CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022496Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

27 September 2011

NDA: **22-496/N-000**

Drug Product Name

Proprietary: Exparel™

Non-proprietary: bupivacaine extended-release liposomal injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
28 September 2010	28 September 2010	14 October 2010	20 October 2010
08 November 2010	09 November 2010	-	-
23 November 2010	24 November 2010	-	-
01 February 2011	01 February 2011	-	-
09 February 2011	09 February 2011	-	-
17 March 2011	17 March 2011	-	-
18 April 2011	18 April 2011	-	-
27 April 2011	27 April 2011	-	-
13 May 2011	13 May 2011	-	-
25 May 2011	25 May 2011	-	-
01 July 2011	01 July 2011	-	-
15 July 2011	15 July 2011	-	-
25 July 2011	25 July 2011	-	-

Submission History (for amendments only): N/A

Applicant/Sponsor

Name: Pacira Pharmaceuticals, Inc.

Address: 10450 Science Center Dr.
San Diego, CA 92121

Representative: Dwain K. Allen
Director, Regulatory Affairs

Telephone: 858-625-2424 (ext. 3262)

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is recommended for approval from microbiology product quality standpoint.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505(b)(2)

2. SUBMISSION PROVIDES FOR: Marketing authorization

3. MANUFACTURING SITE: Pacira Pharmaceuticals Inc. (b) (4)
10450 Science Center Drive
San Diego, CA 92121
(FEI): 3002783962

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile, liposomal injection; wound infiltration; (b) (4)

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Analgesic: for single-dose local administration into the surgical wound to produce post-surgical analgesia.

B. SUPPORTING/RELATED DOCUMENTS:

- (b) (4)

C. REMARKS:

- The submission was filed in electronic CTD format.
- Within the submission, the drug product is referred to as SKY0402 pending approval of the proposed name "Exparel™".
- In response to this reviewer's questions during a teleconference on 23 November 2010, the firm stated that they were implementing major modifications to the (b) (4) In addition, because of the renovations/upgrades, they could no longer manufacture the drug product as had been done for the clinical batches or the submission batches. They stated that they would complete modifications (b) (4) February 2011, and that they would not be ready for inspection until February 2011. Although the facility was not inspection ready at the time of submission, the submission was accepted for filing with the understanding that the facility would be inspection ready and that all (b) (4) (b) (4) would be completed by that date. The final data were ultimately submitted on May 25, 2011, and the CGMP inspection of the drug product manufacturing facility was initiated on June 6, 2011.
- An ONDQA initial quality assessment was filed in DARRTS on 24 November 2011. The IQA Chemist noted in her review that this reviewer considered the (b) (4) information to be insufficient. The Chemist's conclusion was

that the application was fileable "...*(b)ased on applicant's commitment to submit* (b) (4) *data to the NDA in February 2010.*" The final portions of the (b) (4) data were ultimately submitted as amendments on April 18, April 27, May 13 and May 25, 2011. The latter filing was classified as a "*Major Amendment*" since it was submitted within three months of the user fee goal date. As such, the goal date was extended three months from July 28, 2011(original date) to October 28, 2011.

Filename: N22496N000R1.doc

Executive Summary

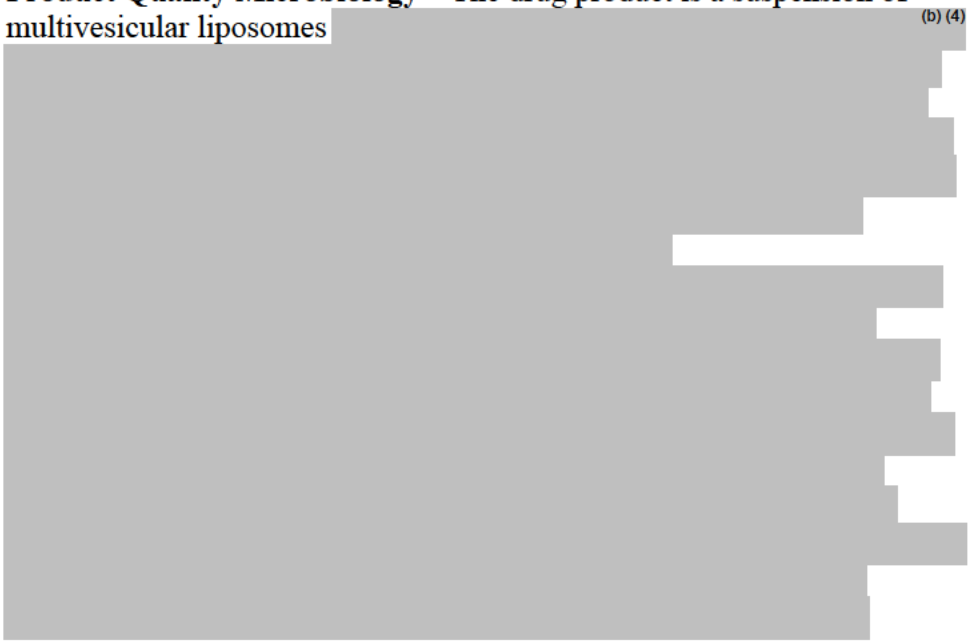
I. Recommendations

A. Recommendation on Approvability – Recommend Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is a suspension of multivesicular liposomes (b) (4)



B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature: _____

Robert J. Mello, Ph.D.
Senior Microbiology Reviewer

B. Endorsement Block: _____

John W. Metcalfe, Ph.D.
Senior Microbiology Reviewer

C. CC Block

NDA 22-496

21 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ROBERT J MELLO
09/28/2011

JOHN W METCALFE
09/28/2011
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 22-496 | **Applicant: Pacira Pharmaceuticals** | **Submit Date: 28 SEPT 2010**

Drug Name: EXPAREL™ bupivacaine E-R liposomal injection | **NDA Type: 505(b)(2)** | **Receipt Date: 28 SEPT 2010**

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		The submission is in eCTD format
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Section 3.2.A.1, (b) (4) validation pages 19-26
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		See attached review comments.
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity (CCI) studies?			Product is not preserved. CCI studies were located in Section 3.2.P.2.5, pages 1-3.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Section 3.2.P.5.1 and 3.2.P.5.2.
7	Has the applicant submitted the results of analytical method verification studies?	X		Section 3.2.P.5.3, reports #010-40030 (Sterility) and #010-40027 (Endotoxin by gel-clot)
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	-	-	Not applicable
9	Is this NDA fileable? If not, then describe why.	X		**See Comments Below**

Additional Comments: The NDA **is fileable ONLY** (b) (4) See review notes on the following pages.

Robert J. Mello, Ph.D., Reviewing Microbiologist Date: 08 November 2010

John W. Metcalfe, Ph.D., Secondary Microbiology Reviewer Date:

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

/s/

ROBERT J MELLO
11/08/2010

JOHN W METCALFE
11/09/2010
I concur.