CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022496Orig1s000

CHEMISTRY REVIEW(S)

Chemistry Review Cover Sheet

NDA 22496
Exparel (bupivacaine) liposomal injection

Arthur B. Shaw, Ph. D.
ONDQA/DNDQA3/DAAAP

Table of Contents

I. Recommendations 6

1. Recommendation and Conclusion on Approvability: 6
2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. 6

II. Summary of Chemistry Assessments 6

A. Description of the Drug Product(s) and Drug Substance(s) 6

1. Drug Substances 6
2. Drug Product 6

B. Description of How the Drug Product is Intended to be Used 8

C. Basis for Approvability or Not-Approval Recommendation 9

III. Administrative 9

I. Review of Common Technical Document-Quality (CTD-Q) Module 3.2: Body of Data 10

S DRUG SUBSTANCE 10

S.1 General Information: 10
S.2 Manufacture 10
S.3 Characterization: 10
S.4 Control of Drug Substance 10
S.5 Reference Standards or Materials 12
S.6 Container Closure System 102
S.7 Stability: 13

P DRUG PRODUCT 13

P.1 Description and Composition of the Drug Product 13
P.2 Pharmaceutical Development: 16
P.3. Manufacture 23
P.4 Control of Excipients 32
P.5 Control of Drug Product 35
P.6 Reference Standards or Materials 64
P.7 Container Closure 64
P.8 Stability 65

R REGIONAL INFORMATION 71
. LABELING 71

Chemistry Review Data Sheet

1. NDA 22496
2. REVIEW #2
3. REVIEW DATE: September 27, 2011
4. REVIEWER: Arthur B. Shaw, Ph. D.
5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date	SDN	
Discipline review Letter	2011-08-18		
Chem Review #1	2011-08-14		
Amendment	2011-07-27	33	Add spec for related substances In vitro release test **ACCEPTABLE**
Biopharm review	2011-08-11		
Amendment	2011-07-27	34	Amend in vitro release method
Amendment	2011-07-22	30	Add spec for [redacted] (b) (4) from [redacted] (b) (4)
Amendment	2011-07-15	27	Withdraw [redacted] (b) (4) of drug product
Amendment	2011-07-14	26	Withdraw [redacted] (b) (4) as excipient supplier
Amendment	2011-05-25	26	Partial data: [redacted] (b) (4) Validation for new facility
Amendment	2011-05-20	25	Info re excipient DMFs
Amendment	2011-05-13	23	Clarification regarding [redacted] (b) (4)
Amendment	2011-05-05	22	Info regarding excipient suppliers Response to 2011-04-11 telecon
Amendment	2011-04-27	21	Partial data: [redacted] (b) (4) Validation for new facility
Amendment	2011-04-18	20	Partial data: [redacted] (b) (4) Validation for new facility
Amendment	2011-04-07	18	Tighten spec for [redacted] (b) (4) from [redacted] (b) (4)
Amendment	2011-03-17	16	Leachables and extractables (IR #7 in FL)
Amendment	2011-02-24	14	In vitro release (IR #11 in FL)
Amendment	2011-02-09	12	[redacted] (b) (4) (IR #6 in FL)
Amendment	2011-02-09	13	Updated stability
Amendment	2011-02-01	10	Response to IR #s 1,4,7,8,9,10,12 in FL
Filing Letter (FL)	2010-12-10		12 IR Questions
Amendment	2010-11-23	6	Stability protocol for [redacted] (b) (4) lots, [redacted] (b) (4) composition for mfg
Original	2010-09-28	1	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	EDR#	SDN	
Amendment	2011-08-26	33	35	Initial Response to DR letter
Telecon	2011-08-29			Discuss issues in 8-26 response
Amendment	2011-09-02	34	36	2nd Response to DR letter
IR e-mail	2011-09-02			Questions regarding specs
Amendment	2011-09-12	36	38	Response to 9/2/2011 IR
Amendment	2011-09-13	37	39	USAN
Amendment	2011-09-20	38	40	Removal of (b) (4) and addition of (b) (4)

7. NAME & ADDRESS OF APPLICANT AND AGENT:

Applicant	
Name	Pacira Pharmaceuticals, Inc.
Address	10450 Science Center Dr. San Diego, CA 92121
Representative Name	Dwain K. Allen, Director, Regulatory Affairs
Phone	858-625-2424 ext. 3262

8. DRUG PRODUCT NAME/CODE/TYPE:

Proposed Proprietary Name: Exparel

USAN Name: bupivacaine

Non-Proprietary Name (INN, BAN): bupivacaine

Chem. Type/Submission Priority

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: analgesic

11. DOSAGE FORM: Injection, liposome

12. STRENGTH/POTENCY: 13.3 mg/mL See discussion below

13. ROUTE OF ADMINISTRATION: intrawound

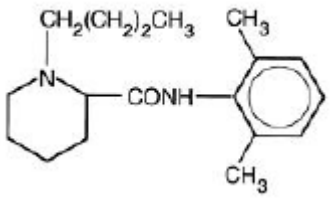
14. Rx/OTC DISPENSED: __X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): None

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(*RS*)-1-butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide;

1-butyl-*N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide



Molecular weight: 288.43

Molecular formula: $C_{18}H_{28}N_2O$

CAS RN 2180-92-9 and 38396-39-3

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:
Reviewed:

DMF	Holder	DMF Subject	Review Date	Comment
(b) (4)		Bupivacaine	2011-07-11	Adequate IR Letter 2011-08-11 No response
		Bupivacaine	2011-07-06	Adequate IR Letter 2011-07-13 Response under review
		Bupivacaine HCl	2011-04-06	Used to support DMF (b) (4) No control of (b) (4) IR letter 2011-04-15
(b) (4)			2011-08-19	Adequate
			2011-07-13	Adequate
			2011-09-23	Adequate
			2011-09-16	Adequate
			2003-07-10	Acceptable for (b) (4)
			2011-01-06	Adequate

B. Other Documents: NDA 16964 Marcaine (bupivacaine HCl) injection

18. STATUS:
CONSULTS/ CMC RELATED REVIEWS:
Microbiology: **ACCEPTABLE** 2011-09-27
Biopharm review: **ACCEPTABLE** 2011-08-11
EA waiver requested in 1.12.14. Granted **ACCEPTABLE**
Inspection: All sites are satisfactory.

The Chemistry Review for NDA 22496

I. Recommendations

1. **Recommendation and Conclusion on Approvability: The NDA can approved at this time from a CMC point of view.**
2. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.** None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substances

The drug substance, bupivacaine, is the free base of a USP item, bupivacaine hydrochloride. Bupivacaine base has never been used in any approved drugs. It is obtained from [redacted] (b) (4) and [redacted] (b) (4) Neither DMF had been previously reviewed. A genotoxic compound is used during the synthetic process for bupivacaine from both suppliers. Pacira has added a control for this compound [redacted] (b) (4) in their acceptance specifications for bupivacaine from both [redacted] (b) (4). This control is sufficient to limit intake of the genotoxin to NMT 1.5 µg/day when the drug product is dosed according to the label.

The bupivacaine free base a white crystalline powder and is soluble in organic solvents. It is stable and the potential degradants have been described. However these are not observed on storage of the drug substance. The specifications are adequate to ensure the quality of the drug substance, including an assay value of 98.5-101.0%, identified impurities controlled at levels qualified or below [redacted] (b) (4) and total impurities at [redacted] (b) (4)

The manufacturing sites for the drug substance [redacted] (b) (4) are acceptable in EES.

The drug substance is stored in [redacted] (b) (4). The re-test period is [redacted] (b) (4) based on data from drug substance suppliers. The applicant does not perform the re-testing. One batch a year is placed on stability and tested for stability on an annual basis by the drug substance suppliers.

2. Drug Product

The drug product is a milky white suspension packaged in sterile glass vials with rubber stoppers and must be resuspended before use. The drug is intended for single use only and contains no preservatives. The inactive ingredients are dierucoyl phosphatidylcholine (DEPC), dipalmitoyl phosphoglycerol (DPPG), tricaprylin, cholesterol and sodium chloride.

The drug product utilizes the applicant's DepoFoam® platform for entrapment of the drug substance in a non-classical, multivesicular liposome (MVL)

system to permit extended release of the drug at its site of action, which is a surgical wound. The applicant uses a multi-step process to create the drug-containing particles. (b) (4) During this process the concentration is adjusted to 13.3 mg bupivacaine/mL. The drug product is then filled into sterile vials with rubber stoppers.

Since the product is intended for injection it must be sterile. (b) (4)

The lipid components of the MVLs are DEPC, DPPG, tricaprylin, and cholesterol. The DEPC is manufactured by (b) (4) The DPPG and tricaprylin are manufactured by (b) (4) The DMFs are acceptable. (b) (4) received satisfactory CGMP inspections. The cholesterol and compounds used for the pH and osmotic adjustment (b) (4) are accepted based on their conformance to the USP/NF.

In the pharmaceutical development the applicant addressed issues regarding the choice of lipids, the lipid composition, (b) (4) processing parameters, and scale-up to the proposed commercial size of (b) (4) After the drug product used for the pivotal clinical trials and stability assessment were prepared, the applicant constructed a new facility. Due to the complex process and the fact that (b) (4) and submitted for review by the New Drug Microbiology group. The information concerning the (b) (4) has been found acceptable by the New Drug

Microbiology reviewer. An inspection of Pacira's facility determined that the facility was compliant with CGMP.

The specifications for the finished drug product include tests and acceptance criteria for bupivacaine identity and content, % free bupivacaine, cholesterol content, in vitro release, (b) (4), particle size, (b) (4) (b) (4) pH, particulate matter, bupivacaine-related substances (degradants), osmolality, uniformity of dosage units, volume in container, bacterial endotoxins and sterility. There are no tests or acceptance criteria for DEPC content, tricaprylin content, DPPG content or (b) (4) (b) (4) (b) (4) The cholesterol content is a measure of the total lipids. Measurement of DEPC, DPPG, tricaprylin, (b) (4) content in developmental batches, including stability, shows that measurement of these compounds is not necessary to ensure adequate control of the drug product.

The applicant's proposed acceptance criterion of (b) (4) for the free bupivacaine is adequate to ensure that sufficient bupivacaine is retained within the MVLs (b) (4) The applicant's proposed acceptance criterion of (b) (4) free bupivacaine on stability is acceptable.

The applicant's proposed acceptance criterion for the (b) (4) is supported by the data.

The in vitro release test is performed by measuring release of bupivacaine from the drug product in the presence of bovine serum albumin (BSA) over 168 hours (7 days). This test is not intended to represent physiological conditions and is not intended to provide an assessment of in vivo release. It is solely a QC test. The test was found acceptable in a Biopharmaceutics review dated 2011-08-11.

The remainder of the tests and acceptance criteria are acceptable.

The stability data supports the proposed expiration date of 24 months when stored at 5°C.

All facilities have a satisfactory CGMP status.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be used for the relief of pain following surgery by injection directly into the surgical wound and is intended to provide pain relief (b) (4).

C. Basis for Approvability or Not-Approval Recommendation

The NDA can be approved at this time from a CMC point of view.
Administrative.

See DARRTS signatures and cc's

63 PAGES HAVE 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/

ARTHUR B SHAW
09/28/2011

PRASAD PERI
09/28/2011
I concur

Chemistry Review Cover Sheet

NDA 22496
Exparel (bupivacaine) liposomal injection

Arthur B. Shaw, Ph. D.
ONDQA/DNDQA3/DAAAP

Table of Contents

I. Recommendations 7

1. Recommendation and Conclusion on Approvability: 7
2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

1. Drug Substances 7
2. Drug Product 7

B. Description of How the Drug Product is Intended to be Used 10

C. Basis for Approvability or Not-Approval Recommendation 10

III. Administrative 10

I. Review of Common Technical Document-Quality (CTD-Q) Module 3.2: Body of Data 11

S DRUG SUBSTANCE 11

S.1 General Information : 11
S.2 Manufacture: 11
S.3 Characterization: 13
S.4 Control of Drug Substance 18
S.5 Reference Standards or Materials: 28
S.6 Container-Closure 28
S.7 Stability: 30

P DRUG PRODUCT 31

P.1 Description and Composition of the Drug Product 31
P.2 Pharmaceutical Development: 34
P.3. Manufacture 85
P.4 Control of Excipients 98
P.5 Control of Drug Product 102
P.7 Container Closure System: 178
P.8 Stability 180
R REGIONAL INFORMATION 203
II. LABELING 203
III. DRAFT COMMENTS TO BE SENT TO APPLICANT: : 204

Chemistry Review Data Sheet

1. NDA 22496
2. REVIEW #1
3. REVIEW DATE: August 12, 2011
4. REVIEWER: Arthur B. Shaw, Ph. D.
5. PREVIOUS DOCUMENTS: IND 69198
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	EDR#	SDN	
Original	2010-09-28	0000	1	
Amendment	2010-11-08	0001	3	Contact info for DS mfrs
Amendment	2010-11-23	0004	6	Stability protocol for (b) (4) lots, (b) (4) composition for mfg
Filing Letter (FL)	2010-12-10			12 IR Questions
Amendment	2011-02-01	0008	10	Response to IR #s 1,4,7,8,9,10,12 in FL
Amendment	2011-02-09	0010	12	(b) (4) (IR #6 in FL)
Amendment	2011-02-09	0011	13	Updated stability
Amendment	2011-02-24	0012	14	In vitro release (IR #11 in FL)
Amendment	2011-03-17	0014	16	Leachables and extractables (IR #7 in FL)
Amendment	2011-04-07	0016	18	Tighten spec for (b) (4) from (b) (4)
Telecon	2011-04-11		Not in DARRTS	Request for info regarding excipient mfrs
Amendment	2011-04-18	0018	20	Partial data: (b) (4) Validation for new facility
Amendment	2011-04-27	0019	21	Partial data: (b) (4) Validation for new facility
Amendment	2011-05-05	0020	22	Info regarding excipient suppliers Response to 2011-04-11 telecon
Amendment	2011-05-13	0021	23	Clarification regarding (b) (4)
Amendment	2011-05-20	0022	25	Info re excipient DMFs
Amendment	2011-05-25	0024	26	Partial data: (b) (4) Validation for new facility
IR	2011-06-21		Not in DARRTS.	Request for info regarding (b) (4) supplied by (b) (4)
Amendment	2011-07-14	0028	26	Withdraw (b) (4) as excipient supplier

Amendment	2011-07-15	29	27	Withdraw (b) (4) of drug product
Amendment	2011-07-22	28	30	Add spec for (b) (4) from (b) (4)
Amendment	2011-07-25	29	31	Response to Obs 2 in 483
Amendment	2011-7-26	30	32	Confirm application for USAN
Amendment	2011-07-27	31	33	Add spec for related substances
Amendment	2011-07-27	32	34	Amend in vitro release method

7. NAME & ADDRESS OF APPLICANT AND AGENT:

Applicant	
Name	Pacira Pharmaceuticals, Inc.
Address	10450 Science Center Dr. San Diego, CA 92121
Representative Name	Dwain K. Allen, Director, Regulatory Affairs
Phone	858-625-2424 ext. 3262

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proposed Proprietary Name: Exparel
b) Non-Proprietary Name (INN, BAN): bupivacaine

Note that there is no USAN for bupivacaine. There is one for bupivacaine hydrochloride. The applicant has requested a name from the USAN council.

c) Chem. Type/Submission Priority
- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: analgesic

11. DOSAGE FORM: Extended release liposomal suspension

The dosage form name in the label is (b) (4)

Note: It is not clear whether the drug product meets the criteria for (b) (4) This is under review by the relevant disciplines.

COMMENT: Change the dosage form name in the label to (b) (4) (b) (4)

12. STRENGTH/POTENCY: (b) (4) See discussion below

13. ROUTE OF ADMINISTRATION:

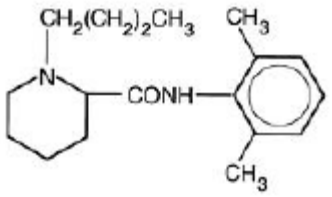
14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): None

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(*RS*)-1-butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide;

1-butyl-*N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide



Molecular weight: 288.43

Molecular formula: $C_{18}H_{28}N_2O$

CAS RN 2180-92-9 and 38396-39-3

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:
Reviewed:

DMF	Holder	DMF Subject	Review Date	Comment
(b) (4)		Bupivacaine	2011-07-11	Adequate IR Letter 2011-08-11
		Bupivacaine	2011-07-06	Adequate IR Letter 2011-07-13
		Bupivacaine HCl	2011-04-06	Used to support IND (b) (4) No control of (b) (4) IR letter 2011-04-15
(b) (4)			2011-08-11	Deficient. Def Letter 2011-08-11
			2011-07-13	Acceptable
			2011-02-11	Deficient. Def letter 2011-02-25 Amendment 2011-05-17 Incomplete
			2011-07-13	Acceptable IR Letter 2011-08-11
			2003-07-10	Acceptable for D7777
			2011-01-06	Acceptable

B. Other Documents: NDA 16964 Marcaine

18. STATUS:
CONSULTS/ CMC RELATED REVIEWS:
Microbiology: Under review
Biopharm review: **ACCEPTABLE** 2011-08-11
EA waiver requested in 1.12.14. Granted **ACCEPTABLE**
Inspection: All sites are satisfactory except one, which is responsible to testing the (b) (4) (see discussion below) under P.3.1: (b) (4)

Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: CONTROL TESTING LABORATORY
OAI Status: OAI ALERT
Last Milestone: EIR RECEIVED BY OC
Milestone Date: 30-MAR-2011

The Chemistry Review for NDA 22496

I. Recommendations

1. **Recommendation and Conclusion on Approvability:** The NDA cannot be approved at this time from a CMC point of view due to outstanding CGMP issues. Review of Microbiology issues is still pending and a DMF for a critical excipient is deficient. This review includes a number of deficiencies to be communicated to the applicant.

2. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.** None ?

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substances

The drug substance, bupivacaine, is the free base of a USP item, bupivacaine hydrochloride. Bupivacaine base has never been used in any approved drugs. It is obtained from [redacted] (b) (4)) and [redacted] (b) (4) Neither DMF had been previously reviewed. A genotoxic compound is during the synthetic process for bupivacaine from both suppliers. Pacira has added a control for this compound [redacted] (b) (4) in their acceptance specifications for bupivacaine from both [redacted] (b) (4) This control is sufficient to limit intake of the genotoxin to NMT 1.5 µg/day when the drug product is dosed according to the label.

The bupivacaine free base a white crystalline powder and is soluble in organic solvents. It is stable and the potential degradants have been described. However these are not observed on storage of the drug substance. The specifications are adequate to ensure the quality of the drug substance, including an assay value of 98.5-101.0%, identified impurities controlled at levels qualified or below [redacted] (b) (4) and total impurities at [redacted] (b) (4)

The manufacturing sites for the drug substance [redacted] (b) (4) are acceptable in EES.

The drug substance is stored in [redacted] (b) (4). The re-test period is [redacted] (b) (4) based on data from drug substance suppliers. The applicant does not perform the re-testing. One batch a year is placed on stability and tested for stability on an annual basis by the drug substance suppliers.

2. Drug Product

The drug product s a milky white suspension packaged in sterile glass vials with rubber stoppers and must be resuspended before use. The drug is intended for single use only and contains no preservatives. The inactive

ingredients are dierucoyl phosphatidylcholine (DEPC), dipalmitoyl phosphoglycerol (DPPG), tricaprylin, cholesterol and sodium chloride.

The drug product utilizes the applicant's DepoFoam® platform for entrapment of the drug substance in a non-classical, multivesicular liposome (MVL) system to permit extended release of the drug at its site of action, which is a surgical wound. The applicant uses a multi-step process to create the drug-containing particles. (b) (4) During this process the concentration is adjusted to (b) (4) The drug product is then filled into sterile vials with rubber stoppers.

Since the product is intended for injection it must be sterile. (b) (4)

The lipid components of the MVLs are DEPC, DPPG, tricaprylin, and cholesterol. The DEPC is manufactured by (b) (4) The DPPG and tricaprylin are manufactured by (b) (4) The (b) (4) DMFs for DEPC and DPPG are deficient and the holder has been notified. (b) (4) received satisfactory CGMP inspections. The cholesterol and compounds used for the pH and osmotic adjustment (b) (4) are accepted based on their conformance to the USP/NF.

In the pharmaceutical development the applicant addressed issues regarding the choice of lipids, the lipid composition, (b) (4) processing parameters, and scale-up to the proposed commercial size of (b) (4) After the drug product used for the pivotal clinical trials and stability assessment were prepared, the applicant constructed a new facility. Due to the complex process and the fact

that [redacted] (b) (4) the issues concerning validation have been challenging for the applicant. A complete [redacted] (b) (4) package had to be prepared and submitted for review by the Microbiology group. Since the Pacira's facility (San Diego, CA)was not ready at the time of filing of the NDA and the applicant experienced delays in completing their validation, the lateness of the filing of this information resulted in an extension of the review clock by three months. The information concerning the [redacted] (b) (4) is currently under review by the New Drug Microbiology reviewer. An inspection of Pacira's facility determined that the facility was not compliant with CGMP for a number of reasons and a 483 was issued. Pacira responded satisfactorily to the 483 and the site is now acceptable.

The specifications for the finished drug product include tests and acceptance criteria for bupivacaine identity and content, % free bupivacaine, cholesterol content, in vitro release, [redacted] (b) (4), particle size, [redacted] (b) (4) [redacted] (b) (4) pH, particulate matter, bupivacaine-related substances (degradants), osmolality, uniformity of dosage units, volume in container, bacterial endotoxins and sterility. There are no tests or acceptance criteria for DEPC content, tricaprylin content, DPPG content or [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted] The cholesterol content is a measure of the total lipids. Measurement of DEPC, DPPG, tricaprylin, [redacted] (b) (4) content in developmental batches, including stability, shows that measurement of these compounds is not necessary to ensure adequate control of the drug product.

The applicant's proposed acceptance criterion of [redacted] (b) (4) for the free bupivacaine is adequate to ensure that sufficient bupivacaine is retained within the MVLs [redacted] (b) (4) The applicant's proposed acceptance criterion of [redacted] (b) (4) free bupivacaine on stability is not supported by the data. See summary of recommendations below.

The applicant's proposed acceptance criterion of [redacted] (b) (4) [redacted] is not supported by the data. See summary of recommendations below.

The in vitro release test is performed by measuring release of bupivacaine from the drug product in the presence of bovine serum albumin (BSA) over 168 hours (7 days). This test is not intended to represent physiological conditions and is not intended to provide an assessment of in vivo release. It is solely a QC test. The test was found acceptable in a review dated 2011-08-11.

The remainder of the tests and acceptance criteria are acceptable.

The stability data supports the proposed expiration date of 24 months when stored at 5°C.

The strength of the drug product is adjusted during manufacturing to yield a strength of (b) (4) (b) (4)

All facilities have a satisfactory CGMP status except for (b) (4)

Recommendations:
1. Amend the acceptance criterion for the % free bupivacaine to (b) (4) on stability.
2. Amend the acceptance criterion for the (b) (4)

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be used for the relief of pain following surgery by injection directly into the surgical wound (b) (4) (b) (4). The label of the proposed product specifically states "Different formulations of bupivacaine are not bioequivalent even if the milligram strength is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL™.Th"

C. Basis for Approvability or Not-Approval Recommendation

The NDA cannot be approved at this time from a CMC point of view due to outstanding CGMP issues. Review of Microbiology issues is pending. This review includes a number of deficiencies to be communicated to the applicant.

III. Administrative

See DARRTS signatures and cc's

199 PAGES HAVE 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/

ARTHUR B SHAW
08/12/2011

PRASAD PERI
08/14/2011
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Arthur Shaw, Reviewing Chemist, HFD-800
E-mail Address: Arthur.Shaw!@fda.hhs.gov
Phone: (301)-796-1460
Fax: (301)-796-9787

FROM: FDA
Division of Pharmaceutical Analysis, HFD-920
James Allgire
Room 1002
1114 Market Street
St. Louis, MO 63101

Through: B. J. Westenberger, Deputy Director, HFD-920
Phone: (314)-539-3869

SUBJECT: Methods Validation Report Summary

Application Number: NDA 22496

Name of Product: Exparel (bupivacaine liposomal extended release) Injection

Applicant: Pacira Pharmaceuticals, Inc.

Applicant's Contact Person: Dwain K. Allen, Director, Regulatory Affairs

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

Telephone: 858-625-2424 ext. 3262 Fax: No Fax email: dwaina@pacira.com

Date NDA Received by DPA: 3/25/2011

Date Samples Received by DPA: 4/12/2011

Date Analytical Completed by DPA: 5/18/2011

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments:

The cover memo and summary of results are attached.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
1114 Market Street, Room 1002
St. Louis, Missouri 63101
Telephone (314) 539-2135
FAX (314) 539-2113

Date: May 18, 2011

To: Arthur Shaw, Ph.D., Reviewing Chemist (HFD-800)

Through: B.J.Westenberger, Deputy Director, Division of Pharmaceutical Analysis (HFD-920)

From: Anjanette Smith, Chemist, Division of Pharmaceutical Analysis (HFD-920)

Subject: Evaluation of NDA 22-496
Exparel (bupivacaine liposomal extended release) Injection, (b) (4)
Pacira Pharmaceuticals, Inc.

Background: The Office of New Drug Quality Assessment requested the Division of Pharmaceutical Analysis (DPA) evaluate the following methods for NDA 22-496 Exparel (bupivacaine liposomal extended release) Injection, (b) (4)

053-40004.005 Particle Size Analysis of SKY0402

053-40008.006 SKY0402 In Vitro Release Assay

Conclusion: The methods are acceptable for quality control and regulatory purposes. The following comments should be addressed;

<u>053-40008.006 SKY0402 In Vitro Release Assay</u>

1. The method for rate of release required analysis of the sample at initial, 4, 24, 48 and 72 hours but only provided specifications for results at 24, 48 and 72 hours. Specifications for results at initial and 4 hours or a statement that says there is no specification for the initial and 4 hour sample times should be provided.
2. The method for rate of release specified centrifuging the samples for 10 minutes at relative centrifugal force (RCF) of (b) (4). Samples at 48 and 72 hours had (b) (4) The applicant should mention that (b) (4) particles may be observed in the supernatant for samples at time points 48 and 72 hours.

<u>053-40004.005 Particle Size Analysis of SKY0402</u>

1. Sympatec HELOS Laser Diffraction System was used to evaluate the method as a Horiba LA910 or LA-950 could not be obtained.
2. The sample did not meet the D10 and D50 specifications. This may be due to the use of a different particle analyzer. The Sympatec HELOS does not use MIE scattering theory and does not correct for the Relative Refractive Index like the Horiba systems.
3. The samples were stored in the refrigerator according to the method, but the method for particle size distribution did not specify if the sample should be tested at room temperature or immediately out of refrigerator. The sample temperature should be specified.

Summary of Results **NDA 22-496**

Method: SKY0402 In Vitro Release Assay, Document 053-40008.006, PCDOC# 130969.01

Time point	%Release	Avg(3) %Release	SD	%RSD	**Specifications**
Initial	9.6, 8.3, 8.4	8.8	0.7	8.3	
4h	18.5, 19.9, 18.8	19.1	0.8	3.9	(b) (4)
24h	48.8, 50.7, 48.3	49.3	1.2	2.5	
48h	66.4, 65.1, 64.0	65.2	1.2	1.9	
72h	72.4, 78.2, 81.2	77.3	4.4	5.8	

Method: Particle Size Analysis of SKY0402, Document 053-40004.005, PCDOC# 12952.01

Percentile	Particle Size	Avg(3) Particle Size	SD	%RSD	**Specifications**
D10 (µm)	(b) (4)	(b) (4)			(b) (4)
D50 (µm)					
D90 (µm)					

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
05/18/2011

BENJAMIN J WESTENBERGER
05/23/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REQUEST

TO: **FDA**
Division of Pharmaceutical Analysis, HFD-920
Attn: Nick Westenberger
Room 1002
1114 Market Street
St. Louis, MO 63101

FROM: Arthur Shaw, Reviewing Chemist, HFD-800
E-mail Address: Arthur.Shaw@fda.hhs.gov
Phone: (301)-796-1460
Fax.: (301)-796-9787

Through: Danae Christodolou, Chemistry Team Leader, HFD-800
Phone: (301)-796-1342
and
Michael Folkendt, ONDC Methods Validation Coordinator, HFD-800
Phone: 301-827-5173

SUBJECT: Methods Validation Request

Application Number: NDA 22496

Name of Product: Exparel (bupivacaine liposomal extended release) Injection

Applicant: Pacira Pharmaceuticals, Inc.

Applicant's Contact Person: Dwain K. Allen, Director, Regulatory Affairs

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

Telephone: 858-625-2424 ext. 3262 Fax: No Fax email dwaina@pacira.com

Date NDA Received by CDER: **9/28/2010**

Date of Amendment(s) containing the MVP: **09/28/2010**

DATE of Request: **March 2, 3011**

Requested Completion Date: **4/15/2011**

PDUFA User Fee Goal Date: **7/28/2011**

Chemical/Therapeutic Type: 3S

Special Handling Required: No

DEA Class: N/A

Format of Methods Validation Package

☐ Paper ☒ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request Form*. Upon receipt of the samples, perform the tests indicated in item 3 of the attached *Methods Validation Request Form* as described in the MV package. We request your report to be submitted in DFS promptly upon completion, but not later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the reviewing chemist of the date the validation process begins. If the requested completion date cannot be met, please promptly notify the reviewing chemist and the ONDC Methods Validation Coordinator.
Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying Methods Validation Report Summary). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DFS. Send the complete report, with the DFS signed *Methods Validation Report Summary*, by overnight courier to the above reviewing chemist. All information relative to this application is to be held confidential as required by 21 CFR 314.430.

ATTACHMENT(S): *Methods Validation Request Form*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	METHODS VALIDATION REQUEST	NDA #

← SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION

↑ Contents of Attached Methods Validation Package:	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	P.1
Specifications/Methods for New Drug Substance(s)	S.4.1
Specifications/Methods for Finished Dosage Form(s)	P.5.1
Supporting Data for Accuracy, Specificity, etc.	S.4.3 and P.5.3
Applicant's Test Results on NDS and Dosage Forms	S.4.5 and P.5.4
Other:	

→ **REQUESTED DETERMINATIONS** (Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.)

Method ID	Method Title	Volume/Page	MV Request Category (see attached page)	Comments
053-40004	Particle Size	N/A	**4**	
053-40008	In vitro release	N/A	**2**	

Additional Comments: **EDR location: \\CDSESUB1\EVSPROD\NDA022496**

Methods Validation Request Criteria

MVP Request Category	Description
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason.

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
03/03/2011

ARTHUR B SHAW
03/03/2011

DANAE D CHRISTODOULOU
03/07/2011

MICHAEL M FOLKENDT
03/07/2011

Initial Quality Assessment
Office of New Drug Quality Assessment
Division III, Branch VIII
Division of Anesthesia, Analgesia and Addiction Products

OND Division:	Anesthesia, Analgesia and Addiction	
NDA:	22496	
Chemical Classification	3S	
Applicant:	Pacira Pharmaceuticals Inc.	
Stamp date:	September 28, 2010	
PDUFA Date:	July 28, 2011	
Trademark:	EXPAREL™	
Established Name:	Bupivacaine extended-release liposomal injection	
Dosage Form:	Liposomal injection(s), [redacted] (b) (4)	
Route of Administration:	Local infiltration into the surgical wound	
Indication:	Post-surgical analgesia	
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.	
	YES	NO
ONDQA Fileability:	√	____
Comments for 74-Day Letter:	√	____

Summary, Critical Issues and Comments

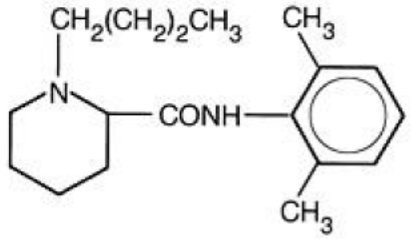
A. Summary

The application is submitted as a 505(b)(2), referencing the approved NDA 16-964, Marcaine® (bupivacaine HCl) injection. A priority review was requested by the applicant but not granted by the Division. The proprietary name has been reviewed and granted by the Agency on May 20. 2009.
The drug product is administered as a single-dose for wound infiltration near the end of surgery, and is intended to induce post-surgical analgesia, by the extended-release liposome of bupivacaine.
The applicant referenced the pre-NDA meeting minutes of February 16, 2010 to support their process scale-up and pooling of batches. Drug product batches 10PD-001 and 10PD-002 were manufactured at the (b) (4) scale and submitted to the NDA with 3-month stability data; batch10PD-003 was "pooled" from the two batches and submitted to the NDA with 3-month stability data. However, the applicant implemented changes to manufacturing equipment for the commercial launch without submitting a complete (b) (4) validation data for the commercial process. Note, that (b) (4) validation has not been discussed in the pre-NDA meeting of February 16, 2010. As a response to CMC information request, to clarify the changes in production equipment, and whether the (b) (4) process for the NDA batches was still in place, the applicant submitted a side-to-side comparison of equipment used for manufacture of the NDA batches and proposed commercial production. In a follow-up teleconference with the Division, the applicant stated that modifications were implemented to the manufacturing facility and almost completed, and that (b) (4) validation data for the commercial process, would be available in February 2010.

B. Review, Comments and Recommendations

Drug Substance Bupivacaine

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight



Chemical Name(s): (*RS*)-1-butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide;
1-butyl-*N*-(2,6-dimethylphenyl)-2-piperidinecarboxamide
Molecular formula: $C_{18}H_{28}N_2O$
Molecular weight: 288.43
CAS: 2180-92-9, 38396-39-3

The drug substance is manufactured by (b) (4) Drug substance batches for the NDA have been manufactured at (b) (4) The applicant proposes to use as alternate site, the (b) (4) Since a site-transfer for (b) (4) product is considered a major change, qualification of this alternate site without a comparability protocol, or comparability data in the NDA is not acceptable. This site may be submitted post-approval in a post-approval supplement, as per the SUPAC-MR Guidance. The (b) (4) manufacturing process for bupivacaine is referenced to DMF (b) (4) Additional manufacturer is (b) (4)

(b) (4) The (b) (4) process is referenced to DMF (b) (4) Three batches, 18212706, 18212707 and 18212709 have been manufactured (b) (4) and have been included in the NDA. Neither DMF has been reviewed previously. Impurity profiles for both processes are similar, but not identical. (b) (4) Both impurities levels and proposed limits should be assessed in consultation with the Toxicology Division.

Impurities are controlled for both processes as follows:

(b) (4)

Table 1. (b) (4) process: Potential Impurities and Degradation Products

Name	Structural Formula	Notes
(b) (4)		

Table 2. (b) (4) process: Potential Impurities and Degradation Products

Name	Structural Formula	Notes
		(b) (4)

Name	Structural Formula	Notes
(b) (4)		

The manufacturing processes, raw material specifications, in-process controls, specifications of impurities and structural alerts should be assessed. Drug substance specifications should be assessed as per ICH Q3A(R2) in consultation with the Toxicology division. Suitability of analytical methods, validation and LOD/LOQs should be assessed as per ICHQ2b(R).

Batch analyses/Stability

(b) (4) Six batches **691665, 691745, 691776** manufactured in (b) (4) and **1069812**, **1069815** manufactured in (b) (4), scale (b) (4) Batch **1069812** was used for manufacture of clinical and primary stability lots of the drug product. The (b) (4) batches have a proposed retest date of (b) (4) and stability data are referenced to DMF (b) (4) (b) (4) Three batches **18212706, 18212707, 18212709** manufactured in (b) (4), scale (b) (4) Batch **18212707** was used for manufacture of a primary stability batch of the drug product. The (b) (4) batches have a proposed retest date of (b) (4) and stability data are referenced to DMF (b) (4)

Batch analyses for both drug substances comply with specifications and show levels of impurities well below the proposed specifications.
Comparability of the drug substance and corresponding drug product lot(s) should be assessed. Since (b) (4) comparability should be assessed in consultation with the Biopharmaceutics review team.

Drug product
The drug product is a sterile, non-pyrogenic, aqueous suspension of lipid-based particles for wound infiltration after surgery. The drug product is filled into 10 ml and 20 ml vials for a single use. The product strength (b) (4) . The drug substance is free bupivacaine, and the applicant was advised in the pre-NDA meeting of February 16, 2010, to express the strength as "anhydrous bupivacaine free base". Note, that bupivacaine is (b) (4) images submitted in 3.2.P.2.1, Figure 2). Note, that in Section 3.2.P.3.2, Table 1, Batch Formula, bupivacaine is expressed as "free bupivacaine", and the applicant should make a revision, accordingly. The drug product is packaged in Type I clear glass vials with (b) (4) grey butyl rubber stoppers and (b) (4) flip-off/tear-up seals, (b) (4). The drug product contains one novel excipient, dierucoylphosphatidylcholine (DEPC).

Table 3. Quantitative Composition for Bupivacaine Liposomal Injection.

Component	Nominal Content per mL	Nominal Content per Vial (10-mL)	Nominal Content per Vial (20-mL)	Molar Ratio (Lipid:Drug Substance)	Weight Ratio (Lipid:Drug Substance)
Bupivacaine	15.0 mg*	150.0 mg*	300.0 mg*	(b) (4)	
Dierucoylphosphatidyl-choline (DEPC)	(b) (4)				
Dipalmitoylphosphatidyl-glycerol (DPPG)					
Cholesterol					
Tricaprylin					
Sodium Chloride					

(b) (4)

*Expressed as anhydrous bupivacaine hydrochloride equivalent.

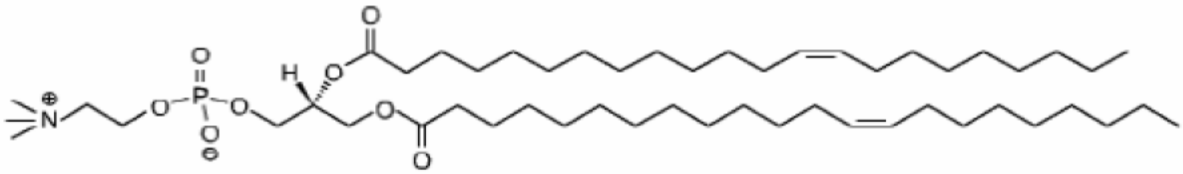
Pharmaceutical Development:

The drug product is formulated as a liposome using the DepoFoam® technology, utilized in the previously approved products: DepoCyt®, NDA 21-041, intrathecal cytarabine for treatment of meningitis; and DepoDur®, NDA 21-671, epidural morphine for treatment of post-surgical pain. DepoFoam® is based on a non-classical, multivesicular liposome (MVL) system. The MVL particles consist of a honeycomb-like structure with numerous non-concentric chambers containing drug (b) (4) and separated from each other by lipid bilayers that are (b) (4). The median diameter of the particles typically range from about (b) (4), and the internal chambers range from (b) (4) (b) (4).

Figure 1. A scanning electron micrograph of a DepoFoam® particle.

Dierucoylphosphatidyl choline (DEPC) is an unsaturated zwitterionic phospholipid comprising the major component of the lipid bilayer structure. (b) (4) (b) (4). DEPC is supplied by (b) (4) (b) (4) Note, that drug product batches supporting the NDA, have been manufactured using the DEPC.

Figure 2. Structure of DEPC



1,2-Dipalmitoylphosphatidylglycerol, sodium salt (DPPG) is supplied by (b) (4) Note, that drug product batches supporting the NDA, have been manufactured using the (b) (4) DPPG.

1,2,3-Trioctanoylglycerol (tricaprylin) is supplied by (b) (4) Note, that drug product batches supporting the NDA, have been manufactured using the (b) (4) tricaprylin.

(b) (4)

Manufacturing Process Development:

(b) (4)

Compatibility with coadministered drug and implants:

The compatibility of the drug product was assessed with potentially co-administered drugs, e.g., bupivacaine solutions, non-bupivacaine local anesthetics, epinephrine, corticosteroids, antibiotics, topical antiseptics, morphine and ketorolac. In some cases, direct mixing of drugs disrupted the liposome. In addition, dilution with saline, effect of needle size, storage in the syringe and potential

(b) (4)

(b) (4)

These studies should be assessed in consultation with the Biopharmaceutics review team (drug release profile and free bupivacaine) and the Clinical Division for clinical relevance and for potential practices that may not have been addressed by the applicant.

Manufacturing Process:

The drug product is manufactured by Pacira Pharmaceuticals in San Diego, CA and secondary packaging/labeling is performed by (b) (4). The proposed batch formula is for a (b) (4) nominal (b) (4) 10-ml vials or (b) (4) 20-ml vials.

The manufacturing process and process controls are described and flow charts are included. The manufacturing process consists of (b) (4)

4 PAGES HAVE BEEN WITHHELD IN FULL AS b4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

(b) (4)

Container Closure System:
The container/closure system has been discussed on p. 10. The product is filled in 10 mL and 20 mL Type I, pre-sterilized glass vials. Summary of the components, suppliers, specifications and DMF references are included in the NDA. Suitability of the container/closure system should be assessed (Section 3.2.P.7) in consultation with the Microbiology Division. The product is packaged in secondary packaging with temperature color-turning indicators to indicate exposure to freezing or extreme temperature during shipping as such conditions would compromise its integrity. Actual samples of the secondary packaging and indicators should be requested for review.

Stability:
Stability testing of the drug product was performed at long-term 5±2°C (refrigerated), intermediate 15±2°C and accelerated 25±2°C storage conditions. The product is unstable at 40°C and compromised if frozen. Testing is performed on inverted and upright vials for all time-points at 5°C and inverted at 15°C and 25°C. Stability protocols are provided.
Primary stability batches (b) (4) **08-2508A, 08-2508B, 08-2509A, 08-2509B, 08-2510A, 08-2510B**; batches have been filled in 10mL (b) (4) and 20mL (b) (4) vials. Longest data: 18 months under normal and intermediate conditions and 6 months under accelearated storage.
In addition, three-month data at 5°C and 25°C have been submitted for batches 10PD-001B, 10PD-002B, manufactured at (b) (4) and "pooled" batch 10PD-003. For supportive batches 05-2502, 05-2502, 05-2502 (b) (4) scale, used in early clinical and toxicology batches), 36-month data at 5°C have been submitted.

Photostability study as per ICH Q1B, temperature cycling (5°C - 25°C), exposure to 40°C, freezing and mechanical stress were performed. The applicant concluded the following trends in attributes: pH decrease, PSD change to (b) (4), decrease of in-vitro release, increase of (b) (4) no change in bupivacaine content or bupivacaine degradants, no loss of sterility, no increase of bacterial endotoxins. The applicant proposed a 24-month expiration dating, when the product is stored refrigerated at 2-8°C.

Labeling: Labeling information on the container labels and packaging insert should be assessed with respect to CMC information. SPL labeling has not been included in M1 and should be requested.

C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the shelf-life:

1. **Drug Substance:** The drug substance DMFs should be assessed. The manufacturing processes, raw material specifications and in-process controls should be assessed. Drug substance specifications should be assessed as per ICH Q3A(R2) in consultation with the Toxicology division. Structural alerts identified by the applicant should be assessed in consultation with the Toxicology Division; levels of structural alerts that are not controlled by the applicant, (b) (4) should be assessed from batch analysis data in the corresponding DMF. Comparability of the two drug substance suppliers and drug substances should be assessed.
2. Suitability of analytical methods for drug substances, validation and LOD/LOQs should be assessed as per ICHQ2b(R).
3. With the exception of the (b) (4) all lipid supporting DMFs, (b) (4) should be assessed. Suitability of the novel excipient DEPC and comparability of excipients should be assessed. Lipids are critical excipients in the formulation and should be controlled equivalent to the drug substance. Critical attributes of excipients should be assessed for manufacturability and performance of the drug product.
4. Suitability of the manufacturing process, for the drug product, (b) (4) in-process controls, microbiolgical integrity of the container/closures should be assessed in consultation with the Microbiology division.
5. Process parameters, in-process controls, and critical attributes for the (b) (4) manufacturing process
6. Hold times of drug product intermediates (b) (4) should be assessed.
7. Compatibility of the drug product with co-administered drugs (b) (4), (b) (4) as discussed on p. 8.
8. The extractables' studies, lack of leachable monitoring and adequacy of the applicant's conclusion that stability of the liposome in upright and inverted storage configurations implies no impact of leachables to the stability of the product. In addition, the adequacy of the applicant's extarctables/leachables evaluation and justification should be assessed with respect to safety of leachables, in consultation of the Toxicology Division.
9. Suitability and specifications of the container/closure system, and review of appropriate packaging DMFs. Suitability of the secondary packaging system for shipping/storage.
10. Specifications (in-process and end product testing) for critical physical attributes of the drug product, e.g., particle size distribution, pH and osmolality.
11. Specifications for drug product impurities/degradants related to bupivacaine (not controlled) and lipid degradants.
12. Proposed expiration dating of 24 months, attributes monitored on stability, and trends of stability attributes, which were described as "slight changes" by the applicant, e.g., pH decrease, median particle (b) (4), DEPC degradants' (b) (4) in drug release rate.
13. Robustness of the liposome to exposure to light, heat, freezing, mechanical stress, agitation, temperature cycling and shipping conditions.

D. **Comments for the 74-day Letter**:

1. You have not provided a complete (b) (4) validation data for your proposed commercial process. As agreed with the Division during the teleconference of November 23, 2010, you must submit a complete process validation data for your proposed commercial process in February 2010, after completion of modifications in your manufacturing equipment for the (b) (4)

2. You have not provided comparability data for the drug product, nor a comparability protocol, to assess (b) (4)

2. Revise (b) (4) 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. We note the discrepancy between quantitative composition per mL versus the batch formula, where the drug substance weight is expressed as bupivacaine free base equivalent.

3. Provide the level of (b) (4) content in your drug product, in batches produced at (b) (4) at release. Monitor and report (b) (4) content in your production scale batches, and propose a limit at release, as appropriate.

4. You have not monitored leachables from the elastomeric closures in your drug product. Provide leachables levels in your NDA batches, e.g., rubber (b) (4) or other identified extractables in your extraction studies.

E. **Recommendation for fileability**: The NDA was filed based on the applicant's commitment to submit complete (b) (4) validation data for the commercial process in the NDA, by February 2010. With the exception of the changes in the size and make of equipment, (b) (4) the manufacturing process remains the same. The (b) (4) have been submitted to the NDA with sufficient amount of stability data.

Recommendation for Team Review: The NDA is recommended for team review. The drug substance is not an NME, but two suppliers have been included, with DMFs that have not been reviewed previously; in addition, several DMFs support the

lipids, which are critical excipients to the liposomal formulation; and the drug product presents complexity with respect to stability and compatibility atrributes.

Consults:

Microbiology consult was requested.
Biopharmaceutics assignment was requested.
The primary reviewers should initiate Toxicology consults for the impurities/degradants and extractables/leachables evaluation.

Danae D. Christodoulou, Ph.D.	11/24/2010
CMC Lead, ONDQA	Date
Prasad Peri, Ph.D.	11/24/2010
Acting Branch VIII Chief, ONDQA	Date

		Established/Proper Name:
NDA Number: 22496	**Supplement Number and Type: 3S**	**Bupivacaine extended-release liposomal injection**
Applicant: Pacira	**Letter Date: 09/27/2010**	**Stamp Date: 09/27/2010**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		Pre-NDA 2/16/2010

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		(M3)
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		X	Clarifications and communications with OC.

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	Drug Product Manufacturing site is not ready for inspection; modifications to be completed by end of 2010.

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		Specifications included in the NDA
16.	Has stability data and analysis been provided for the drug substance?			
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		(b) (4) process validation data for the proposed commercial process deemed insufficient by reviewing Microbuiologist Dr. R. Mello.

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)			Bupivacaine	1/30/2010	Drug Substance
			Bupivacaine	3/16/2010	Drug Substance

(b) (4)

(b) (4)

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		Based on applicant's commitment to submit (b) (4) validation data to the NDA in February 2010.
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		X	
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		See above

{See appended electronic signature page}

Name of
CMC Lead: Danae Christodoulou 11/24/10 Date
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment

{See appended electronic signature page}

Name of
Branch Chief (Acting): Prasad Peri Date
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment

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

/s/

DANAE D CHRISTODOULOU
11/24/2010
Initial Quality Assessment

ERIC P DUFFY
11/29/2010