CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204803Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 204803
Assessment 2

Drug Product Name	Posimir (bupivacaine extended-release solution)
Dosage Form	Sterile solution for injection
Strength	660 mg/5 mL (132 mg/mL free base)
Route of Administration	instillation
Rx/OTC Dispensed	Rx
Applicant	DURECT Corporation
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 27; eCTD 0026	7 Jan 2019	Drug Product/ process/ facilities/ micro
Supporting document 28; eCTD 0027	27 Jun 2019	Resubmission letter responding to clinical deficiencies. No additional, specific CMC data but the letter does require CMC action.
Supporting document 30; eCTD 0029	9 Aug 2019	Facilities
Supporting document 31; eCTD 0030	30 Aug 2019	Facilities
Supporting document 34; eCTD 0033	31 Oct 2019	Micro
Supporting document 37; eCTD 0036	26 Nov 2019	Facilities
Email with commitment to submit formal response 16 Dec 2019	9 Dec 2019	Facilities and micro

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	N/A
Drug Product	Valerie Amspacher	Julia Pinto

Manufacturing	Jonathan Swoboda	Ubrani Venkataram
Microbiology	Bernard Marasa	Neal Sweeney
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	-	-
Environmental	-	-

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

We recommend approval from a CMC perspective. Based on the stability data submitted we recommend a shelf life of 36 months for the drug product Posimir when stored at 20-25°C (see USP controlled room temperature) and protected from light.

NDA 204803 was originally submitted 12 Apr 2013. After CMC review approval was recommended. However, the sponsor was sent a complete response letter 12 Feb 2014 due to clinical deficiencies.
The sponsor resubmitted on 27 June 2019 addressing the clinical deficiencies. Upon facility review it was determined that the sponsor had switched drug product manufacturers and submitted that change 7 Jan 2019.
Drug product comparability data was submitted with the 7 Jan 2019 notification of manufacturer change. The data shows that the batches manufactured at the new facility (Renaissance Lakewood, LLC) provide similar stability to those manufactured at the previous facility (b) (4), (b) (4) and reviewed as part of the original NDA submission in April 2013.
A process, facilities and microbiology review was also performed for the new manufacturing facility. Drug product, process, facilities and microbiology all recommend approval.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product Posimir is a sterile nonpyrogenic, clear, light yellow to amber solution of bupivacaine for instillation into surgical incision. The target fill weight of each glass vial is (b) (4) ml, and the dose is 5 ml. Each mL of Posimir contains bupivacaine 132 mg, benzyl alcohol 242 mg, and sucrose acetate isobutyrate (SAIB) 726 mg. Upon administration, the benzyl alcohol solvent quickly diffuses away from the other components,

resulting in the in-situ formation of an extended-release biodegradable gel like matrix which slowly releases the bupivacaine through diffusion.
The drug product Posimir is packaged in 10 mL USP (b) (4) clear glass vials with 20 mm (b) (4) rubber stoppers coated with (b) (4) and sealed with 20 mm aluminum flipoff crimp seals. Drug product vials are placed in a secondary carton which provides protection from light.

Proposed Indication(s) including Intended Patient Population	Post-surgical analgesia
Duration of Treatment	Single dose administration only
Maximum Daily Dose	(b) (4) mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Choose an item.

N/A

Drug Product: Adequate

New stability data is provided and there is a comparison of stability data between the previous drug product manufacturer (b) (4) and the new/current drug product manufacturer (Renaissance). The stability data comparison provides assurance that there is no difference in drug product performance with the new drug product manufacturer (Renaissance). The data show similar trends and remain within specification.
The container closure has not changed with the change in manufacturer.

Labeling: Adequate

The labels comply with all regulatory requirements from a CMC perspective.

Manufacturing: Adequate

See screenshot below for approval in Panorama.
The associated facilities with this application are recommended for approval. Two post-approval inspections are recommended for the subject application including the drug product manufacturing facility (Renaissance Lakewood, LLC; FEI: 2242829) as well as the microbiology testing laboratory (b) (4).

Biopharmaceutics: Choose an item.

N/A

Microbiology (if applicable): Adequate

The bulk drug product manufacturing involves (b) (4) [redacted]

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Active	16 July 2018	Reviewed by Katie Ciesienski
	II			Active	11 Dec 2018	Reviewed by Joseph Leginus
	IV			Active	20 Feb 2014	Reviewed by Edwin Jao
	IV			Active	20 Feb 2014	Reviewed by Edwin Jao
	V			Active	25 Apr 2017	Reviewed by Laura Moussa
	III			Active	18 Jan 2017	Reviewed by Ben Stevens
	III			Active	20 Oct 2015	Reviewed by Chunchun Zhang

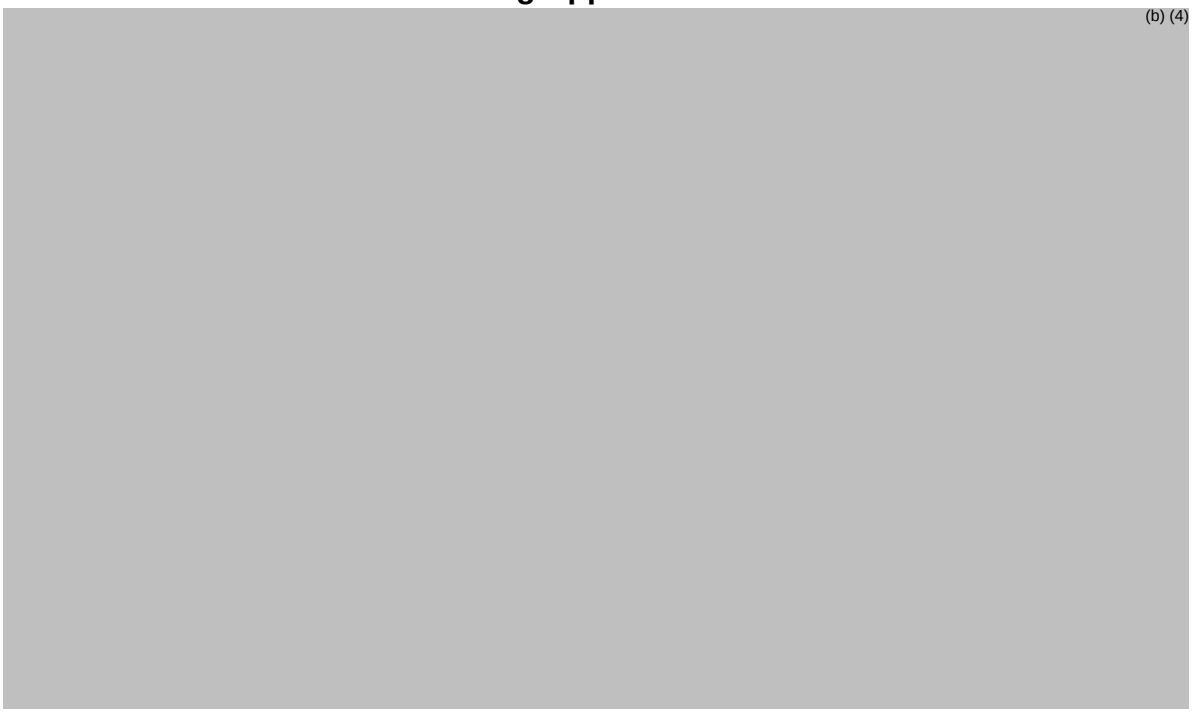
B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	016964	Bupivacaine hydrochloride injection

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics		N/A		
Pharmacology/Toxicology		N/A		
CDRH-ODE		N/A		
CDRH-OC		N/A		
Clinical		N/A		
Other		N/A		

Screenshot of Panorama showing Approval recommendation from OPMA



CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Present	N/A
Established name(s)	Present	N/A
Route(s) of administration	Need to add	Need to add "for instillation" to the Product Title
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Present	Delete (b) (4)

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Present	Single dose appropriately used

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Present	N/A

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Present	N/A
Strength(s) in metric system	Present	Delete (b) (4); add 660 mg / 5 mL
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	API is a free base
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Not present	Add "sterile nonpyrogenic, clear, light yellow to amber solution"
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Not present	Add "single dose"

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Proprietary present, missing established name	Need to add "bupivacaine" after Posimir; delete "[redacted] (b) (4)" at the end of the sentence
Dosage form(s) and route(s) of administration	Not present	Need to add "for instillation"
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Present	N/A
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Quantities not listed	It is acceptable for the quantitaties to not be listed
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	present	N/A
Pharmacological/ therapeutic class	Not present	Need to add Pharmacological/ therapeutic class
Chemical name, structural formula, molecular weight	Present	N/A

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Present	N/A
Strength(s) in metric system	present	Delete (b) (4)
Available units (e.g., bottles of 100 tablets)	Present	N/A
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Not present	Need to add "sterile nonpyrogenic, clear, light yellow to amber solution"
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Present	Single dose correctly used

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Present – “Vial should be protected from light and retained in carton until time of use”	N/A
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Present	N/A
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	N/A
Include information about child-resistant packaging	N/A	N/A

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Present	Present

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Adequate.

The labels comply with all regulatory requirements from a CMC perspective. Defeciencies are listed in the table above and will be corrected during labeling review with the clinical division.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Container Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes	Adequate
Dosage strength	Yes	Adequate
Route of administration	Yes	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	Yes	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	Yes	Adequate
Lot number and expiration date	Yes	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Yes	Single-dose correctly used
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Yes	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Container Labeling
Name of manufacturer/distributor	Yes	Adequate
Medication Guide (if applicable)	N/A	Adequate
No text on Ferrule and Cap overseal	Yes	Adequate

3.2 Carton Labeling

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes	Adequate
Dosage strength	Yes	Adequate
Route of administration	Yes	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	Yes	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	Yes	Adequate
Lot number and expiration date	Yes	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Not listed here but listed correctly on container label	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Yes	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	Adequate
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	Yes	Adequate

Assessment of Carton and Container Labeling: Adequate.

The labels comply with all regulatory requirements from a CMC perspective.

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MICROBIOLOGY

Product Information	
NDA Number	204803
Assessment Cycle Number	2
Drug Product Name/ Strength	POSIMIR/ 660 mg/5 mL (132 mg/mL) 13.2%
Route of Administration	Instillation
Applicant Name	DURECT Corporation, 10260 Bubb Road, Cupertino, CA 95014
Therapeutic Classification/ OND Division	post-surgical analgesia
Manufacturing Site	Renaissance Lakewood, LLC 1200 Paco Way, NJ 08701
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: The bulk drug product manufacturing involves (b) (4)

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Sequence 0026(27)	**01/07/2019**
Sequence 0027(28)	**06/27/2019**
Sequence 0033 (34)*	**10/31/2019**
E-mail response 12/9/19*	**12/09/2019**

***Response to Agency Information Request**

Highlight Key Issues from Last Cycle and Their Resolution:

1. Incomplete information regarding container closure integrity testing.
2. Incomplete information regarding details of major equipment used during drug product manufacture, classifications of their room locations and how the equipment used for exhibit batch manufacturing compare to equipment used during commercial manufacture.
3. Incomplete information regarding environmental monitoring.
4. Incomplete information regarding bulk hold time studies.
5. Incomplete information regarding product contact equipment (b) (4)
6. Incomplete information regarding (b) (4)

All issues were addressed.

Remarks: Application submitted in eCTD format. The original submission was determined to be adequate by (b) (4); however, the applicant received a Complete Response Letter due to other review discipline deficiencies. The current resubmission provides for a drug product manufacturing site change from (b) (4) to Renaissance Lakewood, LLC (Lakewood, NJ). The Applicant responded to Agency Information Request with a Response to Information Request-CMC (eCTD sequence Number-0033 and e-mail response) dated 10/31/2019 and 12/09/2019 respectively which were reviewed and deemed adequate. Agency deficiencies are highlighted in italics followed by Applicant's Response in bold.

Supporting Documents: DMF# (b) (4).

S: DRUG SUBSTANCE

Reviewer's Assessment:

The drug substance is added to the excipients (b) (4) ***at the proposed manufacturing site. Therefore, microbiology review will not be conducted for drug substance.***

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description:
SABER®-Bupivacaine (bupivacaine extended-release solution for instillation) is a sterile nonpyrogenic, clear, light yellow to amber solution.

Primary Container Closure System

Component Type	Description	(b) (4) Commodity (Computer) Number	Supplier Supplier's Drawing Number	DMF Reference
Vial	10 mL (b) (4)	(b) (4)		

Stopper	(b) (4)
Seal	
Seal	

[a] Seal to be used for future SABER-Bupivacaine batches. Seal (b) (4) complies with United States Pharmacopeia (USP) General Chapter <1>*Injections*, Labeling on Ferrules and Cap Overseals. This new standard requires the top surface of the cap overseal to remain blank if no cautionary statement is necessary. This new standard will be effective on 01 December 2013.

Composition:

The detailed composition and the function of each component of SABER-Bupivacaine are provided in Table 1.

Table 1 Composition and Ingredient Functions of SABER-Bupivacaine

Ingredient	Composition % w/w	Composition mg/mL [a]	Amount (mg) Administered in a 5 mL Dose	Function	Specification
Bupivacaine	12	132	660	Active Pharmaceutical Ingredient	In-House Specification
Sucrose acetate isobutyrate	66	726	3630	Extended release agent	In-House Specification
Benzyl alcohol	22	242	1210	Solvent	NF, EP
(b) (4)					
Total	**100**	**1100**	**5500**	**-**	**-**

[a] The density of SABER-Bupivacaine is 1.1 g/mL at 25°C, therefore the concentration expressed as 12% w/w is equivalent to 13.2% w/v.

Assessment: *{Adequate}*

P.2 PHARMACEUTICAL DEVELOPMENT

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2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

Storage temperature: 20°C to 25°C (68°F to 77°F); Route of administration: Protect from light. Instillation; Container: Single dose/ Single use.

No further post-dilution/storage of drug product.

Assessment: *{Adequate}*

Post-Approval Commitments-None.

Assessment: *{Adequate}*

MICROBIOLOGY LIST OF DEFICIENCIES- None.

Primary Microbiology Assessor Name and Date:
Bernard S. Marasa, Ph.D. December 09, 2019

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Neal J. Sweeney, Ph.D. December 09, 2019

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VALERIE R AMSPACHER
12/10/2019 02:35:05 PM

NDA 204,803

Posimir

(Bupivacaine solution)

DURECT Corporation

Chemistry Review #2

February 6, 2014

Edwin Jao, Ph.D.

ONDQA/Division III/Branch VIII

for

Division of Anesthesia, Analgesia, and Addiction Products Product

Table of Contents

Chemistry Review Data Sheet

1. NDA 204,803

2. REVIEW #:2

3. REVIEW DATE: February 6, 2014

4. REVIEWER: Edwin Jao, Ph.D.

5. Related DOCUMENTS:

Previous Documents	Document Date
Original NDA	4-12-2013
Amendment	4-25-2-13
Amendment	11-6-2013
Amendment	1-16-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	
Original NDA	4-12-2013
Amendment	4-25-4013
Amendment	11-6-2013
Amendment	1-16-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	**DURECT Corporation**
Address:	10260 Bubb Road Cupertino, CA 95014
Representative:	Jill H.K. Burns
Telephone:	408-777-1417

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Posimir
b) Non-Proprietary Name (USAN): (bupivacaine solution)
c) Code Name: none provided
d) Chem. Type/Submission Priority:

- Chem. Type: 5 (new formulation)
- Submission Priority: S

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

10. PHARMACOL. CATEGORY:

Locally acting amide-type anesthetic

11. DOSAGE FORM: Sterile solution for instillation

12. STRENGTH/POTENCY:

660 mg/5 mL (132 mg/mL), 13.2% w/v%

13. ROUTE OF ADMINISTRATION: Instillation into the surgical site

14. Rx/OTC DISPENSED: __x_Rx ___OTC

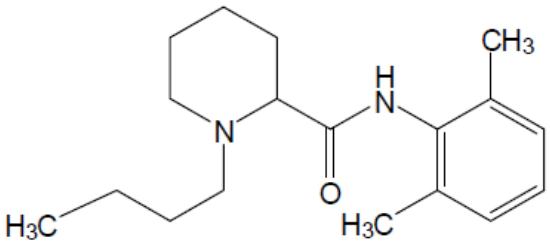
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product

___X___Not a SPOTS product

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

(±)-1-Butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide



Empirical Formula: $C_{18}H_{28}N_2O_2O$

Molecular Weight: 288.43

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	adequate	Edwin Jao 1/8/2014	
	II			1	adequate	Edwin Jao	
	III			1	adequate	Edwin Jao 1/8/2014	

(b) (4)	IV		(b) (4)		adequate	Edwin Jao 1/8/2014	
	IV				adequate	Edwin Jao 1/8/2014	
	III				adequate	Edwin Jao 1/8/2014	
	III				adequate	Neal Sweeney 12/9/2013	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
na		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Approval	12/30/2014	David Petullo
EES	accptable	2/5/2014	
Pharm/Tox	Approval	1/8/2014	Gary Bond
Clinpharm	Approval	1/8/2014	David Lee
LNC	bupivacaine solution	1/8/2014	

Methods Validation	Not necessary		
BioPharm	Approval	12/23/2013	Okponanabofa Eradiri
EA	Approval	1/6/2014	Raanan (Ron) Bloom
Microbiology	Approval	12/9/2013	Neal Sweeney
CDRH	Not necessary		

The Chemistry Review for NDA 22-472

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the ONDQA perspective, this NDA is recommended for approval..

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No

II. Summary of Chemistry Assessments

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

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

The drug substance is free base bupivacaine. It is not an NME. Both the free base and its HCl salt have been approved for injectable drug products in the US. The characterization of this compound has been well documented in the literature, and the manufacturers have adequately confirmed the structure of the drug substance they produced. Bupivacaine is manufactured by (b) (4)*. Both establishments received "Acceptable" recommendation from the Office of Compliance. This compound is prepared through multiple steps* (b) (4)*. DMF* (b) (4) *and DMF* (b) (4) *are incorporated by reference for the detailed CMC information, and both DMFs are considered adequate to support this NDA. The proposed drug substance specifications from the two suppliers are acceptable, and the certificates of analysis of the clinical lots were verified by the drug product manufacturer* (b) (4) *and are satisfactory. The quality and stability of the clinical batches of the drug substance bupivacaine are adequately demonstrated by release and stability data. The drug substance is packaged in* (b) (4) *bags and carries a retest period of* (b) (4)*.*

The drug product Posimir is a sterile nonpyrogenic, clear, light yellow to amber solution of bupivacaine for instillation into surgical incision. The target fill weight of each glass vial is (b) (4) *and the dose is 5 ml. Each mL of Posimir contains bupivacaine 132 mg, benzyl alcohol 242 mg, and sucrose acetate isobutyrate (SAIB) 726 mg. Upon administration, the benzyl alcohol solvent quickly diffuses away from the other components, resulting in the in-situ formation of an extended-release biodegradable gel like matrix which slowly releases the bupivacaine through diffusion over 72 hours.*

The excipients used in the formulation are benzyl alcohol and sucrose acetate isobutyrate (SAIB). Benzyl alcohol is USP grade. SAIB is a fully esterified sugar derivative, listed in 21 CFR172.833 for direct food additive. It is used as a stabilizer of emulsions of flavoring oils in nonalcoholic beverages. However, it has not been used in approved drug products, and therefore is a novel excipient. DMF (b) (4) are incorporated by reference for the CMC information of SAIB. Both DMF are considered adequate to support this NDA. The drug product is manufactured by (b) (4). This establishment has received an acceptable recommendation from the Office of Compliance.

The proposed commercial manufacturing process for Posimir consists of (b) (4) nspection, packaging and labeling processes.

Adequate in-process and material controls are in place. The manufacturing process has been optimized and adequately validated. The sterilization process and sterility controls have been evaluated by the microbiology team and are considered acceptable.

The proposed drug product specification was acceptable, except for the acceptance criterion for (b) (4) which needed to be tightened to NMT (b) (4) as per recommendations from the pharmtox team. Preliminary pharmtox review concurs with the applicant's justification for impurity controls from the safety perspective, except that they recently found out that the proposed acceptance criterion of NMT (b) (4) for (b) (4) is not supported by local toxicity data. This concern was conveyed to the applicant via a tcon dated 1/7/2014. The applicant agreed to tighten it to NMT (b) (4). The proposed specification is generally supported by data. Release data from eight batches of primary and supportive ICH batches, which were manufactured by the commercial process, met the proposed specification. The applicant has provided 36 months of long term stability data to ***support the proposed shelf life of 36 months****. All stability data, including data from the primary, supportive, and additional supportive batches met the specification, and the requested shelf life is granted.*

The drug product Posimir is packaged in 10 mL USP (b) (4) clear glass vials with 20 mm (b) (4) rubber stoppers coated with (b) (4) and sealed with 20 mm aluminum flip-off crimp seals. Drug product vials are placed in a secondary carton which provides protection from light. The secondary carton will contain ten vials, each separated by a plastic divider. DMF (b) (4) are incorporated by reference for the CMC information of the vials and stoppers. Both DMF are considered adequate to support this NDA.

Microbiology and biopharm teams have evaluated dissolution and microbial control aspects of the submission. Both teams have recommended approval for this NDA from their perspective.

The drug product is manufactured and tested by (b) (4). This establishment received an acceptable recommendation from the Office of Compliance on 5/23/2013.

The following critical issues were identified in the application, and are resolved satisfactorily.

- *The original target fill weigh per vial was* (b) (4) *process variability. This represents* (b) (4) *of overfill at the upper limit, and much higher than the USP recommended 10% surplus for viscous liquid for injection. This amount of overfill raised safety concerns from clinical team. In response to the Agency's comments, the applicant has reduced the fill weight to an acceptable* (b) (4)
- *The original controlled extractable studies were conducted at room temperature. Given the high benzyl alcohol content in the drug product formulation (22%), the extraction conditions are not considered vigorous enough to assure all extractables reach their asymptotic levels. Besides,* (b) (4) *was not tested. Upon request by the Agency, another controlled extractable study was conducted used reflex condition. More extractables are identified, and leachable data were reexamined against the new extractable profile.* (b) (4) *were not detected in this vigorous extraction stopper study. The pharmtox team conducts safety evaluation of the leachables, and found no safety concerns. It is acceptable that routine testing for leachables will be performed for commercial batches.*
- *It has brought to our attention that another form of bupivacaine injection drug product was recalled due to observation of some unexpected yellow color as the result of iron contamination of the glass vials (iron embedded) manufactured by* (b) (4)*. In response to the Agency's inquiry, the applicant states that only* (b) (4) *vials from the supplier were affected, and Posimir use* (b) (4) *vials which are manufactured in a totally different process. The applicant confirms that only* (b) (4) *vials will be used for the commercial product. A risk assessment was conducted and it is concluded that this potential risk can be adequately managed under the applicant's internal quality system.*
- *Posimir changes color from light yellow to brown (amber) over its proposed 36 month shelf life. The color change has been noted in all manufactured product lots. A comprehensive investigation was undertaken and the proposed mechanism of bupivacaine catalyzed carmelization of the excipient SAIB as the root cause for the coloration of the drug product seems reasonable. The pharmtox team concurs with the applicant's safety evaluation for the dark colored drug product. Therefore, the proposed acceptance criterion of* (b) (4) *for the degree of coloration of the drug product during shelf life is acceptable.*

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

Posimir is intended for single administration by instillation of 5 mL (660 mg) directly into the surgical incision(s).

C. Basis for Approvability or Not-Approval Recommendation

1. *The applicant of the NDA has provided sufficient information to assure the identity, strength, purity, quality, and batch to batch consistency of the future commercial drug product Posimir.*
2. *The recommendation from the Office of Compliance for this NDA is acceptable. The following is the summary report.*

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 204803/000	**Action Goal:**	
Stamp Date:	12-APR-2013	**District Goal:**	14-DEC-2013
Regulatory:	12-FEB-2014		
Applicant:	DURECT	**Brand Name:**	POSIMIR
	10260 BUBB RD	**Estab. Name:**	
	CUPERTINO, CA 95014	**Generic Name:**	SABER (R)- BUPIVACAINE (BUPIVACAINE EXT
Priority:	3	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	170	001; SOLUTION, FOR INSTILLATION; BUPIVACAINE; 660MG/5ML (132MG/ML)	
Application Comment:			

FDA Contacts:	E. JAO	Prod Qual Reviewer		3017961684
	J. METCALFE	Micro Reviewer	(HFD-805)	3017961576
	L. RIVERA	Product Quality PM		3017964013
	A. AUGUSTUS	Regulatory Project Mgr	(HFD-170)	3017963980
	O. STEPHENS	Team Leader	(HFD-510)	3017963901

Overall Recommendation:	ACCEPTABLE	on 05-FEB-2014	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 01-NOV-2013	by EES_PROD		
	PENDING	on 21-OCT-2013	by EES_PROD		
	PENDING	on 16-OCT-2013	by EES_PROD		
	WITHHOLD	on 16-OCT-2013	by EES_PROD		
	PENDING	on 08-OCT-2013	by EES_PROD		
	PENDING	on 23-MAY-2013	by EES_PROD		
	PENDING	on 23-MAY-2013	by EES_PROD		
	PENDING	on 23-MAY-2013	by EES_PROD		

III. Administrative

A. Reviewer's Signature

(See appended electronic signature page)

Edwin Jao, Ph. D., CMC Reviewer, Division III, Branch VIII, ONDQA

B. Endorsement Block

Prasad Peri, Ph. D., Branch Chief, Division III, Branch VIII, ONDQA.

C. CC Block

Dr. Julia Pinto, Ph. D., CMC Lead, Division III, Branch VIII, ONDQ

APPEARS THIS WAY ON ORIGINAL

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

/s/

EDWIN JAO
02/09/2014

PRASAD PERI
02/09/2014
I concur

NDA 204,803

Posimir

(Bupivacaine solution)

DURECT Corporation

Chemistry Review #1

January 8, 2014

Recommendation: Approval

Edwin Jao, Ph.D.

ONDQA/Division III/Branch VIII

for

Division of Anesthesia, Analgesia, and Addiction Products Product

Table of Contents

Chemistry Review Data Sheet

1. NDA 204,803

2. REVIEW #:1

3. REVIEW DATE: January 8, 2013

4. REVIEWER: Edwin Jao, Ph.D.

5. Related DOCUMENTS:

Previous Documents	Document Date
Original NDA	4-12-2013
Amendment	
Amendment	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Original NDA dated 4-12-2013
Amendment dated
Amendment dated
Amendment dated

7. NAME & ADDRESS OF APPLICANT:

Name:	**DURECT Corporation**
Address:	10260 Bubb Road Cupertino, CA 95014
Representative:	Jill H.K. Burns
Telephone:	408-777-1417

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Posimir
b) Non-Proprietary Name (USAN): (bupivacaine solution)
c) Code Name: none provided
d) Chem. Type/Submission Priority:

- Chem. Type: 5 (new formulation)
- Submission Priority: S

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

10. PHARMACOL. CATEGORY:

Locally acting amide-type anesthetic

11. DOSAGE FORM: Sterile solution for instillation

12. STRENGTH/POTENCY:

660 mg/5 mL (132 mg/mL), 13.2% w/v%

13. ROUTE OF ADMINISTRATION: Instillation into the surgical site

14. Rx/OTC DISPENSED: __x_Rx ___OTC

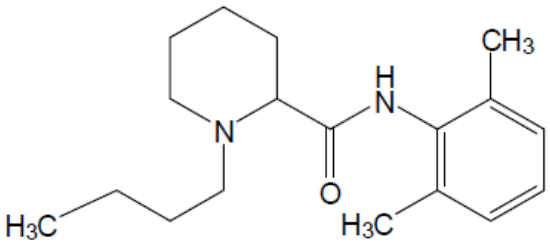
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product

__X__Not a SPOTS product

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

(±)-1-Butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide



Empirical Formula: $C_{18}H_{28}N_2O_2O$

Molecular Weight: 288.43

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	adequate	Edwin Jao 1/8/2014	
	II			1	adequate	Edwin Jao	
	III			1	adequate	Edwin Jao 1/8/2014	

(b) (4)	IV	(b) (4)		adequate	Edwin Jao 1/8/2014	
	IV			adequate	Edwin Jao 1/8/2014	
	III			adequate	Edwin Jao 1/8/2014	
	III			adequate	Neal Sweeney 12/9/2013	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
na		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Approval	12/30/2014	David Petullo
EES	pending		
Pharm/Tox	Approval	1/8/2014	Gary Bond
Clinpharm	Approval	1/8/2014	David Lee
LNC	bupivacaine solution	1/8/2014	
Methods Validation	Not necessary		

BioPharm	Approval	12/23/2013	Okponanabofa Eradiri
EA	Approval	1/6/2014	Raanan (Ron) Bloom
Microbiology	Approval	12/9/2013	Neal Sweeney
CDRH	Not necessary		

The Chemistry Review for NDA 22-472

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the ONDQA perspective, this NDA is recommended for approval, pending on the final recommendation from the Office of compliance and agreement on the recommendations for the labeling.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No

II. Summary of Chemistry Assessments

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

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

The drug substance is free base bupivacaine. It is not an NME. Both the free base and its HCl salt have been approved for injectable drug products in the US. The characterization of this compound has been well documented in the literature, and the manufacturers have adequately confirmed the structure of the drug substance they produced. Bupivacaine is manufactured by (b) (4) *. Both establishments received "Acceptable" recommendation from the Office of Compliance. This compound is prepared through multiple steps* (b) (4) *. DMF* (b) (4) *are incorporated by reference for the detailed CMC information, and both DMFs are considered adequate to support this NDA. The proposed drug substance specifications from the two suppliers are acceptable, and the certificates of analysis of the clinical lots were verified by the drug product manufacturer* (b) (4) *and are satisfactory. The quality and stability of the clinical batches of the drug substance bupivacaine are adequately demonstrated by release and stability data. The drug substance is packaged in* (b) (4) *bags and carries a retest period of* (b) (4) *.*

The drug product Posimir is a sterile nonpyrogenic, clear, light yellow to amber solution of bupivacaine for instillation into surgical incision. The target fill weight of each glass vial is (b) (4) *and the dose is 5 ml. Each mL of Posimir contains bupivacaine 132 mg, benzyl alcohol 242 mg, and sucrose acetate isobutyrate (SAIB) 726 mg. Upon administration, the benzyl alcohol solvent quickly diffuses away from the other components, resulting in the in-situ formation of an extended-release biodegradable gel like matrix which slowly releases the bupivacaine through diffusion over 72 hours.*

The excipients used in the formulation are benzyl alcohol and sucrose acetate isobutyrate (SAIB). Benzyl alcohol is USP grade. SAIB is a fully esterified sugar derivative, listed in 21 CFR172.833 for direct food additive. It is used as a stabilizer of emulsions of flavoring oils in nonalcoholic beverages. However, it has not been used in approved drug products, and therefore is a novel excipient. DMF (b) (4) are incorporated by reference for the CMC information of SAIB. Both DMF are considered adequate to support this NDA. The drug product is manufactured by (b) (4). This establishment has received an acceptable recommendation from the Office of Compliance.

The proposed commercial manufacturing process for Posimir consists of (b) (4) inspection, packaging and labeling processes.

Adequate in-process and material controls are in place. The manufacturing process has been optimized and adequately validated. The sterilization process and sterility controls have been evaluated by the microbiology team and are considered acceptable.

The proposed drug product specification was acceptable, except for the acceptance criterion for (b) (4) which needed to be tightened to NMT (b) (4) as per recommendations from the pharmtox team. Preliminary pharmtox review concurs with the applicant's justification for impurity controls from the safety perspective, except that they recently found out that the proposed acceptance criterion of NMT (b) (4) for (b) (4) is not supported by local toxicity data. This concern was conveyed to the applicant via a tcon dated 1/7/2014. The applicant agreed to tighten it to NMT (b) (4). The proposed specification is generally supported by data. Release data from eight batches of primary and supportive ICH batches, which were manufactured by the commercial process, met the proposed specification. The applicant has provided 36 months of long term stability data to ***support the proposed shelf life of 36 months****. All stability data, including data from the primary, supportive, and additional supportive batches met the specification, and the requested shelf life is granted.*

The drug product Posimir is packaged in 10 mL USP (b) (4) clear glass vials with 20 mm (b) (4) rubber stoppers coated with (b) (4) and sealed with 20 mm aluminum flip-off crimp seals. Drug product vials are placed in a secondary carton which provides protection from light. The secondary carton will contain ten vials, each separated by a plastic divider. DMF (b) (4) are incorporated by reference for the CMC information of the vials and stoppers. Both DMF are considered adequate to support this NDA.

Microbiology and biopharm teams have evaluated dissolution and microbial control aspects of the submission. Both teams have recommended approval for this NDA from their perspective.

The drug product is manufactured and tested by (b) (4). This establishment received an acceptable recommendation from the Office of Compliance on 5/23/2013.

The following critical issues were identified in the application, and are resolved satisfactorily.

- *The original target fill weigh per vial was* (b) (4) *process variability. This represents* (b) (4) *of overfill at the upper limit, and much higher than the USP recommended 10% surplus for viscous liquid for injection. This amount of overfill raised safety concerns from clinical team. In response to the Agency's comments, the applicant has reduced the fill weight to an acceptable* (b) (4).
- *The original controlled extractable studies were conducted at room temperature. Given the high benzyl alcohol content in the drug product formulation (22%), the extraction conditions are not considered vigorous enough to assure all extractables reach their asymptotic levels. Besides,* (b) (4) *was not tested. Upon request by the Agency, another controlled extractable study was conducted used reflex condition. More extractables are identified, and leachable data were reexamined against the new extractable profile.* (b) (4) *were not detected in this vigorous extraction stopper study. The pharmtox team conducts safety evaluation of the leachables, and found no safety concerns. It is acceptable that routine testing for leachables will be performed for commercial batches.*
- *It has brought to our attention that another form of bupivacaine injection drug product was recalled due to observation of some unexpected yellow color as the result of iron contamination of the glass vials (iron embedded) manufactured by* (b) (4). *In response to the Agency's inquiry, the applicant states that only* (b) (4) *vials from the supplier were affected, and Posimir use* (b) (4) *vials which are manufactured in a totally different process. The applicant confirms that only* (b) (4) *vials will be used for the commercial product. A risk assessment was conducted and it is concluded that this potential risk can be adequately managed under the applicant's internal quality system.*
- *Posimir changes color from light yellow to brown (amber) over its proposed 36 month shelf life. The color change has been noted in all manufactured product lots. A comprehensive investigation was undertaken and the proposed mechanism of bupivacaine catalyzed carmelization of the excipient SAIB as the root cause for the coloration of the drug product seems reasonable. The pharmtox team concurs with the applicant's safety evaluation for the dark colored drug product. Therefore, the proposed acceptance criterion of* (b) (4) *for the degree of coloration of the drug product during shelf life is acceptable.*

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

Posimir is intended for single administration by instillation of 5 mL (660 mg) directly into the surgical incision(s).

C. Basis for Approvability or Not-Approval Recommendation

1. *The applicant of the NDA has provided sufficient information to assure the identity, strength, purity, quality, and batch to batch consistency of the future commercial drug product Posimir.*
2. *The recommendation from the Office of Compliance for this NDA is still pending.*

III. Administrative

A. Reviewer's Signature

(See appended electronic signature page)

Edwin Jao, Ph. D., CMC Reviewer, Division III, Branch VIII, ONDQA

B. Endorsement Block

Prasad Peri, Ph. D., Branch Chief, Division III, Branch VIII, ONDQA.

C. CC Block

Dr. Julia Pinto, Ph. D., CMC Lead, Division III, Branch VIII, ONDQA

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/s/

EDWIN JAO
01/08/2014

PRASAD PERI
01/08/2014
I concur

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	204-803	**Biopharmaceutics Reviewer:** Okpo Eradiri, Ph.D.	
Division:	DAAAP		
Applicant:	Durect Corp	**Acting Biopharmaceutics Team Leader:** Elsbeth Chikhale, Ph.D	
Trade Name:			
Generic Name:	Bupivacaine ER Solution for Instillation	**Date Assigned:**	Apr 18, 2013.
Indication:	Post-surgical analgesia, to be administered by instillation into the surgical incision before closure.	**Date of Review:**	Dec 20, 2013.
Formulation/strength	Solution; 660 mg/5 mL (132 mg/mL)		
Route of Administration	Instillation		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
Apr 12, 2013	Apr 12, 2013		October 12, 2013
Type of Submission:	NDA; 505(b)(2)		
Type of Consult:			

SUMMARY:

Submission: NDA 204803 is a 505 (b)(2) submission for Bupivacaine ER Solution for Instillation. The proposed drug product is an extended-release bupivacaine sterile solution for single-dose instillation into surgical wounds to provide post-surgical anesthesia. The Applicant describes the proposed drug product as a sterile non-pyrogenic, clear, light yellow to amber solution. The extended-release agent in the formulation is Sucrose acetate isobutyrate while Benzyl Alcohol serves as the solvent. Following instillation of the solution into the wound, the benzyl alcohol (solvent) quickly diffuses into local tissues, leaving a viscous hydrophobic depot which slowly releases the bupivacaine by diffusion over 72 hours. The bupivacaine concentration in the solution is 660 mg/5 mL (132 mg/mL or 13.2 %w/v); the dosing regimen is 5 mL during surgery.

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed dissolution method and acceptance criteria.

Reviewer's Comments:

a) The Applicant's intent was to developed an in-vitro bupivacaine release characterization

method to mimic in-vivo release of the drug from the depot or hydrophobic film formed in the wound over 72 h. However, an IVIVC or IVIVR could not be established. The dissolution method is acceptable for routine quality control release testing of the product.

b) The dissolution method could not be shown to exhibit adequate discriminating power regarding potential alterations in the rate-controlling excipient's content. However, the unintended or erroneous use of the HCl salt instead of bupivacaine base will be picked up by the method. The proposed dissolution method is found to be acceptable as a drug product quality control test.

c) The Applicant's originally proposed dissolution acceptance criteria were not acceptable. The Agency's recommended dissolution acceptance criteria were communicated to the Applicant in an IR letter dated Oct 21, 2013. The Applicant accepted the Agency's recommended dissolution acceptance criteria and updated the Drug Product Specifications Table on Nov 6, 2013.

RECOMMENDATION

ONDQA-Biopharmaceutics has reviewed NDA 204-803 for Bupivacaine Extended Release Solution for Instillation. We find NDA 204-803 acceptable and therefore recommend APPROVAL from a Biopharmaceutics perspective.

The following dissolution method and acceptance criteria for Bupivacaine Extended-Release Solution for Instillation are agreed upon and acceptable:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium
2	50 rpm	900 mL	37 ± 0.5 °C	0.03 % SDS in 0.025 M Phosphate Buffer ($NaH_2PO_4.H_2O$) pH 7.4 ± 0.05

Time Point, hours	Acceptance Criteria
1	NMT (b)(4)%
8	(b)(4)%
18	%
48	NLT (b)(4)%

Okpo Eradiri, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

Table of Contents

1 INTRODUCTION

The proposed drug product is an extended-release bupivacaine sterile solution for single-dose instillation into the surgical site to provide post-surgical anesthesia. Bupivacaine, a racemate mixture, is a white crystalline powder with a melting point of 105-110 ˚C and is a well-known local anesthetic. The drug molecule is a base with a pKa of approximately 8 and a partition coefficient of 2565 (octanol/aqueous pH 7.4 buffer). The chemical structure of bupivacaine is shown in Figure 1.

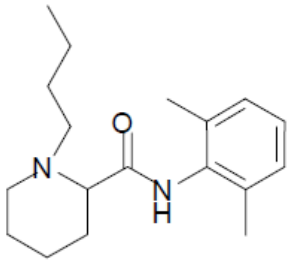

Fig. 1: Chemical structure of bupivacaine (M.W. = 288.43 g/mol).

Bupivacaine is freely soluble in ethanol and acetone; it is sparingly soluble in water.

The Applicant describes the proposed drug product as a sterile non-pyrogenic, clear, light yellow to amber solution. The extended-release agent in the formulation is Sucrose acetate isobutyrate while Benzyl Alcohol serves as the solvent. Following instillation of the solution into the wound, the benzyl alcohol (solvent) quickly diffuses into local tissues, leaving a viscous hydrophobic depot which slowly releases the bupivacaine by diffusion over 72 hours. The bupivacaine concentration in the solution is 660 mg/5 mL (132 mg/mL or 13.2 %w/v); the dosing regimen is 5 mL during surgery. The composition of the solution is displayed in Table 1.

Table 1: Composition of proposed bupivacaine ER solution for instillation (from Module 2, section 2.3.P, Table 1)

Ingredient	Composition % w/w	Composition mg/mL [a]	Amount (mg) Administered in a 5 mL Dose	Function	Specification
Bupivacaine	12	132	660	Active Pharmaceutical Ingredient	In-House Specification
Sucrose acetate isobutyrate	66	726	3630	Extended release agent	In-House Specification
Benzyl alcohol	22	242	1210	Solvent	NF, EP
					(b) (4)
Total	**100**	**1100**	**5500**	-	-

[a] The density of SABER-Bupivacaine is 1.1 g/mL at 25°C, therefore the concentration expressed as 12% w/w is equivalent to 13.2% w/v

2 PROPOSED DISSOLUTION METHOD

(b) (4)

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(b) (4)

2.2 *Investigation of Discriminating Power of Dissolution Method*

The Applicant investigated the impact of changing the amount of the release-controlling excipient, Sucrose Acetate Isobutyrate (SAIB), in the formulation but only observed a different profile at -70 % of the target amount. Two other formulation variants with +20% and -20% SAIB gave the same in-vitro bupivacaine release profile as the target formulation.

Thereafter, the Applicant made two additional formulation variants by altering two manufacturing variables: use of an HCl salt of bupivacaine and creating an extreme temperature excursion for SAIB during the manufacturing process. In the latter case, a sample of SAIB (b) (4). In both cases, significant differences in release profile from the target formulation were observed (Figure 5 and Table 4).

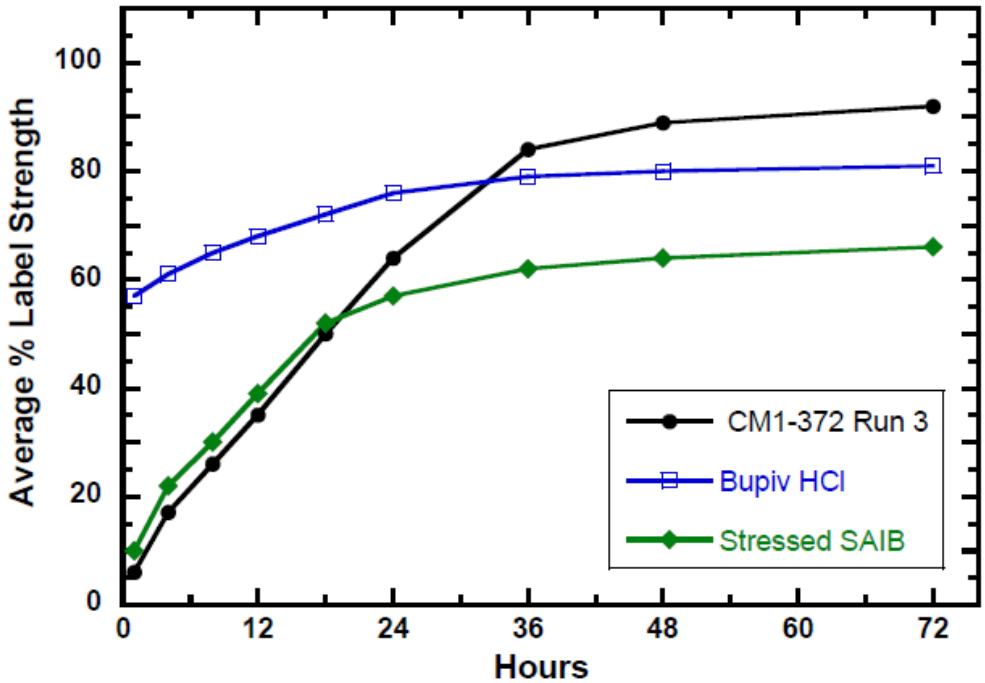


Fig. 5: Dissolution profiles of target bupivacaine ER solution (Lot CM1-372) and two variant formulations made by altering two manufacturing variables.

Table 4: Difference (f_1) and Similarity (f_2) Factors for two variant formulations compared to the target formulation.

Sample Identification	Composition (% w/w)			Variant Formulation or Manufacturing Variable	Difference Factor f_1	Similarity Factor f_2
	Bupivacaine Base	Benzyl Alcohol	SAIB			
Formulation 5	12.0	22.0	66.0[a]	Bupivacaine HCl monohydrate instead of Bupivacaine base	49	26
Formulation 6	12.0	22.0	66.0	Heat Stressed SAIB – (b) (4) (b) (4)	21	42

[a] Formulation 5 contained 12.0 grams of bupivacaine HCl monohydrate salt per 100 grams of formulation.

Reviewer's Comments:

The Applicant investigated the dissolution method's ability to detect intentional changes to the composition of the formulation and to one manufacturing variable. Since SAIB is the release-rate controlling excipient, it is proper to have altered its proportion in the formulation as well as exposing it to temperature excursions during the manufacturing process. The experiments showed that the method is sensitive to SAIB content only when the deviation from the target amount is varied by at least 70 %. In the case of the temperature excursion on SAIB ((b) (4)), a marked difference in release rate was observed relative to the target formulation (Fig 5). However, the percentage temperature differential is approximately 86 %. The dissolution method therefore lacks discriminating power regarding potential alterations in the rate-controlling excipient's content. The unintended or erroneous use of the HCl salt instead of bupivacaine base will be picked up by the method (Fig 5) but this is not a standard 'parameter' to investigate. The proposed dissolution method is acceptable as a drug product quality control test.

3 SETTING OF DISSOLUTION ACCEPTANCE CRITERIA

3.1 *Applicant's Proposed Acceptance Criteria*

The Applicant's initially proposed dissolution acceptance criteria for QC testing and batch release as well as for stability are presented in Table 5.

Table 5: Applicant proposed dissolution acceptance criteria for Bupivacaine ER Solution

Time Point, h	Acceptance Range
	(b) (4)

The Applicant used dissolution data of three clinical batches and seven stability batches (4 Primary, 3 Supporting) to set the acceptance criteria (Table 6). The dissolution profiles for all 7 lots of the proposed drug product are depicted in Figures 6 and 7.

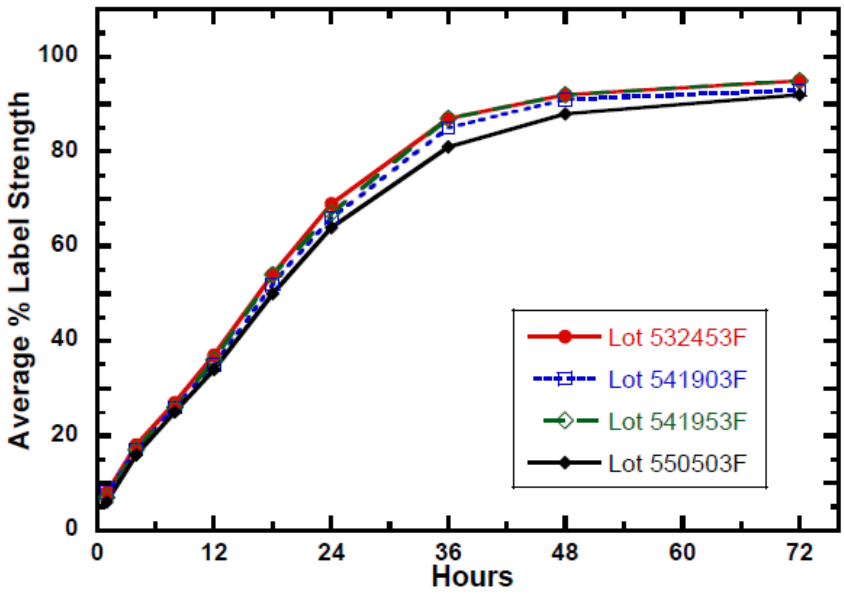


Figure 6: Dissolution profiles of Primary and Supporting stability batches.

Table 6: Summary of clinical and stability batches used for setting dissolution acceptance criteria.

SABER-Bupivacaine Lot Number [a]	Lot Use	Batch Size (kg)	Fill Size (mL)	Drug Substance Vendor and Lot Number
532453F	Primary Stability	(b) (4)	5	(b) (4) 1069812
532463F	Supporting Stability		7.5	
541903F	Primary Stability		5	(b) (4) 1069815
541913F	Pivotal Clinical Trial BU-002-IM Supporting Stability		7.5	
541953F	Primary Stability		5	(b) (4) 971526
541963F	Supporting Stability		7.5	
550503F	Primary Stability		5	(b) (4) 18212706
550513F	Supporting Stability		7.5	
721053F	Pivotal Clinical Trial BU-002-IM Supportive Stability		7.5	(b) (4) 1069812 and 1069815
094-06	Pivotal Clinical Trial CLIN-803-006-0006		7.5	(b) (4) 971526

[a] All lots listed in the table were manufactured at (b) (4) except that lot 094-06 was manufactured at DURECT, Cupertino, CA.

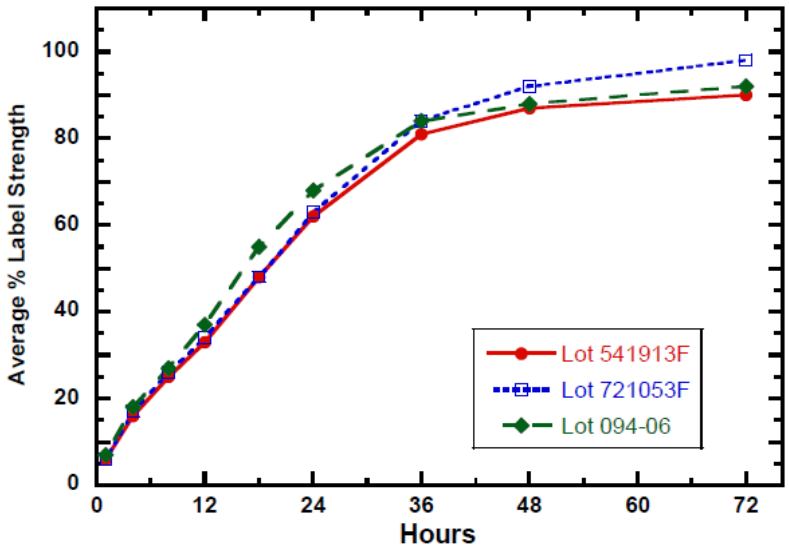


Figure 7: Dissolution profiles of Clinical batches of Bupivacaine ER Solution.

The dissolution data for the stability samples over 36 months (25 ˚C/60 % RH) at the proposed regulatory sampling time points are displayed in Figure 8. The trend that emerges indicates no significant changes in bupivacaine release rate over 36 months.

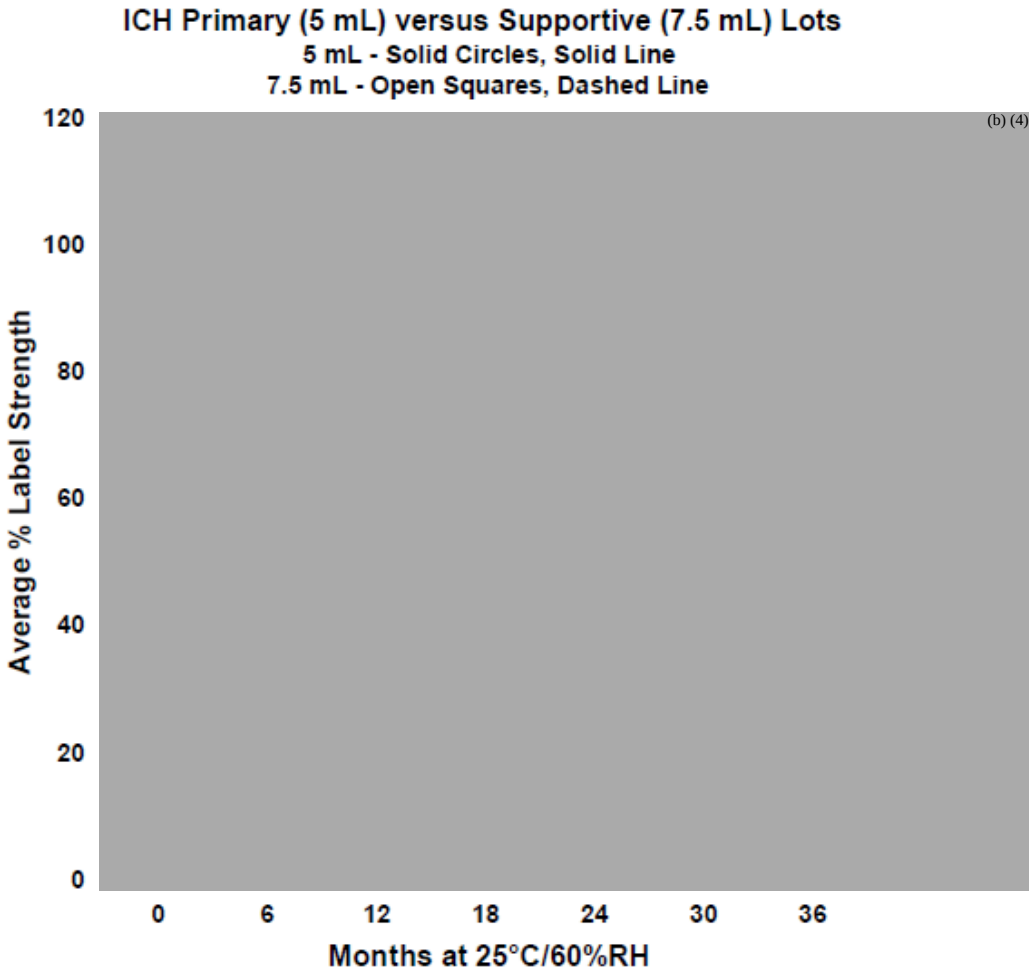


Figure 8: Dissolution profiles of Primary and Supportive stability batches of Bupivacaine ER Solution at 25 ˚C/60 % RH over 36 months.

Reviewer's Comments:

The dissolution profile data for the clinical and primary stability batches were examined (Section 3.2.P.8.3.1.7) and the proposed acceptance criteria are not acceptable for the QC release testing of Bupivacaine Extended-Release Solution. We recommend the following dissolution testing time points and acceptance criteria:

Time Point, h	Acceptance Criteria Range
1	NMT (b) (4) %
8	(b) (4) %
18	%
48	NLT (b) (4) %

The stability data at 25 ˚C/ 60 % RH over 36 months demonstrate that acceptable batches of the drug product are likely to pass in Stage 1 or Stage 2 levels of testing.

4 APPENDIX I: SUMMARY OF ANALYTICAL METHOD VALIDATION

Validation Characteristics	Acceptance Criteria	Result
Specificity [Section 5.1]	No peaks interfere with BUPI quantitation from the mobile phase, dissolution medium and placebo blanks (pre-filtered and post filtered).	No interfering peaks
System Suitability (4 Runs) [Section 5.2]	No peak interferes with BUPI quantitation from injections of analytical blanks (MeOH, mobile phase and dissolution medium)	Complies
	S/N (CS1/SEN): ≥ 10	11 - 57
	Capacity factor of 5th injection of CS3 (50 µg/mL): report	10.0 – 10.7
	USP tailing factor of 5th injection of CS3 (50 µg/mL): < 2.0	1.0 – 1.1
	Theoretical plates of 5th injection of CS3 (50 µg/mL): > 2000	5733 - 6127
	Retention time of 5th injection of CS3: 2.5 – 4.5 min	3.7 – 3.9 min
	RSD of BUPI retention time of five consecutive injections of CS3: ≤ 5.0%	0.01 - 0.03%
	RSD of BUPI peak area of five consecutive injections of CS3: ≤ 2.0%	0.1 - 0.2%
	Peak area of individual CS3 injection compared with the average of the peak area of the 5 consecutive injection of CS3 in the beginning of the run: 95.0 – 105.0%	99.4 - 100.2%
	RSD of RF of calibration standards (CS1 – CS5) and CS3 throughout the run: ≤ 3.0%	0.4 – 1.8%
	R^2 of calibration standards (CS1 – CS5) ≥ 0.98	1.00
	Slope of calibration standards (CS1 – CS5): report	7.72 - 8.38
	RSD of RF of calibration standards (CS1 – CS5) in the beginning of the run: ≤ 5%	1 – 3%
Calibration Standard Linearity [Section 5.3.1]	Report the slope and R^2 of the response curves with and without forcing through the origin Forcing through the origin R^2 ≥ 0.98	With forcing through the origin: Slope 7.716; R^2 1.00 Without forcing through the origin: Intercept 0.593; Slope 7.711; R^2 1.00
Method Linearity [Section 5.3.2]	R^2 ≥ 0.98 Slope: 1.00 ± 0.05 Intercept: ± 5.0% S_{yx}: ≤ 3.0%	R^2 1.00; Slope 1.04; Intercept -0.3; S_{yx} 1.6%

APPENDIX I: SUMMARY OF ANALYTICAL METHOD VALIDATION (CONT'D)

Validation Characteristics	Acceptance Criteria	Result
Accuracy [Section 5.4]	Mean % recovery for each concentration level (n=3): report	Mean % recovery for each level (n=3): 93 - 104%
	Mean % recovery for each preparation (A, B and C, n=6): 95% - 105%	Mean % recovery for each preparation (A, B and C, n=6): 99 – 103%
	Overall mean % recovery (n=18): report	Overall mean % recovery (n=18): 101%
Range [Section 5.3.2]	Report range	2.4 – 102.8 µg/mL (3.3 – 140.2% TAC)
Standard Repeatability [Section 5.5.1]	RSD of retention time of five consecutive injections of CS3: ≤ 5.0%	0.01 - 0.03%
	RSD of peak area of five consecutive injections of CS3: ≤ 2.0%	0.1 - 0.2%
Analysis Repeatability [Section 5.5.2]	SD and RSD of %recovery for each level (n=3): report	SD = 1.0 – 2.6 RSD = 1.0 – 2.7%
	SD and RSD of %recovery for each set sample (n=6): report	SD = 4.2 – 5.0 RSD = 4.2 – 4.9%
	SD and RSD of %recovery of all samples (n=18): report	SD = 4.7 RSD = 4.7%
Intermediate Precision [Section 5.5.3]	Mean % cumulative drug released at 1-hour time point (n=6): ≤ 10%	6%
	RSD of % cumulative drug released at 1-hour (n=24): ≤ 15%	0%
	RSD of % cumulative drug released at 4, 8, 12, 18, 24, 36, 48 an d72 hours (n=24): ≤ 10%	2 - 8%
DL and QL [Section 5.6]	Report the estimated value of DL and QL	DL = 0.08 µg/mL (0.11% LS) QL = 0.26 µg/mL (0.35% LS)
Stock Standard Solution Stability [Section 5.7.1]	Stability of SS_A and SS_B (500 µg/mL): report	Stable for 62 days at 2-8°C %Recovery of 62 days at 2-8°C = 101 -102%
Calibration Standard Solution Stability [Section 5.7.2]	Stability of calibration standards (2 – 150 µg/mL): report	Stable for 10 days at RT % Relative difference between the slope of calibration curve at time zero and the slope at 10 days at RT : 0.1 - 1.1%
Sample Solution Stability during Dissolution Testing (72 hours at 37°C) [Section 5.7.3]	Stability of the spiked sample solutions at four concentration levels L1 to L4 (4.4 – 71.6 µg/mL, corresponding to 6% LS – 98% LS) • Mean % recovery for each concentration level and each time point at 1, 18 and 24 hours should be within 90% -110%. • Mean % recovery at other time points: report	Mean % recovery of all the time points (1, 18 and 72 hours) at each concentration level (L1 - L4) = 100 - 103% Mean % recovery of all the concentration levels (L1 – L4) at each time point (1, 18 and 72 hours) = 100 - 102% Mean % recovery of all the time points (4, 8, 12, 24, 36 and 48 hours) at each concentration level (L1 - L4) = 99 - 103% Mean % recovery of all the concentration levels (L1 – L4) at each time point (4, 8, 12, 24, 36 and 48 hours) = 99 - 102%

APPENDIX I: SUMMARY OF ANALYTICAL METHOD VALIDATION (CONT'D)

<table>
<tr><th>Validation Characteristics</th><th>Acceptance Criteria</th><th>Result</th></tr>
<tr><td>Sample Solution Stability
[Section 5.7.4]</td><td>Dissolution sample solution stability: report</td><td>Stable for 10 days at RT
% Recovery of 10 days at RT = 98 – 100% at all the time points (1, 4, 8, 12, 18, 24, 36, 48 and 72 hours)</td></tr>
<tr><td>Filter Adsorption Study
[Section 5.8]</td><td>Mean % recovery of post filtered solution = 95 – 105% of pre-filtered solution</td><td>Mean % recovery = 97 - 100% at each concentration level (4.51 – 71.82 µg/mL)</td></tr>
<tr><td rowspan="5">Robustness
[Section 5.9]</td><td>All system suitability parameter criteria from method should be met</td><td>All system suitability parameter criteria from the method were met.</td></tr>
<tr><td>Mean % cumulative drug released at the 1-hour time point of all 17 runs (n=6): ≤ 10% LS</td><td>Mean % cumulative drug released at the 1-hour time point: 5 - 9% LS for Runs 1 - 9 (n=5 for Runs 1, 3, and 4)

Mean % cumulative drug released at the 1-hour time point: 4 - 9% LS for Runs 1A, 4A, 5A, 6A, 6B, 6C, 7A, and 8A (n=5 for Runs 1A and 4A)</td></tr>
<tr><td>The absolute difference of the mean % cumulative drug released between samples and control at each time point for all 8 runs:
• 1 and 4-hour time points: ≤ 6%
• 8 and 12-hour time points: ≤ 10%
• 18, 24, 36, 48 and 72-hour time points: ≤ 15%</td><td>• 1 and 4-hour time points: 0 - 5% for all 8 runs
• 8 and 12-hour time points: 11% at 12 hours for Run 6 and 1 - 8% for the other runs
• 18, 24, 36, 48 and 72-hour time points: 18% at 36 hours for Run 5; 17% at 24 hours and 19% at 36 hours for Run 8; 0% - 15% for other runs</td></tr>
<tr><td>Additional calculations :
Similarity factor (f2) testing and difference factor (f1) testing</td><td>f2 values: 50 - 85
f1 values: 5 – 14 except Run 6 (f1 = 19)</td></tr>
<tr><td>Determine the robust range of the method</td><td>Robust ranges of the method parameters:
<table>
<tr><th>Method Parameter</th><th>Range</th></tr>
<tr><td>Dissolution Buffer Concentration</td><td>25 ± 2 mM</td></tr>
<tr><td>SDS in Dissolution Medium</td><td>0.030 ± 0.005 % w/v</td></tr>
<tr><td>Paddle Speed</td><td>50 ± 5 rpm</td></tr>
<tr><td>Bath Temperature</td><td>37 ± 1°C</td></tr>
<tr><td>Dissolution Medium pH</td><td>7.40 ± 0.05</td></tr>
<tr><td>Acetonitrile in Mobile Phase</td><td>40 ± 2%</td></tr>
<tr><td>Column Temperature</td><td>40 ± 2°C</td></tr>
<tr><td>Detector Wavelength</td><td>225 ± 1 nm</td></tr>
</table></td></tr>
</table>

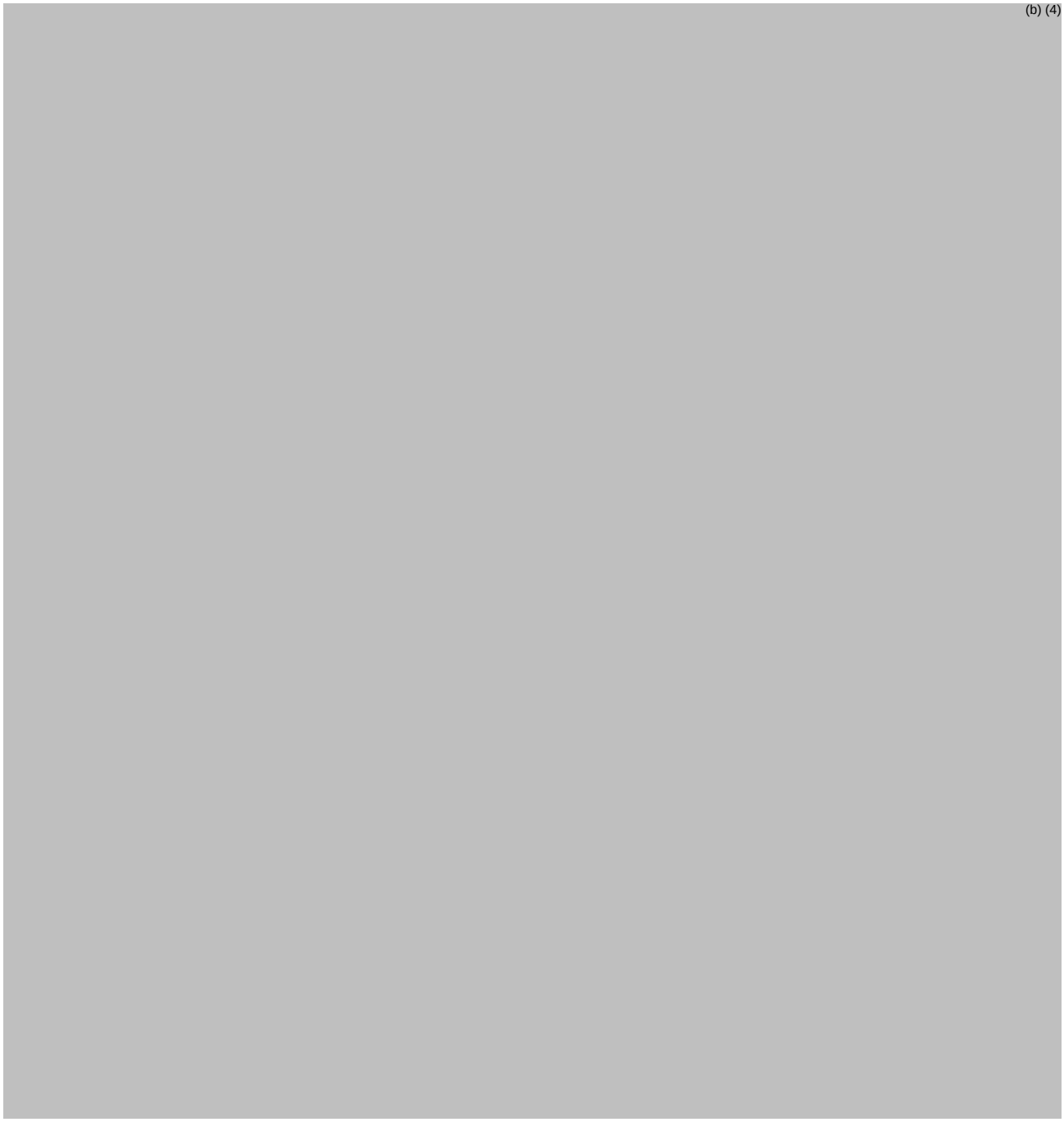
5 APPENDIX II: OCT 21, 2013 IR COMMENTS AND APPLICANT'S RESPONSES

IR Comment #1:

The experiments that were conducted to select the paddle speed, surfactant and pH seem to have produced confounding results. For example, SDS concentration of (b) (4)% appears to have given a (b) (4) dissolution rate of bupivacaine than 0.03% (Figure 8 in section 3.2.P.2). In addition, bupivacaine dissolution in pH (b) (4) medium is initially (b) (4) when compared to the pH 7.4 medium at the same paddle speed of 50 rpm (Figure 9 in section 3.2.P.2); this is anomalous since the solubility of bupivacaine at (b) (4) at pH 7.4. Explain the afore- mentioned anomalous results of the method development experiments, indicating the rationale for selection of the final dissolution method conditions.

Applicant's Response:

(b) (4)



IR Comment #2:

Your proposed dissolution acceptance criteriado not properly cover the entire dissolution profile of your proposed product and therefore we recommend that you add a samplingtime at 8 hours. Also, theprovided data show that >85%mean dissolution is reached at48 hours, indicating that the [redacted] time point is not adequate and should be revised. The following sampling time points and limits are recommended for the dissolution acceptance criteria of your product.

Time Point, hours	Acceptance Criteria
1	NMT [redacted]%
8	[redacted]%
18	[redacted]%
48	NLT [redacted]%

Indicate in your response that the recommended dissolution acceptance criteria are acceptable and will be implemented for batch release and on stability testing. Provide the updated specification table for your drug product with the revised dissolution acceptance criteria.

Applicant's Response:

The recommended dissolution acceptance criteria are acceptable to DURECT. They will be implemented for batch release and on stability testing. The updated commercial specification for Posimir™ is provided in Section 3.2.P.5.1.

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/s/

OKPONANABOFA ERADIRI
12/23/2013

ELSBETH G CHIKHALE
12/23/2013

Product Quality Microbiology Review

26 NOV 2013

NDA: 204803

Drug Product Name
Proprietary: POSIMIR™ (SABER®-Bupivacaine)
Non-proprietary: bupivacaine extended-release solution for instillation

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
4/12/2013	4/12/2013	4/17/2013	4/18/2013

Applicant/Sponsor
Name: DURECT Corporation
Address: 10260 Bubb Road, Cupertino CA 95014

Representative: James Edward Brown
10260 Bubb Road
Cupertino CA 95014

Telephone: 408-777-1419

Name of Reviewer: Neal J. Sweeney, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

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

2. SUBMISSION PROVIDES FOR: New drug product

3. MANUFACTURING SITE: (b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Bupivacaine extended-release solution for instillation (5 mL) directly into the surgical incision, packaged in 5 mL single-use vial, 13.2% (132 mg/mL).

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

6. PHARMACOLOGICAL CATEGORY: Anesthetic indicated for administration into the surgical incision to produce post-surgical analgesia.

B. SUPPORTING/RELATED DOCUMENTS: DMF (b) (4) rubber stopper (b) (4))

C. REMARKS: Letter of Authorization (b) (4) provided in Module 1.4.1., authorized FDA to refer to DMF (b) (4) (for rubber stopper (b) (4) information for the stoppers) in its entirety for review of DURECT Corporation NDA for SABER®-Bupivacaine .

During the development program, SABER-Bupivacaine formulation has also been referred to as Posidur, POSIDUR (SABER-Bupivacaine) 132 mg/mL, SABER-Bupivacaine 120 mg/g, SABER™-Bupivacaine [BA] 12 wt%, SABER™-Bupivacaine-12 wt%, SAIB/BA-12 wt%, and Optesia™.

File name: N204803R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for 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 – (b) (4)

B. Brief Description of Microbiology Deficiencies – Based upon the information provided, no microbiology deficiencies were identified.

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

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**
(If yes, provide a brief description and a reference to the page where the precedent is discussed in depth)

III. Administrative

A. Reviewer's Signature _____
Neal J. Sweeney, Ph.D.

B. Endorsement Block _____
Bryan S. Riley, Acting Team Leader

C. CC Block
N/A

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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.

/s/

NEAL J SWEENEY
12/09/2013

BRYAN S RILEY
12/09/2013
I concur.