediatric population until the safety and efficacy of SKY0402 has been demonstrated in the adult population. Does the Agency concur with this plan?

FDA Response

Yes

Clinical Comments (Presented at the meeting)

- The surgical approach to herniorrhaphy should be similar between the control and SKY0402 arms to study efficacy. For example, laparoscopic surgery may be associated with less post operative pain than an open procedure so the type of surgical management should be balanced between treatment arms.
- [REDACTED] (b) (4)
- The results of drug-drug interaction studies and compatibility studies of SKY0402 with other products used in wounds, [REDACTED] (b) (4) should be provided.
- Time to onset of analgesia and duration of effect should be captured as secondary endpoints to facilitate concomitant dosing of other analgesics.
- Data from previously conducted studies will be considered as part of the safety database as long as the studies are adequate in design to provide meaningful information.

Statistical Comments (Presented at the meeting)

- Specify a strategy to handle missing data.
- In the [REDACTED] (b) (4) study, the primary endpoint and analysis do not appear to be consistent.

Discussion of Comments presented at the meeting

The sponsor stated that they will use equal dose volumes for [REDACTED] (b) (4) injections of the product.

Closing Discussion

The sponsor stated that safety (based on PK) will be looked at before proceeding on to the next dose level. The sponsor feels the program is not executable if there is a requirement for real-time monitoring. The sponsor stated that even if the entire dose were released at once, it is close to the maximum allowed dose for unencapsulated bupivacaine.

Dr. Hertz stated that the sponsor is welcome to make a strong argument based on what is known about unencapsulated bupivacaine levels and preliminary PK data associated with the sponsor's product, but if blood levels approach known thresholds for bupivacaine-related QT prolongation, observation and real-time EKG monitoring will be required or the Division will need a compelling understanding of why a reduction in monitoring will be safe. Preliminary PK data at the proposed dosing will be the basis of support for the proposed monitoring plan.

The sponsor summarized their understanding of the meeting as follows (Includes Action Items):

- The sponsor understands that they are to provide *in vitro* data on the effect of [REDACTED] (b) (4) on the liposome.
- The sponsor will pursue *in vitro* studies on compatibility of the product with local anesthetics and corticosteroids.
- The sponsor understands that they will need to conduct a repeat-dose study in two species of one month duration per route of administration. The sponsor may determine the dosing regimen based on the worst-case clinical dosing. The sponsor plans to submit the protocols for these studies and request comment from the Division.
- The sponsor will examine which species is most sensitive for the [REDACTED] (b) (4) route of administration, and provide a justification of why a study in only a single species would be sufficient.
- The sponsor understands that a study in hernia repair procedures will need to cover all variety of patients, including those of advanced age.
- The sponsor understands there is potential for exposure of the vasculature to the product, and so will examine the toxicology data for more information in this regard. They further understand that additional information might be required in this regard. The sponsor understands that this does not decrease the number of deep block patients that will be required to demonstrate safety exposure.

- The sponsor understands that the Agency will require a study of the (b) (4) route of administration to include a wide range of procedures, but that there is the possibility this could be accomplished in one study.
- In regard to Question # 10, the sponsor will consider examining a different endpoint depending on the outcome of discussions with the (b) (4) regulatory agencies so as to have one global development program.
- (b) (4)
- The required number of patients for pivotal studies is 300 for the (b) (4) route of administration, 200 for the hernia repair, (b) (4), (b) (4), (b) (4), that if (b) (4)
- The sponsor understands that no dose adjustment in patients with hepatic or renal impairment is acceptable.
- The sponsor understands that the will need to provide appropriate justification for not conducting monitoring for QT segment changes.
- The sponsor will look at the pre-clinical data to determine if additional specific laboratory values need monitoring.
- The sponsor will submit their justification for the volume and concentrations tested in the nonclinical studies and how they are related to the proposed clinical dosing regimen to assist in the interpretation of the nonclinical data.

Minutes prepared by: Kim Compton

Minutes concurred by Chair: Sharon Hertz, M.D.

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

/s/

Kimberly Compton
2/9/2006 03:12:43 PM