

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022496Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**



**Food and Drug Administration**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
Division of Anesthesia, Analgesia, and Addiction Products  
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**Cross-Discipline Team Leader Review**

<b>Date</b>	October 9, 2011
<b>From</b>	Rigoberto Roca, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/Supplement #</b>	022496/000
<b>Applicant Name</b>	Pacira Pharmaceuticals, Inc.
<b>Date of Submission</b>	September 28, 2011
<b>PDUFA Goal Date (original)</b>	July 28, 2011
<b>PDUFA Goal Date</b>	October 28, 2011 (extended due to major amendment)
<b>Proprietary Name / Established (USAN) Name</b>	Exparel / bupivacaine extended-release liposome injection
<b>Dosage Forms / Strength</b>	Sterile injection / 13.3 mg/mL
<b>Proposed Indication(s)</b>	To produce post-surgical analgesia
<b>Recommended Action</b>	Approval

## 1. Introduction

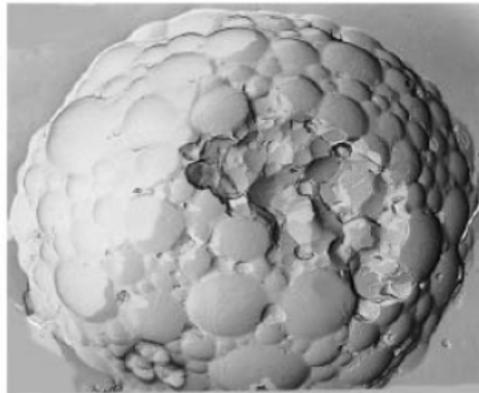
The applicant has submitted a 505(b)(2) application for a liposomal formulation of bupivacaine hydrochloride for the indication of post-surgical analgesia.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant.

## 2. Background

Exparel consists of a new formulation of bupivacaine, a currently marketed approved product (Marcaine, NDA 016964). In this formulation, the bupivacaine is contained within microscopic spherical multivesicular liposomes which, unlike traditional liposomes, consist of a non-lamellar honeycomb structure with numerous non-concentric aqueous chambers that contain the dissolved drug. (b) (4)

(b) (4) Erosion and/or reorganization of the lipid membranes results in the release of the drug over a period of time. The following micrograph represents a typical multivesicular liposome (reproduced from Dr. Bond's review).



Scanning electron micrograph of a typical DepoFoam particle

Exparel's drug delivery system, known as DepoFoam<sup>®</sup>, is a proprietary technology own by the Applicant and is extremely similar to the system that is present in two currently-marketed approved products, DepoCyt (NDA 021041) and DepoDur (NDA 021671). (b) (4)

(b) (4) the liposomes in Exparel contain a novel lipid excipient, dieurocoylphosphatidylcholine (DEPC).

The sponsor of the initial IND for this product, IND 069198, was SkyePharma, Incorporated (that is the reason why the reviews of the team contain references to "SKYE0402," either in referring to the product as it was being studied during various phases of the development program, or in the clinical trial identifiers). Their first meeting with the Agency occurred in

October 2002. In 2007, the current Applicant assumed ownership of the IND and the drug development program.

The various meetings and advice that have been conveyed to the IND holder during this drug's development, first SkyePharma, then Pacira, are well-detailed in Dr. Simone's review. The following are the major milestones and issues that were discussed:

- Pre-IND meeting (October 2, 2002): the proposed indication was [REDACTED] (b) (4) Discussion included what type of non-clinical support would be needed, and what questions would need to be addressed regarding the potential other routes of administration that would be encountered in the clinical setting.
- New IND submission (December 9, 2004): two protocols were proposed, one in patients who had undergone inguinal hernia repair and the other in patients who had undergone a bunionectomy. The IND was inactivated by the sponsor on January 6, 2005, after they were informed that there was inadequate nonclinical support to permit the clinical trials to go forward.
- Request for re-activation of the IND / End-of-Phase 2 meeting (January 12, 2006): in the interim between the inactivation of the IND and the request for reactivation, the Sponsor had conducted clinical studies outside the United States, and had completed several nonclinical studies intended to answer the questions posed to them at the previous meetings. Issues discussed during that meeting included issues related to the chemistry, manufacturing, and controls (CMC), the types of clinical trials that would be required and what their endpoints should be, the information needed in the event a comparative claim was being entertained by the sponsor, and the type and amount of safety data that would be expected in the NDA submission.
- Reactivation of the IND (March 31, 2006): clinical trials in patients who had undergone inguinal hernia repair were allowed to proceed.
- Pre-NDA meeting (February 16, 2010): the key discussion points revolved around the CMC information that would be needed in the NDA submission, the nonclinical data that would be needed to support trials in pediatric patients less than 12 years of age, the clinical data needed to assess the potential for cardiotoxicity, the data needed to support [REDACTED] (b) (4) and the type and amount of data that would be needed in the safety database.
- Submission of NDA (September 28, 2011)
- Submission of major amendment to the NDA (May 25, 2011): this submission resulted in a 3-month extension of the review clock resulting in a new PDUFA goal date of October 28, 2011.

There were several interactions between the Agency and the Applicant in the period between the reactivation of the IND and the submission of the NDA, which have been well-described

by Dr. Simone in his review. This included discussions about the proposed protocols for the pivotal studies, the proposed pediatric development plan, and the acceptability of the proposed proprietary name for the drug product.

For the purposes of the 505(b)(2) requirements, the Applicant has identified Marcaine, (NDA 016964) as the listed drug which they intend to use for reliance on Agency's prior findings of safety and efficacy of the active pharmaceutical ingredient, bupivacaine hydrochloride.

Exparel has not been approved for use or marketed in any foreign country; therefore, there is no post-marketing data for the review team to evaluate.

### 3. Chemistry, Manufacturing, and Controls (CMC)

#### *General Product Considerations*

Exparel utilizes the Applicant's DepoFoam® drug delivery system for entrapment of the drug substance in a non-classical, multivesicular liposome (MVL). Two other products have been approved with similar platforms: DepoCyt® (NDA 021041, approved in 1999) and DepoDur® (NDA 021671, approved in 2004). (b)(4) is slightly (b)(4), with Exparel containing a novel excipient, dierucoylphosphatidylcholine (DEPC). The adequacy of the data submitted to support this novel excipient will be discussed in the pharmacology/toxicology section of this review.

#### *Drug Substance*

As noted in Dr. Shaw's review, the drug substance is bupivacaine, the free base of a USP item, bupivacaine hydrochloride. The manufacturing sites are (b)(4) and (b)(4) both were found acceptable in the Establishment Evaluation System (EES).

Dr. Shaw noted that a genotoxic compound, (b)(4) is used during the synthetic process for bupivacaine hydrochloride by both suppliers, and the Applicant has added a control for the compound (NMT (b)(4)) in the acceptance specification for the drug substance. The control was deemed sufficient to limit the intake of the genotoxin to NMT 1.5 µg/day when the drug product is used according to the label.

The bupivacaine free base is a white crystalline powder, soluble in organic solvents, and the data in the application indicated it was stable and the potential degradants were adequately described. Dr. Shaw's assessment was that the proposed specifications were adequate to ensure the quality of the drug substance.

#### *Drug Product*

The drug product is a sterile, non-pyrogenic, milky white, preservative-free, aqueous suspension of multivesicular liposomes; it must be re-suspended before use. It will be packaged in Type I clear glass vials with (b)(4) rubber stoppers and (b)(4) flip-up/tear-off seals, and the headspace in the vials (b)(4). The Applicant proposes to market two presentations: a 10 mL vial and a 20 mL vial. Since there is no preservative present in the formulation, it is intended for single use only.

The inactive ingredients are dierucoylphosphatidylcholine (DEPC), dipalmitoyl phosphoglycerol (DPPG), tricaprylin, cholesterol and sodium chloride. The DMFs for the DPPG and tricaprylin components were reviewed and deemed acceptable, and the manufacturing sites for the DEPC (b) (4) were inspected and found to be satisfactory. The cholesterol and compounds used for pH and osmotic adjustments (b) (4) were deemed acceptable based on their conformance with the USP/NF.

Dr. Shaw reviewed the data supporting the manufacture, characterization, and control of the drug substance and found it to be acceptable. His review of the data supporting the formulation development, overages, physiochemical and biological properties of the drug product found that to be acceptable, as well.

Dr. Shaw's final assessment of the stepwise description of the manufacturing process and flowchart, which included (b) (4) container closure system, and stability testing, was that the data were acceptable. It was noted that the compatibility evaluation indicated that mixing Exparel with non-bupivacaine local anesthetics (such as lidocaine) could result in rapid release of the bupivacaine hydrochloride from the liposome; the Applicant proposed to include language in the label regarding this observation and the recommendation that, if it was clinically necessary to administer both types of anesthetics, there be an appropriate time interval between the administration of the two products.

The Applicant had indicated that the strength of the product should be described as (b) (4). As noted in Dr. Shaw's review, the Applicant's rationale that (b) (4) was unacceptable. Dr. Shaw indicated that the formulation should be expressed as 13.3 mg/mL of bupivacaine, and that all specification, tests, etc., should conform to this expression of strength.

#### Facilities Review/Inspections

The Office of Compliance completed the manufacturing site inspections and found them all to be acceptable.

(b) (4)

(b) (4)

In his review, Dr. Mello evaluated the following aspects of the product: microbiological attributes of the product; manufacturing process and the process controls, including the (b) (4) manufacturing process; process validation; product control; and stability. The data provided by the Applicant in the original submission and subsequent amendments to the application were deemed acceptable, and Dr. Mello's final recommendation was for approval of the application.

#### Outstanding or Unresolved Issues

I concur with the conclusions reached by Drs. Shaw and Mello regarding the acceptability of the data supporting the manufacturing process of the drug product and drug substance. Stability testing supports an expiry of 24 months when stored at 5° C. There are no outstanding issues that would preclude approval from a CMC perspective.

## **4. Nonclinical Pharmacology/Toxicology**

### General Considerations

As noted above, the Applicant has identified Marcaine as the listed drug for this application, relying on the Agency's prior finding of safety and efficacy of the active pharmaceutical ingredient, bupivacaine hydrochloride. The Applicant's formulation for Exparel utilizes the Applicant's proprietary DepoFoam® drug delivery system which, as previously stated, is very similar to the lipid component in the formulation of the approved products DepoDur and DepoCyt. (b) (4) the Exparel formulation is the presence of the novel excipient, DEPC. Therefore, the main focus of the Applicant's nonclinical program was to assess local tolerability and potential systemic toxicity of the DEPC, via single- and repeat-dose subcutaneous evaluation and acute surgical models of wound infiltration, each assessment in two species, and evaluation with different routes of administration.

### Carcinogenicity

Carcinogenicity studies were not conducted with the product as it is not indicated for chronic administration.

### Genotoxicity

The Applicant conducted a standard battery of genetic toxicology studies (Ames Reverse Mutation Assay, in vitro chromosomal aberration assay using peripheral human lymphocytes, and rodent micronucleus assay) with the liposomal component of the drug product (a non-bupivacaine containing formulation of Exparel, or Exparel "placebo"). The studies were all negative for any evidence of genotoxicity.

### Reproductive Toxicology

The Applicant submitted the results from several studies intended to evaluate the reproductive toxicology of the liposomal component of Exparel. The effects on fertility and early embryonic development, as well as prenatal and postnatal development were evaluated in rats, and the effects on embryo-fetal development were evaluated in rabbits. As noted in the reviews by Dr. Bond and Dr. Wasserman, these studies did not demonstrate any apparent DepoFoam/DEPC toxicity.

Other nonclinical evaluation of interest*Inadvertent intravenous dosing*

The potential for toxicity due to an inadvertent intravascular dosing was evaluated by slow bolus injection into the tail vein of rats. As noted in Dr. Bond's review, there were three progressively detailed GLP studies that were designed based upon the results of the previous study. The results indicated no treatment-related effects on body weight, food consumption, hematology, clinical chemistry, urinalysis parameters, macroscopic observations, organ weight changes, or microscopic evaluations at exposure levels that would be considered equivalent to the proposed human doses.

*Local toxicity*

The Applicant evaluated local toxicity by evaluating acute subcutaneous administration in rabbits and dogs, acute wound infiltration in hernia repair models in rabbits and dogs, and 28-day repeat-dose (bi-weekly) subcutaneous administration studies in rats, rabbits, and dogs.

There were no apparent significant treatment-related effects observed in the clinical signs, body weight, food consumption or clinical pathology.

*Drug interactions*

The potential for interaction between Exparel and lidocaine hydrochloride solution when administered together was evaluated in Yucatan minpigs. There was a more rapid release of the bupivacaine from Exparel when it was co-administered with lidocaine than when Exparel was administered alone. This effect was not observed when Exparel was co-administered with bupivacaine hydrochloride, and it was reduced when the timing of the administration of the Exparel after the lidocaine was delayed by at least 20 minutes.

*DepoFoam® clearance*

The retention of bupivacaine hydrochloride and DEPC at the injection site was evaluated with radiolabeled studies in guinea pigs and rats. The highest concentration of radioactivity was in the lymphatic, excretory, and adipose tissues, consistent with lipid distribution and metabolism. The bupivacaine hydrochloride was not detected at the injection site by the 2-week time point, with DEPC remaining about a week longer.

*Impurities and degradants*

During the course of the review of this application, five chemicals were identified by the review team as having the potential for genotoxicity or carcinogenicity. Four are related to

(b) (4)

As noted above, (b) (4) (b) (4)

and the Applicant has added a control so that it has been reduced to acceptable levels (potential exposure to less than 1.5 µg/day) as recommended in the draft CDER Guidance for Industry: *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (Dec 2008)*.

Dr. Bond notes in his review that (b) (4) has previously been noted to produce tumors in rodents; (b) (4)

(b) (4)  
was that the finding had little relevance to humans. Nevertheless, the Applicant will be asked by ONDQA to lower the levels of (b) (4) levels to as low as technically feasible. For this submission, that level has been identified as NMT (b) (4) which is consistent with the levels allowed in other approved applications for drug products in which (b) (4) is an impurity.

As for (b) (4) and (b) (4) although initially identified as containing structural alerts, the final determination by the review team is that these are not structural alerts and are not predicted to be genotoxic in the Ames bacterial mutation assay based on an FDA CompTox analysis (FDA CDER Informational and Computational Safety Analysis Staff – ICSAS). Furthermore, since the levels of these impurities are within ICH specifications, no further action is warranted.

(b) (4)  
(b) (4). The Applicant is proposing a drug product specification of NMT (b) (4) (with a specification of NMT (b) (4) at time of release), and the highest value observed in the analyses of the batches was (b) (4). When the concentration of the drug product and the Applicant's proposed dosing recommendations are taken into account, the ICH qualification threshold level for the drug product is exceeded by the proposed specifications and the observed value in the batch analyses.

Dr. Bond notes in his review that the (b) (4) values in the batches of Exparel that were used in 3 of the clinical trials at doses of 120 mg in 8 mL (bunionectomy), 300 mg in 20 mL (hemorrhoidectomy), (b) (4), and in the 28-day repeat dose nonclinical studies in rabbits and dogs, ranged from (b) (4) and that these are considered comparable on a µg/mL basis. Therefore, Dr. Bond concluded that adequate nonclinical-based human safety for Exparel and the (b) (4) alone exist at the proposed human doses of Exparel. Furthermore, he noted that ONDQA will request that the drug product specification to be lowered to NMT (b) (4) based on the reported batch analyses and variability.

#### *Extractables and leachables*

Lots that were stored for up to 30 months in the proposed commercial container/closure system were analyzed for any potential leachables. None were detected in any of the lots analyzed; therefore, no additional nonclinical studies are needed to evaluate for this potential concern.

#### *Outstanding or Unresolved Issues*

I concur with the conclusions reached by Drs. Bond and Wasserman that the Applicant has submitted sufficient nonclinical data to support the application, and that no additional nonclinical data are needed.

## 5. Clinical Pharmacology/Biopharmaceutics

### General Considerations

The clinical pharmacology database included 21 clinical studies across the different phases of drug development, but the clinical pharmacology review focused on five clinical studies in which pharmacokinetic data were collected from patients, and a pharmacokinetic study in subjects with hepatic impairment. All studies were single-dose administration.

The five clinical studies were (tables adapted from Dr. Li's review):

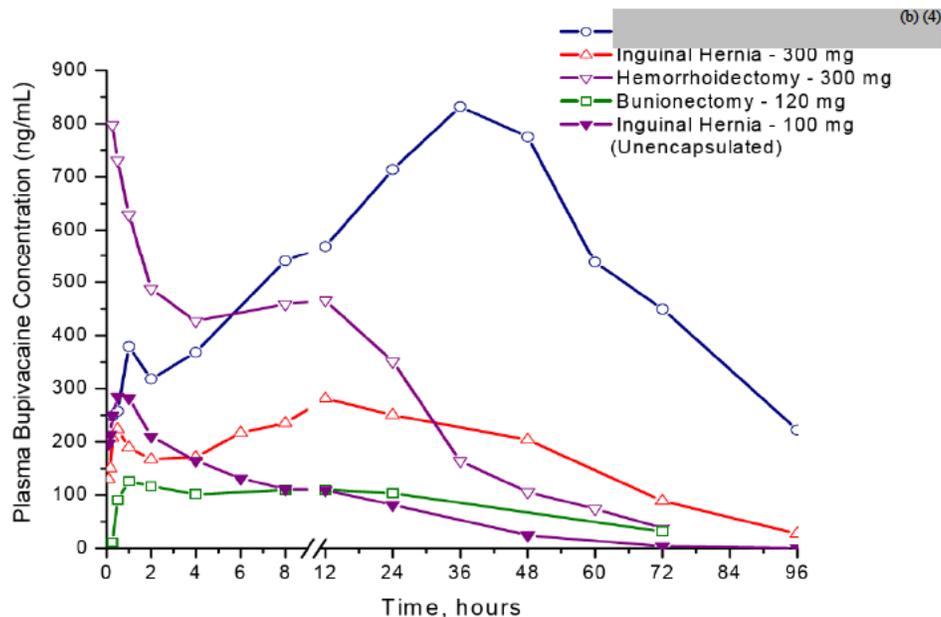
Study Identifier	Phase	Patient Population	Study Design and Control	Test Product and Dosage Regimen	Number of Subjects	Route of administration and volume
SKY0402-C-201	2	S/P inguinal hernia repair	Randomized, double-blind, dose escalating, active control	Exparel 175 mg	12	Local infiltration 40 mL
				Exparel 225 mg	12	
				Exparel 300 mg	12	
				Exparel 350 mg	14	
				Bupivacaine 100 mg	26	
SKY0402-C-203	2	S/P bunionectomy	Randomized, double-blind, active control	Exparel 175 mg	12	Perineural ankle nerve block (25 mL)
				Exparel 225 mg	12	
				Exparel 350 mg	14	
				Bupivacaine 125 mg	20	
(b) (4)						
SKY0402-C-316	3	S/P hemorrhoidectomy	Randomized, double-blind, dose escalating, placebo control	Exparel 300 mg	95	Local infiltration 30 mL
				Saline (placebo)	94	
SKY0402-C-317	3	S/P bunionectomy	Randomized, double-blind, dose escalating, placebo control	Exparel 120 mg	97	Local infiltration 8 mL
				Saline (placebo)	96	

### *Pharmacokinetics of Exparel*

#### *Absorption:*

As noted in Dr. Li's review, the rate of systemic absorption is dependent on the total dose administered, the route of administration (infiltration, subcutaneous, etc.) and the regional vascularity of the site of administration. The graph below, reproduced from Dr. Li's review illustrates this point.

**Figure 1: Mean Plasma Concentrations of Bupivacaine After Administration of Single Doses of SKY0402 and Bupivacaine HCl (Unencapsulated)**



The mean plasma concentration-time profiles of bupivacaine after administration of Exparel by infiltration exhibit two peaks: an early peak at a median time of 0.25 to 2 hours, followed by a second peak at a median time of 12 to 24 hours.

*Distribution:*

Once the bupivacaine is released from the multivesicular liposome, the distribution is expected to be similar to other bupivacaine hydrochloride solution formulation. It will be distributed to some extent to all body tissues, with higher concentrations found in highly perfused organs, such as liver, lung, heart, and brain.

*Metabolism:*

Bupivacaine is metabolized primarily in the liver via conjugation with glucuronic acid, and pipercolylxylidine is the major metabolite. Dr. Li noted that approximately 5% of the bupivacaine is converted into pipercolylxylidine.

*Elimination/Excretion:*

The primary route of elimination is via the kidneys, with approximately 6% of bupivacaine being excreted unchanged in the urine. Factors which affect the urinary pH or the urinary perfusion would potentially alter the rate of elimination.

*Pharmacodynamics of Exparel*

As noted in Dr. Simone's review, the onset of action of Exparel was evaluated in clinical trials that assessed pain intensity (b) (4)

These studies demonstrated that the onset of action for Exparel was less than 2 minutes, which was similar to conventional bupivacaine hydrochloride. In the clinical trials described in the sections below, the duration of Exparel's analgesic effect appears to be no more than 24 hours and not longer than that of bupivacaine hydrochloride.

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### Critical Intrinsic Factors

#### *Age:*

The ages of the subjects across the clinical studies that collected pharmacokinetic data ranged from 18 to 85 years. Dr. Li noted in his review that, although there were statistically significant increases in  $C_{\max}$  and AUC with increasing age, there was no trend toward an increase in the  $t_{1/2}$  with age, and the regression analysis of that parameter was not significant.

#### *Renal impairment:*

Bupivacaine hydrochloride is substantially excreted by the kidney, therefore the risk of adverse reactions would be greater in patients with impaired renal function. In order to be consistent with the label for Marcaine, the Applicant proposes that the label for Exparel have language indicating that care should be taken in dose selection and that the of the monitoring of renal function may be useful in this patient population.

#### *Hepatic impairment:*

The pharmacokinetic study in subjects with hepatic impairment (Study SKY0402-C-110) was an open-label parallel group study in 9 patients with moderate hepatic impairment (a Child-Pugh score of 7 to 9, Class B) and 9 subjects with normal hepatic function. Each group received one 300-mg dose of Exparel subcutaneously.

The subjects with hepatic impairment had a 1.5-fold increase in the mean values of the  $C_{\max}$ , and a 1.6-fold increase in the  $AUC_{\text{inf}}$ . The major metabolite of bupivacaine, pipercolylxylidine, also had comparable increases in the  $C_{\max}$  and  $AUC_{\text{inf}}$  (1.9-fold and 1.6-fold increases, respectively).

Although no dose adjustment was deemed necessary, Dr. Li noted that the label would indicate that Exparel should be used with caution in patients with hepatic impairment, which would be consistent with the label of the listed drug, Marcaine.

#### Thorough QT Study

The potential for Exparel to cause QT prolongation was evaluated by the Applicant in two QT studies (Study SKY0402-C-105 and Study SKY0402-C-107). The second QT study was conducted because of difficulties establishing assay sensitivity in the first study. The results of the studies were reviewed by the Interdisciplinary Review Team for QT Studies (IRT-QT). Their assessment was that Exparel does not appear to have any apparent QT prolongation effect at the doses studied (300, 450, 600, and 750 mg). A concentration-dependent QTc interval shortening was noted, but was not considered as clinically meaningful by the IRT-QT group.

#### Drug-drug Interactions

No clinical drug-drug interaction studies conducted by the Applicant. As noted above, there were nonclinical studies conducted which demonstrated an increase in the release of the bupivacaine hydrochloride when Exparel was co-administered with lidocaine; this observation will be reflected in the label with a recommendation to space the administration of the two products by a time interval of at least 20 minutes.

(b) (4)

As noted above, the mean plasma concentration-time profiles of bupivacaine after administration of Exparel by infiltration exhibit two peaks; an early one at a median time of 0.25 to 2 hours followed by a second peak at a median time of 12 to 24 hours.

(b) (4)

#### Outstanding or Unresolved Issues

I concur with the conclusions reached by Drs. Li and Xu that there are no outstanding clinical pharmacology issues that preclude approval. (b) (4)

## 6. Clinical Microbiology

Exparel is not a therapeutic antimicrobial, therefore clinical microbiology data were not required or submitted for this application. A product quality microbiology review was performed by Dr. Robert Mello; his conclusions are described above in the CMC section.

I concur with the conclusions reached by Dr. Mello that there are no outstanding sterility issues that preclude approval.

## 7. Clinical/Statistical-Efficacy

The portion of the clinical development program intended to demonstrate the efficacy of Exparel consisted of five clinical trials, (b) (4)

Summary descriptions of the trials are noted in the chart below (adapted from Dr. Simone's review).

Study Identifier	Surgical Procedure	Exparel Dose	Comparator Dose	Method of Administration	Duration of Pain Assessment (for primary endpoint)	Was Exparel superior to comparator? [Yes/No] (p value)
<i>Active Comparator (bupivacaine hydrochloride)</i>						
(b) (4)						
SIMPLE Hemorrhoid-ectomy - 312	Hemorrhoid-ectomy	300 mg	150 mg	Infiltration if incision was >3 cm in length	96 <sup>R</sup>	No (0.15)
(b) (4)						
<i>Placebo controlled</i>						
SKY0402-C-316	Hemorrhoid-ectomy	300 mg	normal saline	Infiltration in 6 locations around the anal sphincter	72 <sup>R</sup>	Yes (<.0001)
SKY0402-C-317	Bunion-ectomy	120 mg	normal saline	Infiltration into incision site and the soft tissue around the osteotomy	24 <sup>N</sup>	Yes (0.001)

<sup>A</sup> Pain level with activity

<sup>R</sup> Pain level at rest

<sup>N</sup> Pain level at set time point regardless of activity level

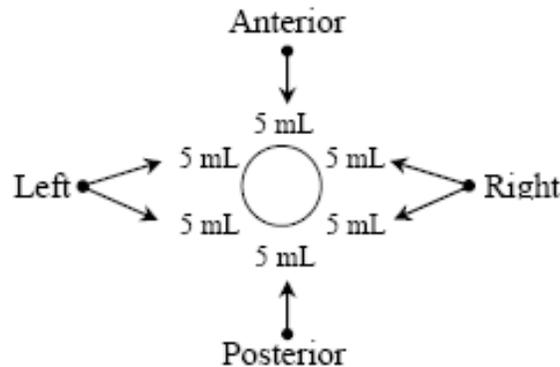
(b) (4)

Exparel was able to demonstrate superiority to placebo in the two placebo-controlled trials. Both placebo-controlled trials used the same primary efficacy endpoint: the area under the curve of pain intensity scores out to a pre-specified point in time; 72 hours in the hemorrhoidectomy trial, and 24 hours in the bunionectomy trial.

### SKY0402-C-316

*A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Local Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing Hemorrhoidectomy*

According to the protocol, eligible patients were randomized to either placebo or Exparel, 300 mg, in a 1:1 ratio. After the surgery was completed, a single dose was administered by infiltration into 6 separate areas around the surgical area, as denoted in the diagram below, where the anal sphincter is being represented by the circle (reproduced from page 27 of the final study report).



The only analgesic agent permitted for break-through pain was morphine every 4 to 6 hours for the first 72 hours. Patients were discharged 72 hours after surgery.

Pain intensity was measured using an 11-point scale, with “0” representing no pain and “10” representing the worst pain. It was assessed at baseline (prior to surgery), at the end of general anesthesia, before the first dose of rescue medication and at the following time points: 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after surgery.

The pre-specified primary outcome was the area under the curve (AUC) of the pain intensity scores out to 72 hours. The Applicant identified several secondary efficacy endpoints, including the AUC at other time points, the proportion of patients who were pain free (defined as patients who reported a pain intensity score of “0” or “1”), and time to first use of rescue.

The analysis population for the primary efficacy outcome was defined as all patients who underwent the surgical procedure, received study drug, and had at least 2 post-treatment pain intensity scores. An AUC was calculated for each patient using the pain intensity scores measured at the time points noted above.

As Dr. Petullo noted in his review, the Applicant proposed the following strategy to handle missing data:

- Missing scores before the first non-missing score would be replaced by the median score from other subjects in the same treatment group.
- Missing scores after the last non-missing score would be replaced by the last recorded observation. This is analogous to a last observation carried forward strategy for study dropouts.
- Missing scores between two non-missing scores would use linear interpolation.

If a patient required rescue medication, it was accounted for by using the worst observation carried forward within a specified window. For example, if a patient received morphine at time  $x$ , for any time point within  $x + 4$  hours, the highest score from time 0 up until time  $x$  was used. If the pain intensity score for the windowed observation was higher than the worst observed score, it was not replaced.

The trial was conducted in clinical sites in Poland, Serbia and the Republic of Georgia. The demographic description of the patient population which was treated in the trial is summarized in the table below (adapted from Dr. Simone's review).

Demographic Variable		Treatment Group	
		Exparel (300 mg) N = 95	Placebo (Saline) N = 94
Age (years)	18-64	86	84
	≥65	9	10
	≥75	2	2
Gender	Male	63	67
	Female	32	27
Race	White	95	94
	Black	0	0
	Other	0	0
ASA-PS	1	57	49
	2	36	42
	3	2	3
	4	0	0

The scheme used to classify the patient's physical status was the American Society of Anesthesiologists Physical Status system, defined below:

- ASA-PS 1 - A normal healthy patient
- ASA-PS 2 - A patient with mild systemic disease
- ASA-PS 3 - A patient with severe systemic disease
- ASA-PS 4 - A patient with severe systemic disease that is a constant threat to life

The distribution for the demographic variables was relatively comparable between the treatment groups, although it was notable that patient population consisted entirely of one ethnic group.

The disposition of the patients enrolled in the trial is summarized in the table below (adapted from Dr. Simone's and Dr. Petullo's reviews):

	Treatment Group	
	Exparel (300 mg)	Placebo (Saline)
Randomized	96	94
Treated	95	94
Completed trial	94	92
Discontinued trial	1	2
Reason for discontinuation Withdrew consent	1	2

Of the 189 patients who were treated during the trial, 187 were evaluated for efficacy.

#### *Summary of Efficacy Findings*

The Applicant conducted an analysis of the primary efficacy outcome using an analysis of variance (ANOVA) model with treatment and country as the main effects. Dr. Petullo utilized the same type of analysis, but included the baseline pain intensity score as a covariate in the ANOVA model. The results of the two analyses were consistent with each other, and are summarized in the table below (reproduced from Dr. Petullo's review).

	AUC <sub>72hrs</sub> (pi*hr) – mean (stderr)		Diff [95% CI]*	p-value
	Placebo (N=93)	Exparel (N=94)		
Applicant	202 (11)	142 (11)	60, [31, 90]	< 0.0001
Reviewer	207 (10)	144 (11)	62, [33, 92]	<0.0001

Source: Reviewer

\* difference in LSMEANS

Dr. Petullo also conducted sensitivity analysis on the primary efficacy endpoint. In one analysis, he utilized the mean pain intensity score of the other patients in the same treatment group as an imputation strategy for intermittent missing data for two patients, and found that it did not differ from the Applicant's analysis which had utilized the last observation carried forward as the imputation strategy; there was still a significant treatment effect in favor of Exparel.

In another analysis of the primary endpoint, Dr. Petullo examined the impact of the exclusion from the analysis of two patients who had been randomized and treated, which the Applicant had excluded because they did not have at least two post-treatment pain intensity scores. His conclusions did not change, as there was still a significant difference in favor of Exparel.

There were several secondary endpoints identified by the Applicant; however, as pointed out by Dr. Petullo in his review, there were no pre-specified statistical adjustments to the analyses to account for multiple comparisons. Nevertheless, Dr. Petullo evaluated the following secondary endpoints to see if they supported the observed treatment effect:

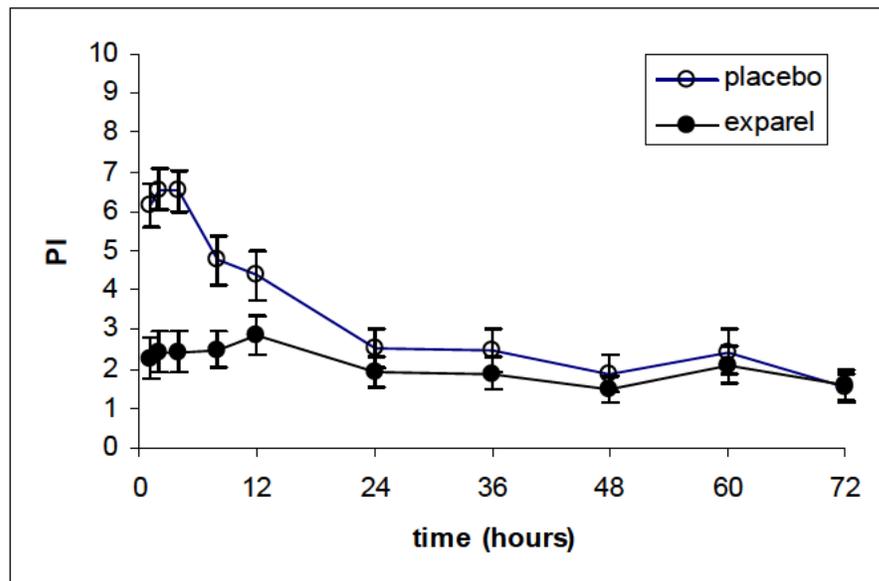
- The AUC values at 12, 24, 36, 48, and 60 hours post-surgery
- The percentage of patients that were pain free at each time point

- The median time to the first use of post-operative rescue medication
- The total amount of rescue medication used through 72 hours post-surgery

Each of these analyses demonstrated an apparent treatment effect in favor of Exparel and supported the finding of efficacy.

One of the analyses conducted by the review team was an evaluation of the mean pain intensity score by treatment group at each time point. Dr. Petullo accounted for the use of rescue medication by utilizing the Applicant-specified strategy described above.

The result of this analysis is summarized in the graph below, reproduced from Dr. Petullo's review.



The graph illustrates that there is separation between the two curves out to approximately the 24-hour time point; after that point, the mean intensity score for the placebo treatment group diminish to levels that are similar to the Exparel treatment group. The implication of this finding is that it is unclear what benefits Exparel offers for this particular surgical procedure after the 24-hour time point.

#### SKY0402-C-317

*A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of a Single Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing First Metatarsal Osteotomy (Bunionectomy)*

In this trial, eligible patients were randomized to either placebo or Exparel, 120 mg, in a 1:1 fashion. Once the surgery was completed and prior to the closure of the surgical wound, the single dose of the study drug was infiltrated into the cut tissue around the osteotomy and into the cut edges of the soft tissue around the surgical wound. The protocol was quite detailed with respect to the manner the infiltration was to be performed, in order to ensure that the

techniques used were consistent. Percocet and, if needed, a single intravenous dose of ketorolac were permitted for relief of break-through pain.

Pain intensity scores were obtained using an 11-point scale at the following time points: prior to surgery (baseline), before first use of rescue, and at 2, 4, 8, 12, and 24 hours post-treatment. Patients were discharged after 24 hours but were instructed to record pain scores and any use of rescue medication at approximately 36, 48, 60, and 72 hours post-treatment.

The pre-specified primary outcome was similar to the trial in patients who underwent a hemorrhoidectomy in that it was AUC of the pain intensity scores, but differed in that it was only out to 24 hours. Several secondary endpoints were identified by the Applicant, including an assessment of the AUC at various time points, an assessment of the proportion of patients who were pain free, and time to first use of rescue medication.

The statistical methodologies were similar to the methods used for Study SKY0402-C-316, with respect to the definition of the population that would be used for the primary efficacy analysis, and the imputation scheme to be used for missing data. A similar imputation strategy was used to account for the use of rescue medication as was used for that trial, except that the imputation window was 6 hours instead of 4 hours. An AUC was calculated for each patient using the pain intensity scores measured at the time points noted above.

The trial was conducted at four clinical sites in the United States; three in Texas and one in Utah. The number of patients older than 65 years and the number of women treated was higher in the placebo treatment group, otherwise the groups were comparable between the two treatments. The demographic characteristics of the patient population which was treated are summarized in the table below (adapted from Dr. Simone's review).

Demographic Variable		Treatment Group	
		Exparel (120 mg) N = 97	Placebo (Saline) N = 96
Age (years)	18-64	96	91
	≥65	1	5
	≥75	0	0
Gender	Male	22	12
	Female	75	84
Race	White	66	72
	Black	25	21
	Other	6	3
ASA-PS	1	78	82
	2	19	14
	3	0	0
	4	0	0

The disposition of the patients enrolled in the trial is summarized in the table below (adapted from Dr. Simone's and Dr. Petullo's reviews).

	Treatment Group	
	Exparel (120 mg)	Placebo (Saline)
Randomized		
Treated	97	96
Completed trial	93	92
Discontinued trial	4	4
Reason for discontinuation		
Withdrew consent	1	3
Adverse event		1
Other	3	

The adverse event noted in the table above was a deep venous thrombosis and the three events listed as "other" were protocol violations. Of the 193 patients who were treated during the trial, 187 were evaluated for efficacy.

#### *Summary of Efficacy Findings*

The results of the Applicant and Dr. Petullo respective analyses of the primary efficacy outcome are summarized in the table below (reproduced from Dr. Petullo's review).

	AUC <sub>24hrs</sub> (pi*hr) – mean (stderr)		Diff [95% CI]*	p-value
	Placebo	Exparel		
Applicant	146 (4)	125 (5)	22 [10, 35]	0.0005
Reviewer	146 (4)	123 (5)	24 [11, 37]	0.0002

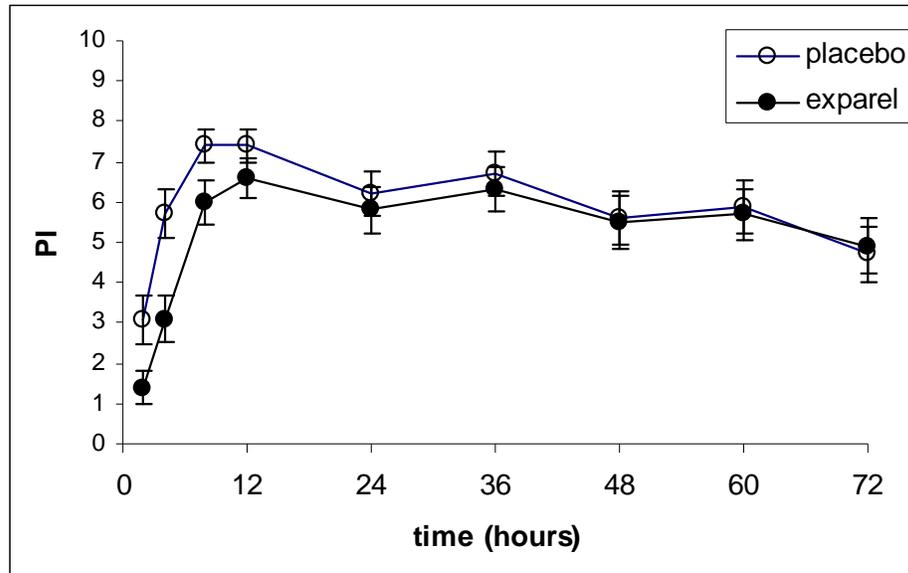
Source: Reviewer

\*difference in LSMEANS

Analyses of the following secondary outcomes, AUC values at other time points, the proportion of patients that were pain free at each time point, and the median time to rescue medications generally supported the finding of a treatment effect in favor of Exparel.

It was noted by Dr. Petullo that the difference in the proportion of patients that were pain free was significantly different only up to the eighth hour post-surgery; after that time point, the statistical significance was no longer present.

The analyses of the mean pain intensity score by treatment group at each time point was also conducted, and the results are summarized in the graph below (reproduced from Dr. Petullo's review).



As noted by Dr. Simone and Dr. Petullo in their reviews, the graph indicates that the analgesic effect of Exparel exceeds that of placebo for the initial 12 to 24 hours, after that time point, the curves are very similar. Furthermore, at the 8-hour time point after study drug administration, both treatment groups have mean pain intensity scores that are indicative of moderate pain.

## 8. Safety

The primary safety database is derived from the 22 clinical studies conducted by the Applicant in the development program. These studies were 9 Phase 1 studies (which included 2 QT studies and a study in patients with hepatic impairment), 7 Phase 2 studies, 5 Phase 3 trials, and a single Phase 3 long-term follow-up observational study.

A total of 1307 subjects received a dose of Exparel, ranging from 10 mg to 750 mg. The vast majority of them received a single administration; subjects who participated the early studies, or in the thorough QTc studies received multiple doses, but there was usually a washout period between the doses. Since the clinical development program had consisted of trials with different surgical procedures, the Applicant divided the safety database into the following categories:

1. All Wound Infiltration Studies (Phase 2 and 3 wound infiltration studies)
2. General Surgery Studies
3. Orthopedic Surgery Studies
4. Phase 1 Studies
5. All Studies (all Phase 1, 2, and 3 studies)

*Deaths*

There were 2 deaths reported in the clinical development program. Both deaths occurred in the trial in patients who had undergone a total knee arthroplasty; one had received Exparel and the other had received bupivacaine hydrochloride. After reviewing the case report forms and the narratives of the cases, the review team concurred with the Applicant that the cause of death was unrelated to the study treatment.

*Serious Adverse Events*

Across the studies in the clinical development program, there were 51 serious adverse events reported: 25 in subjects treated with Exparel, 24 in subjects treated with bupivacaine hydrochloride, and 2 in subjects treated with placebo.

Of the serious adverse events reported in the patients exposed to placebo, the investigators, the Applicant and the review team are in agreement that they were not related to study drug treatment.

Of the serious adverse events reported in the patients exposed to bupivacaine hydrochloride, the investigator deemed 7 to be related to study drug treatment (scar, hypoglycemia, hemarthrosis, joint swelling, knee arthroplasty, and two episodes of arthrofibrosis), and, after reviewing the documentation submitted, the team concurred.

Of the serious events report in the patients exposed to Exparel, the investigators, the Applicant, and the review team concurred that all but one were not related to study drug treatment. The investigator and the Applicant differed on whether a case of hepatitis, on Day 48 after treatment, could be attributable to the study drug treatment. After reviewing the documentation, Dr. Simone concluded that it was not possible to rule out Exparel as the cause of the hepatitis, but considered it possibly-related rather than probably-related.

*Adverse Event Leading to Discontinuation*

There were 12 discontinuations due to an adverse event from the group of subjects who received any study drug. Since some of the subjects were enrolled in the early phase studies, they may have been exposed to more than one study drug. The distribution among the study treatment was as follows: 3 had received both Exparel and bupivacaine hydrochloride, 4 had received Exparel (with or without saline control), 4 had received bupivacaine hydrochloride (with or without saline control), and 1 had received placebo.

Review of the documentation did not identify any clinically relevant safety issue that could be attributed to the use of Exparel.

*Common Adverse Events*

The types of common adverse events reported were consistent with the types of adverse events associated with bupivacaine hydrochloride. In addition, Dr. Simone noted in his review that many of the adverse events reported in the trials in the development program commonly occur in the peri-operative period and can be related to the anesthetic technique, anesthetic medications, the surgical procedure or technique, or a combination of surgical stress and anesthetic medications. The table below summarizes the adverse events which were reported at an incidence of 5% or greater (reproduced from Dr. Simone's review).

Adverse Event	Treatment					
	Exparel		(b) (4)	Bupivacaine HCl		Placebo [N=190] n (%)
	120 mg [N=97] n (%)	300 mg [N=196] n (%)		100 mg [N=103] n (%)	200 mg [N=194] n (%)	
Anemia				28 (14)		
Anemia Postoperative				10 (5)		
Arthralgia	1 (1)	2 (1)		3 (3)	9 (5)	2 (1)
Constipation	2 (2)	18 (9)		22 (21)	93 (48)	6 (3)
Diarrhea		2 (1)		5 (5)	2 (1)	1 (1)
Dizziness	11 (11)	3 (2)		4 (4)	5 (3)	31 (16)
Headache	6 (6)	3 (2)		7 (7)	7 (4)	8 (4)
Hypotension	1 (1)	1 (1)			4 (2)	1 (1)
Insomnia		1 (1)		1 (1)	13 (7)	
Muscle Spasms	1 (1)				12 (6)	2 (1)
Nausea	52 (54)	63 (32)		94 (91)	166 (86)	85 (45)
Edema Peripheral				1 (1)	5 (3)	
Procedural Pain		2 (1)		1 (1)	12 (6)	
Pruritus	3 (3)	4 (2)		5 (5)	30 (15)	1 (1)
Pruritus Generalized	6 (6)	1 (1)		2 (2)	3 (2)	11 (6)
Pyrexia	2 (2)	9 (5)		1 (1)	16 (8)	1 (1)
Somnolence	8 (8)				2 (1)	2 (1)
Tachycardia				1 (1)	11 (6)	
Vomiting	39 (40)	22 (11)		13 (13)	37 (19)	34 (18)

Dr. Simone made the following points in his review about the adverse events in the table:

1. The only dose-dependent adverse event for the Exparel-treated subjects was constipation; however, these rates were consistent with those for the bupivacaine hydrochloride-treated subjects, and higher rates would be expected for patients undergoing major surgery (b) (4)

2. Dizziness, an adverse event that has been associated with high systemic levels of bupivacaine, did not increase in incidence with increasing doses of Exparel and was consistent at all doses with incidences observed in both the bupivacaine hydrochloride and placebo groups. The 16% incidence of dizziness for placebo-treated subjects suggests that the etiology of this adverse event is due to factors other than the study drugs.
3. The adverse events for the highest dose of Exparel were similar to those of the bupivacaine hydrochloride and placebo treatment groups.

#### *Specific Adverse Events of Clinical Interest*

There were two types of potential adverse events that were of interest due to the specific characteristics of the drug product and the route of administration. The first was whether there would be sufficient systemic absorption with subsequent cardiac and/or neurotoxicity, and the second was whether the infiltration into the surgical wound area would interfere with wound healing.

#### Assessment of Elevated Plasma Levels

There have been literature reports that bupivacaine plasma levels > 1 µg/mL are associated with seizure activity and cardiac arrhythmias. These two adverse events were not reported in the clinical development program, but the team was interested to see whether any subjects had plasma levels in that range and, if so, what type of adverse event, if any, they experienced.

Although several subjects had pharmacokinetic assessments performed, the surgical population was felt to be the most relevant population for this safety assessment; therefore, subjects in the thorough QT studies or the hepatic impairment study were not considered. The table below summarizes, by Exparel dose, the distribution of plasma levels above 750 µg/mL (adapted from Dr. Simone's review).

Exparel Dose	Plasma Bupivacaine Concentration (µg/L)			
	750-999 n (%)	1,000-1,999 n (%)	2,000-9,999 n (%)	> 10,000 n (%)
150 [N=26]		1 (4)	1 (4)	
300 [N=62]	6 (10)	8 (13)	1 (2)	
350 [N=28]	1 (4)			
450 [N=26]	1 (4)			2 (8)
(b) (4)				
Total	12	20	2	3

Based on these plasma level results, it would have been expected that there would be several patients reporting severe adverse events, or worse. In actuality, only the two highest doses of Exparel were associated with either a neurological or cardiac adverse event, and the events reported were all mild or moderate; the other events reported are not uncommon in the post-operative setting. The table below summarizes the adverse events reported with the two highest doses (adapted from Dr. Simone's review).

Treatment Emergent Adverse Events		Exparel Dose for Subjects with Systemic Bupivacaine Levels $\geq$ 750 mcg/mL		
System	MedDRA Code	450 mg [N=3] n (%)	(b) (4)	Total [N=19]
Neurological	Anxiety	1 (33)		1 (5)
	Confusion or Hallucination			3 (16)
	Dizziness			3 (16)
	Lethargy, Sedation or Fatigue			4 (21)
	Headache	1 (33)		1 (5)
Cardiac	Bradycardia			2 (11)
	Tachycardia			7 (37)
	Ventricular Tachycardia			1 (5)

As Dr. Simone noted, the findings would indicate that the plasma levels reported do not accurately reflect systemic exposure to Exparel. There could be several possible explanations for the observation that plasma bupivacaine levels that would be expected to be associated with adverse events were reported yet the elevated levels were not associated clinical signs or symptoms of toxicity. Nevertheless, in clinical practice, the management of adverse events in patients treated with local anesthetics is driven by the clinical presentation; therefore, these unexpected findings are not expected to impact patient safety in the clinical setting.

#### Assessment of Interference with Wound healing

The assessment of interference with wound healing was conducted in seven studies, by having evaluations done of the wound status and overall satisfaction with the progress of the wound on Day 8 or Day 10, and Day 30 or Day 36 following treatment, depending on the surgical procedure being conducted in the trial. Study SKY0402-C-317 also had a radiographic assessment of the surgical area 4 to 6 weeks after the bunionectomy had been performed to evaluate for improper union or non-union.

The findings were comparable between the Exparel and bupivacaine hydrochloride treatment groups.

#### Outstanding or Unresolved Issues

I concur with Dr. Simone's assessment that the safety profile of Exparel did not differ in a clinically significant manner from bupivacaine hydrochloride. Further, there was no evidence that Exparel adversely affected wound healing or was more likely than bupivacaine hydrochloride to cause neurological or cardiac toxicity.

## 9. Advisory Committee Meeting

The convening of an advisory committee meeting for discussion of this application was deemed to be unnecessary. This decision was reached in view of the observation that the results of the trials, the clinical experience with bupivacaine hydrochloride, the indication

being sought in the application, and the lack of any specific issues identified in the application that would warrant discussion at an advisory committee meeting.

## 10. Pediatrics

(b) (4)

The Division concurred with the Applicant's request for deferral for age groups between 2 years old and 16, (b) (4)

The Division's position on the Applicant's proposed pediatric development plan was presented to the Pediatric Review Committee (PeRC) on October 5, 2011, and they concurred with the Division.

## 11. Other Relevant Regulatory Issues

Consultations were obtained from the Division of Scientific Investigations, the Division of Drug Marketing, Advertising and Communication, and the Division of Medication Error Prevention and Analysis.

### Division of Scientific Investigations (DSI) Audits

The Division of Scientific Investigations inspected four clinical sites in the Republic of Georgia that were involved with Study SKY0402-C-316, the trial in patients who had undergone a hemorrhoidectomy:

Rema Gvamichava, M.D.  
Chemotherapy & Immunotherapy  
Clinic - Medulla, 6 Jikia Str, 0186  
Tbilisi, Republic of Georgia  
Georgia

Erekle Tchubabria, M.D., Ph.D.  
E.O.P.L. Al Aladashvili #1 Clinic of Tbilisi State  
Medical University  
103 Uznadze Street  
Tbilisi, 0102  
Georgia

Baadur Mosidze, M.D., Ph.D.  
National Center of Experimental & Clinical Surgery  
5 Chachava Street, 0159  
Tbilisi  
Georgia

Gia Mukhashavria, M.D.  
Society with Limited Responsibility  
Proctological Center  
29 Vazha-Pshavela Ave  
Tbilisi, 0160  
Georgia

The inspectors did not identify any regulatory violations.

### Financial Disclosure

The Applicant certified that there was no financial arrangement with the study investigators whereby the value of compensation to the investigators could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that no listed investigator was the recipient of significant payments of sorts as defined in 21 CFR 54.2 (f). The Applicant also indicated that the clinical investigators were required to disclose to the Applicant whether the investigator had a proprietary interest in the product or a significant equity in the Applicant, as defined in 21 CFR 54.2(b).

### Consult from Division of Drug Marketing, Advertising, and Communications

The Division of Drug Marketing, Advertising, and Communications provided several comments regarding the package insert, and the carton and container labeling. The comments are being conveyed and addressed with the Applicant at this time, and final resolution is not available as this review is being completed.

### Consult from Division of Medication Error Prevention and Analysis

The Division of Medication Error Prevention and Analysis provided several comments regarding the package insert, and the carton and container labeling. The comments are being conveyed and addressed with the Applicant at this time, and final resolution is not available as this review is being completed.

### Outstanding or Unresolved Issues

The only outstanding issue at this time is reaching an agreement with the Applicant on the package insert and labeling.

## 12. Labeling

The Applicant has submitted enough information to support portions of their proposed labeling. As noted above, the Office of Surveillance and Epidemiology and the Division of Drug Marketing, Advertising and Communications were consulted and their recommendations were incorporated during the discussion of the label. Several sections of the labeling are currently being discussed with the Applicant; therefore, a final assessment of the appropriateness of the package insert and labeling is not possible at this time. However, the following issues are main points being discussed with the Applicant:

- [REDACTED] (b) (4)
- The appropriate description of the concentration of the formulation (i.e., 13.3 mg/mL [REDACTED] (b) (4) because it should not be expressed as [REDACTED] (b) (4) as proposed by the Applicant.
- Appropriate description in the Dosage and administration section that does not indicate that dosing is based [REDACTED] (b) (4)
- The description of the clinical trials and their results (particularly the inclusion of the [REDACTED] (b) (4)
- Data supporting the validity of the temperature indicators present on the product packaging [REDACTED] (b) (4)

### 13. Decision/Action/Risk Benefit Assessment

#### Recommended Regulatory Action

The recommended regulatory action is approval, with inclusion in the Clinical Studies section of the labels the results of the studies conducted by the Applicant in the different surgical procedures.

#### Risk:Benefit Assessment

I concur with the review team that sufficient evidence for the safety and effectiveness of Exparel has been submitted and that the benefits of the product, when used according to the directions on the package insert and labeling, will outweigh the risks. (b) (4)

#### Recommendation for Postmarketing Risk Evaluation and Management Strategies

Routine post-marketing pharmacovigilance.

#### Recommendation for other Postmarketing Requirements and Commitments

The applicant should conduct the required pediatric studies as stipulated by the Pediatric Research Equity Act (PREA); a deferral is appropriate as the adult studies are completed and the application is ready for approval.

#### Recommended Comments to the Applicant

None.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RIGOBERTO A ROCA  
10/09/2011