

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211988Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 211988 Assessment # 3

Drug Product Name	Zynrelef (bupivacaine and meloxicam) solution for application to surgical site
Dosage Form	Solution for application to surgical site
Strength	400mg/ 12mg bupivacaine / meloxicam 300mg/ 9mg bupivacaine / meloxicam 60mg/ 1.8mg bupivacaine / meloxicam
Route of Administration	application to surgical site
Rx/OTC Dispensed	Rx
Applicant	Heron Therapeutics, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting Document 66; eCTD 0066	12 Nov 20	Facilities, Drug Product
Supporting Document 69; eCTD 0069	16 Dec 20	Drug Product
Supporting Document 70; eCTD 0070	15 Jan 21	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	N/A
Drug Product	Valerie Amspacher	Julia Pinto
Manufacturing	Yoon Oh	Jonathan Swoboda
Microbiology	N/A	N/A
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A

Environmental	N/A	N/A
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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval of this application based on drug product and facility reviews.

The proposed shelf-life is acceptable when stored at controlled room temperature, protected from light.

The proposed shelf-life for HTX-011 is 36 months for the 400 mg/12 mg and 300 mg/9 mg product presentations in a 20 mL vial, 36 months for the 200 mg/6 mg product presentation in a 10 mL vial, and 24 months for the 60 mg/1.8 mg product presentation in a 10 mL vial.

The proposed shelf-life is acceptable when stored at controlled room temperature, protected from light.

Note that the 200 mg/ 6 mg product will not be marketed at this time.

See also CMC IQA's dated 18 Jun 20 (review 2) and 19 Apr 19 (review 1).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

HTX-011 is an extended-release solution containing a fixed-dose combination of bupivacaine (29.25 mg/mL) and meloxicam (0.88 mg/mL) that is intended for single-dose local administration into the surgical site. HTX-011 is filled in a 10 mL or 20 mL vial.

The to-be-marketed presentations are:

-400 mg bupivacaine and 12 mg meloxicam (20 mL vial)

-300 mg bupivacaine and 9 mg meloxicam (20 mL vial)

-60 mg bupivacaine and 1.8 mg meloxicam (10 mL vial)

The proposed shelf-life is acceptable when stored at controlled room temperature, protected from light.

The proposed shelf-life for HTX-011 is 36 months for the 400 mg/12 mg and 300 mg/9 mg product presentations in a 20 mL vial, 36 months for the 200 mg/6 mg product presentation in a 10 mL vial, and 24 months for the 60 mg/1.8 mg product presentation in a 10 mL vial.

Note that the 200 mg/ 6 mg product will not be marketed at this time.

Review 2 recommended approval for CMC for this application but a CR letter was sent on 26 Jun 20 due to pharm/tox deficiencies.

Review 1 recommended complete response for CMC for this application due to a lack of information about leachables and a CR letter was sent 30 Apr 2019.

Proposed Indication(s) including Intended Patient Population	(b) (4)
Duration of Treatment	acute
Maximum Daily Dose	400 mg Bupivacaine and 12 mg meloxicam
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

See CMC IQA's dated 18 Jun 20 (review 2) and 19 Apr 19 (review 1).

Drug Product: Adequate

The CMC recommendation was for approval in the last review cycle and it remains approval for this review cycle. The sponsor provided updated specifications and stability data which are adequate.

Labeling: Adequate

See CMC IQA's dated 18 Jun 20 (review 2) and 19 Apr 19 (review 1).

Manufacturing: Adequate

Facilities remain adequate. See CMC IQA's dated 18 Jun 20 (review 2) and 19 Apr 19 (review 1).

Biopharmaceutics: Adequate

See CMC IQA's dated 18 Jun 20 (review 2) and 19 Apr 19 (review 1).

Microbiology (if applicable): Choose an item.

See CMC IQA's dated 18 Jun 20 (review 2) and 19 Apr 19 (review 1).

C. Risk Assessment

From Initial Risk Identification	Assessment
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Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, stability (APIs)	Stability of the drugs (APIs) in solid state	Moderate	(b) (4)	Acceptable	
Physical stability (Drug Product)	Drug(s) in dissolved state	High		Acceptable	
Degradation Products (Drug Product)	Drug(s) in dissolved state, (b) (4) manufacturing	High		Acceptable	
Content uniformity	Highly Viscous solution	Moderate		Acceptable	
Microbial Limits	(b) (4)	High		Acceptable	
In Vitro Release (ER Solution)	Modified In Vitro Release (IVR) methods employed for quality control	Moderate		Acceptable	
Extractables and Leachables	(b) (4)	High		Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

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)	(b) (4)	3	11 Dec 2018	
	II		(b) (4)	3	10 Jan 2019	
	III		(b) (4)	4		
	III		(b) (4)	4		

(b) (4)	III	(b) (4)	4		
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Action codes for DMF Table:

- 1 – DMF Reviewed.
- 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")

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

Document	Application Number	Description
IND	125927	Basis for NDA 211988
NDA	016964	RLD, MARCAINE (bupivacaine HCl) injection
NDA	020938	RLD, MOBIC (meloxicam) tablets

2. CONSULTS

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

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Valerie
Amspacher

Digitally signed by Valerie Amspacher

Date: 2/18/2021 10:06:54AM

GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

Recommendation: Approval
NDA 211988
Review 2

Drug Name/Dosage Form	Zynrelef (bupivacaine and meloxicam) Solution
Strength	400 mg/12 mg, 300 mg/9 mg, 200 mg/6 mg, 60 mg/1.8 mg
Route of Administration	(b) (4)
Rx/OTC Dispensed	Rx
Applicant	Heron Therapeutics, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
<i>eCTD SN 0040</i>	<i>26-SEP-2019</i>	<i>OPQ/Drug Product, Process and Facilities; CDRH</i>
<i>0043</i>	<i>24-OCT-2019</i>	<i>Microbiology/Facilities</i>
<i>0044</i>	<i>22-NOV-2019</i>	<i>Facilities/Drug Substance</i>
<i>0047</i>	<i>19-DEC-2019</i>	<i>Drug Product</i>
<i>0055</i>	<i>05-FEB-2020</i>	<i>Facilities and Process</i>
<i>0056</i>	<i>01-APR-2020</i>	<i>Labeling</i>

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Joe Leginus	Donna Christner
Drug Product / Labeling	Venkat Pavuluri	Julia Pinto
Process	Yoon Oh	Pei-I Chu
Microbiology	Christine Craig	TBD
Facility	Yoon Oh	Jonathan Swoboda
Biopharmaceutics	Hansong Chen	Kelly Kitchens
Regulatory Business Process Manager	Anika Lalmansingh	N/A
Application Technical Lead	Venkateswara Pavuluri	N/A
Laboratory (OTR)	Xiaofei Liu; Cindy Diem Ngo	Cynthia Sommers, Method Verification Coordinator
ORA Lead	Caryn McNab	Michael Tollon
Environmental	N/A	N/A

APPEARS THIS WAY ON ORIGINAL

Quality Review Data Sheet

[IQA Review Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	11-DEC-2018	
	Type II			Adequate	13-JUN-2019	
	Type III (if applicable)					Adequate information included in submission
	Type III (if applicable)					Adequate information included in submission
	Type III (if applicable)					Adequate information included in submission
	Other 510(k)					510(k) cleared for marketing
	Other 510(k)					510(k) cleared for marketing

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	125927	Basis for NDA 211988
NDA	016964	RLD, MARCAINE™ (bupivacaine HCl) injection, USP
NDA	020938	RLD, MOBIC® (meloxicam) tablets
NDA	020243 and 021519	LUVOX (fluvoxamine maleate) Tablets,

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			

CDRH	Complete	Approvable	04-FEB-2020	Florencia Wilson
Clinical	NA			
Other (Method Verification by OTR)	Complete	Acceptable	06-MAR-2019	Cynthia Sommers
CDRH OC - Device Facility Inspection: (b) (4) - (b) (4) (FEI (b) (4))	Complete	Approve Facility	16-APR-2019	Payal Patel

Executive Summary

[IQA Review Guide Reference](#)

I. Recommendations and Conclusion on Approvability

Based on evaluation of quality information provided in the resubmission (SN#0040) and subsequent amendments to date (SN#0040 to #0056), recent pre-approval inspection of drug product manufacturing facilities (b) (4) (b) (4) **NDA 211988 for ZYNRELEF™ (bupivacaine and meloxicam) solution is APPROVABLE** from quality (CMC) perspective. The deficiencies outlined in the previous review cycle were adequately addressed during the resubmission.

II. Summary of Quality Assessments

A. Product Overview

ZYNRELEF™ (bupivacaine and meloxicam) solution is a fixed-dose combination product intended for soft tissue instillation and periarticular instillation use. The drug product containing sterile non-aqueous viscous solution of bupivacaine and meloxicam in a vial is supplied as kit for hospital use, along with device components required for preparation and administration in carton. The device components included in the kit for preparation and application of the drug solution include syringe(s), tip cap(s), vented vial spike [VVS], Luer lock applicator(s) [LLA(s)]. ZYNRELEF™ is supplied in four different dose strengths, i.e. 60 mg/1.8 mg, 200 mg/6 mg, 300 mg/9 mg, or 400 mg/12 mg of bupivacaine base and meloxicam respectively. The syringes are made of (b) (4) barrel and (b) (4) piston; the tip cap and LLAs are made of (b) (4) and VVS are made of (b) (4) materials.

NA	 Total Number of Comparability Protocols (ANDA only)
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Proposed Indication(s) including Intended Patient Population	For soft tissue and periarticular instillation use. (b) (4) (b) (4)
Duration of Treatment	One-time use during surgery
Maximum Daily Dose	400 mg Bupivacaine and 12 mg meloxicam
Alternative Methods of Administration	None, Bupivacaine is approved for parenteral use, while meloxicam is currently approved for oral use only.

B. Quality Assessment Overview

The drug product is a sterile, viscous, non-aqueous solution of bupivacaine and meloxicam. Each mL of the solution contains active ingredients bupivacaine 29.25 mg and meloxicam 0.88 mg; and inactive ingredients tri(ethylene glycol) poly(orthoester) (730 mg), triacetin (293 mg), dimethyl sulfoxide (117 mg), and maleic acid (0.59 mg). The drug substances are referenced to DMF (b) (4) (Bupivacaine) and DMF (b) (4) (Meloxicam) that were reviewed as adequate to use in the manufacture of the drug product. Bupivacaine has a retest period of (b) (4) months (b) (4) years and meloxicam has a retest period of (b) (4) months (b) (4) years. Tri(ethylene glycol) poly(orthoester), designated as AP135, is considered a novel excipient. Applicant provided adequate information on synthesis and characterization of impurities in AP135, along with toxicological assessment in support of its safety. The drug product is prepared (b) (4)

(b) (4)

(b) (4) The four dosage strengths are prepared by filling appropriate volumes of the solution in either a 10 mL or 20 mL (b) (4) clear glass vials, capped with 20 mm (b) (4) gray (b) (4) stopper (b) (4)

(b) (4)

(b) (4) and secured with a 20 mm aluminum overseal. In-use compatibility study reports, for the device components and drug product during preparation and use, included in the submission indicated that the device components are compatible with the drug solution.

Upon follow-up inspection of the drug manufacturing facility (b) (4)

(b) (4) FEI: (b) (4), deficiencies identified during earlier inspection were adequately addressed and the facility portion is now acceptable for manufacturing of the drug product at (b) (4) kg batch size. Quality deficiency #2 from previous review cycle is now adequately addressed. (b) (4)

(b) (4)

Analytical methods used for monitoring the quality of the drug substances and finished drug product; including test methods used for monitoring elemental impurities and leachables in the drug product and tests for sterility and endotoxin content are adequately validated. Suitability of primary container closure system (CCS), clear USP

(b) (4) glass vials (b) (4) 20 mm (b) (4) stoppers (b) (4)

(b) (4)

(b) (4) is adequately justified through stability testing of the finished drug product. The new information provided in the resubmission, on leachables and the root cause analysis for sources of

(b) (4) is adequate to address the quality deficiency #1 from previous review cycle. Additional information

provided on the tip cap (a 510(k) cleared device component) ensure that the tip cap will be provided sterile and will remain sterile throughout its shelf-life and the device is safe for use and addresses the CDRH deficiency identified in CRL.

Therefore, the NDA 211988 is approvable from quality (CMC) perspective.

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (see Attachment)

All OPQ deficiencies affecting NDA approval are now resolved. Refer the IQA document attached for discipline specific reviews.

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CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Submitted in eCTD SN 0040 dated 26-SEP-2019

Reviewer Note: Suggested changes are based on the internal review document as on SharePoint site as of 16-JUN-2020.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	ZYNRELEF™	Acceptable.

Established name(s)	(bupivacaine and meloxicam) extended-release solution.	Not Acceptable. Revise established name as (bupivacaine and meloxicam) solution.
Route(s) of administration	No information provided in highlights of the PI	Not Acceptable. Route of administration, e.g. “for soft tissue instillation and periarticular instillation use” must be included after the dosage form, per 21 CFR 201.57(a)(2).
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	ZYNRELEF (bupivacaine and meloxicam) extended-release solution: (b) (4)	Not Acceptable. Revise the text as “ZYNRELEF (bupivacaine and meloxicam) solution is available in three dosage strengths as single dose glass vials: • 400 mg bupivacaine and 12 mg meloxicam • 300 mg bupivacaine and 9 mg meloxicam • • 60 mg bupivacaine and 1.8 mg meloxicam
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	Not applicable	Not Applicable
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	single-dose glass vials.	Acceptable.

pharmacy bulk package and imaging bulk package.		
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1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Preparation

(b) (4)



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)	(b) (4)	Not Acceptable. Revise step 1 as "Visually inspect the ZYNRELEF vial for particulate matter and discoloration. Obtain a new vial if particulate matter or discoloration is observed." Replace steps 5 and 6 with the statement "Prepare product immediately prior to use and apply syringe tip caps until product delivery."

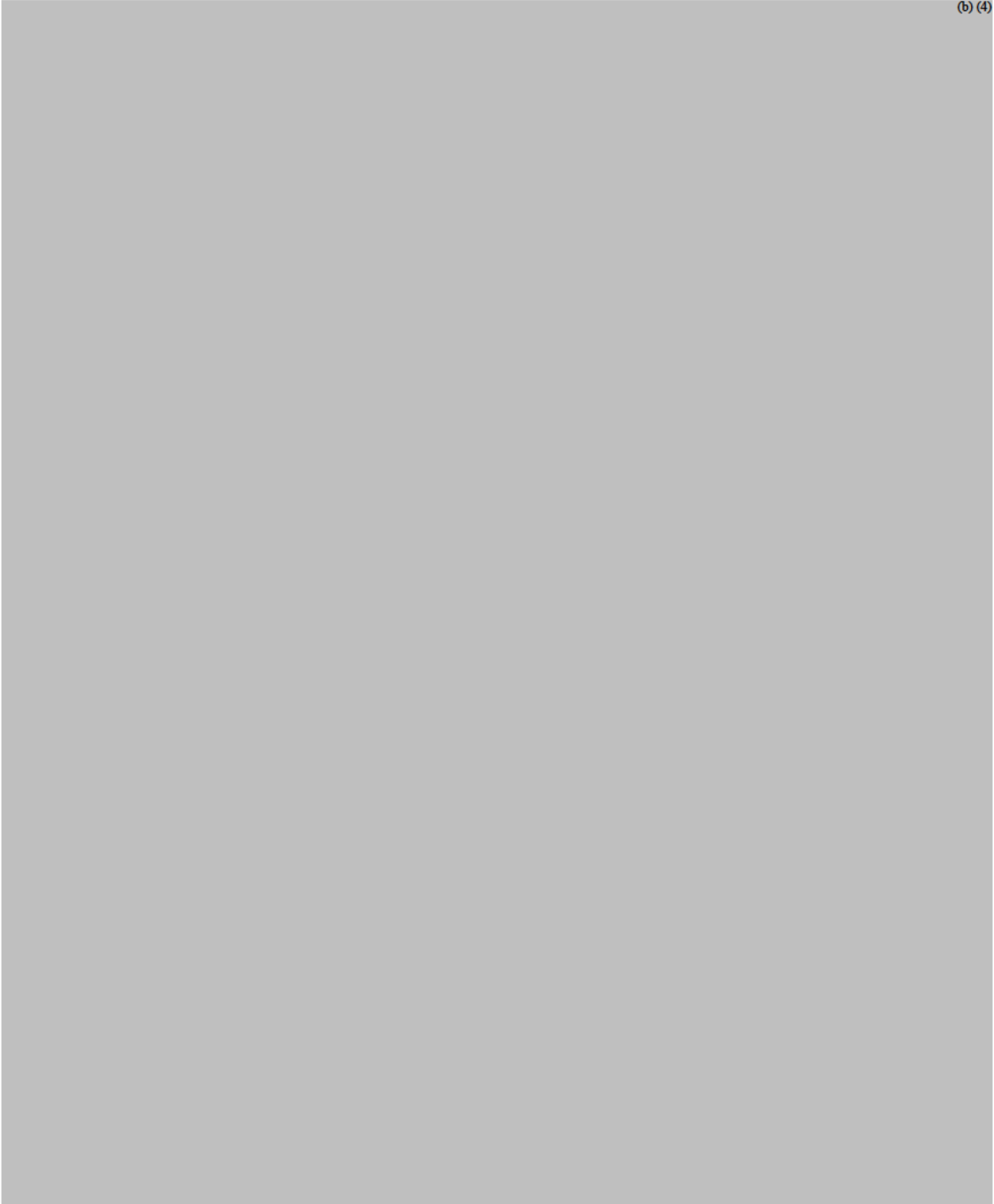
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Extended-release solution	Not Acceptable. Change to "solution"
Strength(s) in metric system	29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not applicable.	Not Applicable.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	clear, pale yellow to yellow, viscous liquid in a single dose vial	Acceptable.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not applicable	
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.	(b) (4)	Not Acceptable. Revise the text as "ZYNRELEF (bupivacaine and meloxicam) solution, is available in three dosage strengths as single-dose glass vials: • 400 mg bupivacaine and 12 mg meloxicam • 300 mg bupivacaine and 9 mg meloxicam • 60 mg bupivacaine and 1.8 mg meloxicam (3)

1.2.3 Section 11 (DESCRIPTION)

11 DESCRIPTION



(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	ZYNRELEF (bupivacaine and meloxicam)	Acceptable.
Dosage form(s) and route(s) of administration	extended-release solution; Route of administration not specified.	Not Acceptable. Delete the wording "extended-release" from dosage form description. Route of administration as "for soft tissue instillation and periarticular instillation use," must be included after the type of dosage form, per 21 CFR 201.57(b)(12)(i)(B)
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Not applicable.	Not applicable.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	(b) (4) inactive ingredients (b) (4) tri(ethylene glycol) poly(orthoester) (730 mg/mL), triacetin (293 mg/mL), dimethyl sulfoxide (117 mg/mL), and maleic acid (0.59 mg/mL).	Not Acceptable. Revise as "Each mL of the solution contains.....; and inactive ingredients tri(ethylene glycol) poly(orthoester) (730 mg), triacetin (293 mg), dimethyl sulfoxide (117 mg), and maleic acid (0.59 mg)."
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.	(b) (4) inactive ingredients (b) (4) tri(ethylene glycol) poly(orthoester) (730 mg/mL), triacetin (293 mg/mL), dimethyl sulfoxide (117 mg/mL), and maleic acid (0.59 mg/mL).	Not Acceptable. Revise as "Each mL of the solution contains.....; and inactive ingredients tri(ethylene glycol) poly(orthoester) (730 mg), triacetin (293 mg), dimethyl sulfoxide (117 mg), and maleic acid (0.59 mg)."
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not applicable, alcohol not present	Not Applicable

Statement of being sterile (if applicable)	(b) (4)	Acceptable. But combine the two sentences describing the dosage form into one as: "ZYNRELEF is a sterile, clear, pale yellow to yellow, viscous liquid provided in single-dose vials (10 mL or 20 mL) for instillation into the surgical site."
Pharmacological/therapeutic class	bupivacaine, a local anesthetic, and meloxicam, a nonsteroidal anti-inflammatory drug (NSAID).	Acceptable.
Chemical name, structural formula, molecular weight	See the information reproduced above for the two drugs	Acceptable.
If radioactive, statement of important nuclear characteristics.		
Other important chemical or physical properties (such as pKa or pH)		

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	Not Applicable	Not Applicable
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	(b) (4)	Not Acceptable. Remove the wording (b) (4)

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

HOW SUPPLIED/STORAGE AND HANDLING section

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	extended-release solution	Not Acceptable. Revise to "solution"
Strength(s) in metric system	a solution of 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam.	Acceptable.
Available units (e.g., bottles of 100 tablets)	in 2 vial sizes and 4 presentations.	Not Acceptable. Revise as "in 3 presentations"
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	clear, pale-yellow to yellow viscous liquid; NDC 47426-301-02 for 400/12 mg kit, NDC 47426-302-02 for 300/9 mg kit, NDC 47426-303-01 for 200/6 mg kit, and NDC 47426-304-01 for 60/1.8 mg kit.	Not Acceptable. Revise the table removing the row for 200/6 mg kit that is not considered for approval at this time.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not applicable	Not applicable
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.	single-dose glass vial	Acceptable.

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.)	Protect from moisture and light.	Acceptable
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."	Not applicable	Not applicable
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	(b) (4)	Not Acceptable. Revise the storage statements as "Store ZYNRELEF kits at 20°C to 25°C (68°F to 77° F) with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]." "If ZYNRELEF vials are removed from the kit, store them at controlled room temperature. Protect from light during storage."
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."	Not Applicable	Not Applicable
Include information about child-resistant packaging	Not Applicable, for Hospital Use only	Not Applicable

1.2.5 Other Sections of Labeling

None

1.2.6 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	Manufactured for: Heron Therapeutics, Inc., San Diego, CA, 92121, USA	Not Acceptable. Street address must be included after manufacturer/distributor Name(s), as per 21 CFR 201.1(i).

Assessment of Packaging Insert: Inadequate.

The Packaging Insert, as submitted in the resubmission (eCTD SN 0040 dated 26-SEP-2019), is not acceptable from CMC perspective. Refer to the deficiencies listed at the end of this review.

2.0 PATIENT LABELING

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

The IFUs (Instructions for use) have no specific CMC information to review, other than the pictorial representation of the kit components and syringe preparation procedure for instillation in to surgical site.

3.0 CARTON AND CONTAINER LABELING

(As submitted in SN 0056 of eCTD dated 01-APR-2020)

3.1 Container Label

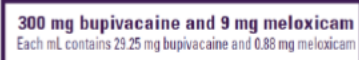
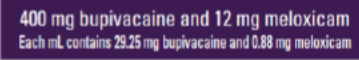
(60 mg /1.8 mg vial label reproduced here as a representative example of the 4 different container labels)



3.2 Carton Labeling

(60 mg /1.8 mg vial carton, reproduced here as a representative example of the 4 vial cartons)



Item	Information Provided in the NDA	Assessor's Comments about Vial Label and Vial carton
Proprietary name, established name, and dosage form (font size and prominence)		Not Acceptable. Revise the established name as "bupivacaine and meloxicam solution"
Dosage strength	  	Acceptable
Route of administration	(b) (4)	Not Acceptable Revise the route of administration as "for soft tissue instillation and periarticular instillation use. Include the statement "Not for any other route of administration" to appear prominently on all vial labels (if space permits) and cartons.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not applicable	Not applicable.
Net contents (e.g. tablet count)	"Vial Contents: 2.3 mL"	Acceptable.
"Rx only" displayed on the principal display	"Rx Only"	Acceptable.
NDC number	47426-301-06 for 400 mg/12 mg vial 47426-302-06, 300 mg/9 mg vial 47426-304-05, 60 mg/1.8 mg vial	Acceptable

Lot number and expiration date	LOT XXXXXXXX EXP DDMMYYYYY	Not acceptable. Provide details on how assigned lot number on the vial labels and cartons are capable of yielding the complete manufacturing history of the drug, required per 21 CFR 201.18 Drugs; significance of control numbers.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4) Protect from light during storage	Not Acceptable. Revise the storage conditions to “Store at 20°C to 25°C (68°F to 77° F) with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light” on vial labels, if space permits, and on vial cartons.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-Dose vial	Acceptable.
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	(b) (4)	Not Acceptable. Revise the statement as “for soft tissue instillation and periarticular instillation use”. Include the statement “Not for any other route of administration” to appear prominently on all vial labels (if space permits) and cartons.

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not applicable	Not applicable
Bar code		Acceptable
Item	Information Provided in the NDA	Assessor's Comments about Vial Labeling
Name of manufacturer/distributor	Manufactured for: Heron Therapeutics, Inc. San Diego, CA	Not Acceptable. Include street address after manufacturer /distributor name on all vial labels (If space permits) and cartons.
Medication Guide (if applicable)	Not Provided	Acceptable
No text on Ferrule and Cap overseal	No information or figure included	Acceptable
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	Not Applicable, not a compendial drug product.	Not applicable

And others, if space is available	<u>On vial labels and cartons:</u> <i>For 400 mg / 12 mg:</i> Withdraw 14 mL to deliver 13.5 mL. <i>For 300 mg / 9 mg:</i> Withdraw 10.5 mL to deliver 10.2 mL. <i>For 200 mg / 6 mg:</i> Withdraw 7 mL to deliver 6.7 mL. <i>For 60 mg /1.8 mg:</i> Withdraw 2.3 mL to deliver (b) (4) Do not remove crimp seal Discard unused portion <u>On vial cartons only:</u> *Vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, Luer lock applicator, and syringe(s) during drug withdrawal and administration.	Not Acceptable. Revise the text for 60 mg /1.8 mg vial label and carton as “Withdraw 2.3 mL to deliver 2 mL.”, (b) (4)
--	--	---

3.3 Kit Carton Labeling

(60 mg /1.8 mg vial carton, component labels and kit carton reproduced here as a representative example of the 4 kits)

Item	Information Provided in the NDA	Assessor's Comments about Kit Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)		Not Acceptable. Revise the established name as "bupivacaine and meloxicam solution"
Dosage strength	60 mg bupivacaine and 1.8 mg meloxicam Each mL contains 29.25 mg bupivacaine and 0.88 mg meloxicam 300 mg bupivacaine and 9 mg meloxicam Each mL contains 29.25 mg bupivacaine and 0.88 mg meloxicam 400 mg bupivacaine and 12 mg meloxicam Each mL contains 29.25 mg bupivacaine and 0.88 mg meloxicam	Acceptable
Route of administration	(b) (4)	Not Acceptable Revise the text for route of administration as "for soft tissue instillation and periarticular instillation use". Include the statement "Not for any other route of administration" to appear prominently on all kit cartons.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not Applicable	Not Applicable
Net contents (e.g. tablet count)	(b) (4)	Not Acceptable. Revise the text for 60 mg /1.8 mg vial label and carton as "Withdraw 2.3 mL to deliver 2 mL.", (b) (4) (b) (4)
"Rx only" displayed on the principal display	Rx Only	Acceptable
NDC number	47426-301-02 for 400 mg /12 mg kit 47426-302-02 for 300 mg/ 9 mg kit NDC 47426-304-01 for 60 mg/ 1.8 mg kit	Acceptable

Lot number and expiration date	LOT 12345678 EXP DDMMYYYYYY SN 12345678901	Not Acceptable. Provide details on how assigned lot number on the kit cartons are capable of yielding the complete manufacturing history of the drug, required per 21 CFR 201.18 Drugs; significance of control numbers.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4) Protect from light and moisture	Not Acceptable. Revise the storage conditions to “Store at 20°C to 25°C (68°F to 77° F) with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light” on all kit cartons.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	(b) (4)	Not Acceptable. Revise the statement as “for soft tissue instillation and periarticular instillation use”. Include the statement “Not for any other route of administration” to appear prominently on all kit cartons.

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	(b) (4)	Not Acceptable. Revise the text on kit cartons as follows, as applicable to respective dosage strengths’ kit cartons. Each Kit Contains: • One single-dose vial containing xx mg bupivacaine and yy mg meloxicam • One sterile vented vial spike • One/two sterile x mL Norm-Ject® Luer Lock Syringe(s) • One/two sterile Luer lock applicator(s) • One/two sterile syringe tip cap(s) • Instructions for Use and • Prescribing Information Delete the text highlighted in red and move Boxed text [Vial contents sterile/vial exterior not sterile] to a space above or below the kit carton contents statement.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		Not applicable
Bar code	Unique bar codes present on all kit cartons	Acceptable

Item	Information Provided in the NDA	Assessor's Comments about Kit Carton Labeling
Name of manufacturer/distributor	Manufactured for: Heron Therapeutics, Inc. San Diego, CA	Not Acceptable. Include street address after manufacturer /distributor name on all kit cartons.
Medication Guide (if applicable)	Not Provided	Not applicable
No text on Ferrule and Cap over seal	Not Applicable	Not applicable
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	Not a compendial dosage form	Not applicable
And others, if space is available	On the side panel: *Vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, Luer lock applicator, and syringe(s) during drug withdrawal and administration.	Acceptable

Additional information on kit cartons	All Kit Cartons: <i>For 400 mg / 12 mg:</i> Withdraw 14 mL to deliver 13.5 mL. <i>For 300 mg / 9 mg:</i> Withdraw 10.5 mL to deliver 10.2 mL. <i>For 200 mg / 6 mg:</i> Withdraw 7 mL to deliver 6.7 mL. <i>For 60 mg / 1.8 mg:</i> Withdraw 2.3 mL to deliver (b) (4) Do not remove crimp seal Discard unused portion *Vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, Luer lock applicator, and syringe(s) during drug withdrawal and administration.	Not Acceptable. Revise the text for 60 mg / 1.8 mg kit carton as “Withdraw 2.3 mL to deliver 2 mL.”, (b) (4) (b) (4)
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Assessment of Carton and Container Labeling: Inadequate.

The labels and labeling material as submitted in eCTD SN 0056 dated 01-APR-20202) are not adequate.

Refer to deficiencies listed below under “ITEMS FOR ADDITIONAL ASSESSMENT.”

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies:

The following specific deficiency is relevant to all labeling text (sections of PI, Cartons for vials and kits and container labels).

- Include route of administration, e.g. “for soft tissue instillation and periarticular instillation use” immediately after the established name(s) and dosage form when relevant.

Therefore, the title of the drug should be **ZYNRELEF™ (bupivacaine and meloxicam) solution, for soft tissue instillation and periarticular instillation use**, where required.

A. Regarding Full Prescribing Information submitted as in eCTD SN 0040, dated 26-SEP-2019:

1. Highlight Section

- Include route of administration, e.g. “for soft tissue instillation and periarticular instillation use” after the established name(s) and dosage form, required per 21 CFR 201.57(a)(2).
- The drug name and strengths information in “**Dosage form and Strength**” section should be revised to “ZYNRELEF™ (bupivacaine and meloxicam) solution is available in three dosage strengths as single-dose glass vials:
 - 400 mg bupivacaine and 12 mg meloxicam (3)
 - 300 mg bupivacaine and 9 mg meloxicam (3)
 - 60 mg bupivacaine and 1.8 mg meloxicam (3).

2. Section 2 (DOSAGE AND ADMINISTRATION)

- In section “**2.2 Preparation Instructions**”
 - Revise step 1 as “Visually inspect the ZYNRELEF vial for particulate matter and discoloration. Obtain a new vial if particulate matter or discoloration is observed.”
 - replace steps 5 and 6 with the statement “Prepare product immediately prior to use and apply syringe tip caps until product delivery.”

3. Section 3 (DOSAGE FORMS AND STRENGTHS)

- Revise the text in “DOSAGEFORMS AND STRENGTHS” section as: ZYNRELEF (bupivacaine and meloxicam) solution is a sterile, clear, pale- yellow to yellow, viscous liquid in a single dose vial containing 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam and is available in the following three presentations:

400 mg bupivacaine and 12 mg meloxicam
 300 mg bupivacaine and 9 mg meloxicam
 60 mg bupivacaine and 1.8 mg meloxicam

4. Section 11 (DESCRIPTION)

- Include the route of administration “for soft tissue instillation and periarticular instillation use,” after the name of dosage form
- Revise the two statements below the structural formula of meloxicam, by combining them as “ZYNRELEF is a sterile, clear, pale yellow to yellow, viscous liquid provided in single-dose vials (10 mL or 20 mL) for soft tissue instillation and periarticular instillation use.”
- Separate the list of the active ingredients from the inactive ingredients by “;” and revise the statement as: “Each mL of the solution contains active ingredients bupivacaine 29.25 mg and meloxicam 0.88 mg; and inactive ingredients tri(ethylene glycol) poly(orthoester) (730 mg),

triacetin (293 mg), dimethyl sulfoxide (117 mg), and maleic acid (0.59 mg).”

5. Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

- Revise the table removing the NDC number for 200/6 mg kit that is not considered for approval at this time.
- Revise the storage statement as “Store ZYNRELEF kits at 20°C to 25°C (68°F to 77° F) with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. room temperature. Protect from moisture and light.”

6. Section 17

- Full street address should be stated after the name of manufacturer /distributor, as per 21 CFR 201.1(i).

B. Regarding Cartons and Container Labeling (for Vials), and Cartons for kits (containing Vial, and device components) submitted in SN 0056, Dt 01-APR-2020

- Revise the text for route of administration as “for soft tissue instillation and periarticular instillation use”. Include the statement “Not for any other route of administration” to appear prominently on vial labels and all cartons.
- Revise the storage condition to “Store at 20°C to 25°C (68°F to 77° F) with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light.” on vial labels (if space permits) and all cartons.
- Provide details on how the assigned Lot numbers on each of the components of the kit (kit cartons, and vial cartons and labels) are capable of yielding the complete manufacturing history of the drug, required as per 21 CFR 201.18 Drugs; significance of control numbers.
- Revise the statement “Each vial delivers:” on vial cartons to “Each vial delivers up to:” on vial labels (if space permits) and all cartons.
- Revise the text for 60 mg /1.8 mg vial label and cartons as “Withdraw 2.3 mL to deliver 2 mL.” (b) (4)
- Include full street address after manufacturer/ distributor name on vial labels (if space permits) and all cartons, required per 201.1(i).

Overall Assessment and Recommendation:

As of this review, this application is not deemed ready for approval in its present form per 21 CFR 314.125(6) from the CMC labeling/labels perspective until the remaining deficiencies delineated in the **List of Deficiencies** above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Venkateswara R. Pavuluri, Ph. D., R. Ph.; 17-JUN-2020

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Julia C. Pinto, Ph.D.;
Branch Chief,
Branch 3 / DNDPII
ONDP/OPQ/CDER



Venkateswara
Pavuluri

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Julia
Pinto

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BIOPHARMACEUTICS

Product Background:

NDA: NDA 211988-ORIG-1-RESUB-40

Drug Product Name / Strength: ZYNRELEF (Bupivacaine and Meloxicam) Extended-Release Solution / 400 mg/12 mg, 200 mg/6 mg, 60 mg/1.8 mg

Route of Administration: Injection

Applicant Name: Heron Therapeutics, Inc.

Review Summary:

Heron Therapeutics, Inc. developed ZYNRELEF (Bupivacaine and Meloxicam) Extended-Release Solution and submitted the application under NDA 211988 to seek approval through 505(b)(2) regulatory pathways on 9/21/2019. The proposed drug product is indicated for (b) (4)

(b) (4) On 3/30/2019, a complete response (CR) letter was issued to NDA 211988. On 9/26/2019, the Applicant resubmitted this NDA to the Agency to address the deficiencies listed in the CR letter. From the Biopharmaceutics perspective, NDA 211988 for ZYNRELEF (Bupivacaine and Meloxicam) Extended-Release Solution was **adequate** for approval during the last review cycle.

(b) (4)

Biopharmaceutics review focuses on whether the (b) (4) data is scientifically acceptable.

Conclusion

From a Biopharmaceutics perspective, this Reviewer concludes that it is not acceptable for the Applicant to calculate maximum daily exposure of both bupivacaine and meloxicam based on the in vitro release data given that a valid IVIVC model was not established.

List Submissions being reviewed (table):

9/26/2019	NDA 211988/resubmission
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Highlight Key Outstanding Issues from Last Cycle: None.

Concise Description Outstanding Issues Remaining: None.

(b) (4)

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(b) (4)

Reviewer's comment:

It is not appropriate for the Applicant to calculate maximum daily exposure of both bupivacaine and meloxicam based on the in vitro release data. As discussed in the previous section, the Applicant did not establish an IVIVC model for their proposed drug products. Without an established IVIVC, the Applicant should not extrapolate data from in vitro to in vivo.

Primary Biopharmaceutics Reviewer Name:*Hansong Chen, PharmD, Ph.D.,**Biopharmaceutics Reviewer**OPQ/ONDP/DB*



Hansong
Chen

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Date: 2/24/2020 11:01:23AM

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MEMORANDUM



**U.S. FOOD & DRUG
ADMINISTRATION**

DATE: March 11, 2020

TO: NDA 211988 Amendment 40

FROM: Christine M. Craig, Ph.D.
Review Microbiologist
CDER/OPQ/OPMA/DMAI

THROUGH: Erika Pfeiler, Ph.D.
Branch Chief
CDER/OPQ/OPMA/DMAI

SUBJECT: Submission Date: 9/26/2019
Drug Product: ZYNRELEF (bupivacaine/meloxicam)
Sponsor: Heron Therapeutics, Inc.

The 9/26/2019 resubmission includes a response to the Agency's 4/30/2019 complete response letter. There were no DMA microbiology deficiencies in the last review cycle; however, the complete response letter included deficiencies from other disciplines, including a CDRH microbiology deficiency. The response to the CDRH deficiency is being assessed by the CDRH microbiologist. The 9/26/2019 resubmission also proposes to add a 300 mg/9 mg presentation of the drug product, for a total of four presentations displayed in the table below (Module 1.2, Cover Letter 2019-09-26, pg. 23).

Product Presentation			
Bupivacaine/meloxicam	Concentration (mg/mL)	Vial	Stopper
400 mg / 12 mg	29.5 mg/mL / 0.88 mg/mL	20 mL	20 mm
300 mg / 9 mg	29.5 mg/mL / 0.88 mg/mL	20 mL	20 mm
200 mg / 6 mg	29.5 mg/mL / 0.88 mg/mL	10 mL	20 mm
60 mg / 1.8 mg	29.5 mg/mL / 0.88 mg/mL	10 mL	20 mm

No changes are proposed to the drug product formulation and the newly proposed presentation will utilize the same container closure system as the 400 mg/12 mg presentation of the drug product. In addition, there are no proposed changes to the overall manufacturing process

(b) (4)

(b) (4) As such, the previously assessed sterility assurance validation information covers the proposed addition of a 300 mg/9 mg presentation of the drug product (see microbiology review N211988MR01.doc deemed adequate on March 7, 2019).



Christine
Craig

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Erika
Pfeiler

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Date: 6/17/2020 03:54:06PM

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DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	11/26/2019		
To:	Allison Meyer, RBPM Anika Lalmansingh, RPM		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From:	Florencia Wilson OPEQ/OHT3/DHT3C		
Through (Team):	Rumi Young, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division): *optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: NDA (b) (4) Case # 00011124 ICC1900822		
Recommendation:	Device Constituents Parts of the Combination Product are Approvable. The response to the CRL Deficiency is deemed to be adequate. It is noted that an additional dose presentation of 300mg/9mg is added, there are no changes to the administration kit content, therefore the additional presentation is Approvable.		

***Of note, words in *italics* are taken directly from the application.**

Digital Signature Concurrence Table		
Reviewer	Team Lead (TL)	Division (optional)

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	Case # 00011124
Consult Request Link	https://force-dsc.lightning.force.com/lightning/r/Case/500t000000JLZEBAA5/view
ICC tracking #	ICC1900822
Submission Number	NDA (b) (4)
Sponsor	Heron Therapeutics, Inc.
Drug/Biologic	Zynrelef (bupivacaine/meloxicam)
Indications for Use	management of postoperative pain
Device Constituent	Administration Kit (vented vial spike, luer lock syringe [3 mL, 12 mL], syringe tip cap, luer lock applicator)
Related Files	ICC1800971

Table 2. Review Team				
Were other disciplines consulted?			☒ Yes	☐ No
Below is a list of the Discipline Specific ICCR#, ICC# and CON#.				
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	Case #	ICC #	CON #
Sterility	David Wolloscheck	00011124	ICC1900822	CON1923757

2. CDRH REVIEW

ICC Review Request from CDER/OPQ, Other:	Please review the complete response submission dated 9/26/19
Device Presentation(s) being evaluated:	Administration Kit (vented vial spike, luer lock syringe [3 mL, 12 mL], syringe tip cap, luer lock applicator (LLA))
Objective of this Memo:	Evaluation of the following changes: The objective of this memo is to evaluate the provided response to the deficiency provided to the sponsor regarding the sterility information of the syringe tip cap.
Review Comments:	Response to CDRH Deficiency (syringe tip cap sterility): There are no outstanding deficiencies related to the sterility, bacterial endotoxin testing, and packaging of the seal tip cap. The Sponsor has provided summary level information for the tip cap consistent with recommendations set in the 2016 FDA guidance <i>Submission and Review of Sterility Information in Premarket Notification (510(k)) Submission for Devices Labeled as Sterile</i>. The provided information does not raise concerns regarding the safety of the accessory. Additional dose presentation of 300mg/9mg (10.5 mL):

	The response to the CRL letter stated that an additional dose of 300 mg / 9 mg (10.5 mL). This added presentation contains vented vial spike, luer lock syringe [12 mL], syringe tip cap, and luer lock applicator. The devices in the kit of the this newly added presentation is the same as the other presentation in which reviewed has been performed and found to be adequate. In this kit, the drug vial included is the 20 mL vial similar to the one included in the 400 mg/ 12 mg presentation. In addition, Luer lock syringe (b) (4) have graduations to provide control of dose delivery volumes within ± 0.5 mL for the 10 mL [nominal volume] (12 mL[max volume]) syringe. Therefore, there is no concern that the intended extracted volume (10.5 mL) per labeling will be achieved. The syringe included has graduation to ensure that the intended dose is extracted from the drug vial. As stated in the previous review, the hold up volume (residual volume) in the LLA has been evaluated and accounted for to ensure dose accuracy when the drug product is extracted from the vial. The consultant memo and the Salesforce link to the original review for this application is appended at the end of this memo under Section 3.2.
Review Recommendation:	The response to the CRL is adequate per the Sterility consultant. In addition, the Sponsor added a fourth dose presentation of 300 mg / 9 mg (10.5 mL) with no changes to the Administration Kit. Therefore, the device constituents parts of the Combination Product are Approvable.

Notes:

The NDA resubmission includes the addition of the 300 mg/9 mg product presentation. The additional product presentation is included to provide an additional option to healthcare providers for surgical procedures. Modules 1, 2 and 3 have been updated throughout to reflect 4 product presentations:

400 mg bupivacaine and 12 mg meloxicam in a 20 mL single-dose glass vial

300 mg bupivacaine and 9 mg meloxicam in a 20 mL single-dose glass vial

200 mg bupivacaine and 6 mg meloxicam in a 10 mL single-dose glass vial

60 mg bupivacaine and 1.8 mg meloxicam in a 10 mL single-dose glass vial

The following are taken from Seq. 0040/3.2.P.5., specifications pdf p. 3 of 4:

Table 1: Specification for HTX-011 Extended-Release Solution

Attribute	Acceptance Criteria		Method Reference
Sterility ^a	No growth		(b) (4)
Extractable Volume ^a	60 mg bupivacaine / 1.8 mg meloxicam	NLT (b) (4) mL	
	200 mg bupivacaine / 6 mg meloxicam	NLT (b) (4) mL	
	300 mg bupivacaine / 9 mg meloxicam	NLT (b) (4) mL	
	400 mg bupivacaine / 12 mg meloxicam	NLT (b) (4) mL	

Abbreviations: GPC, gel permeation chromatography; GC, gas chromatography; HPLC, high performance liquid chromatography; M_w, weight average molecular weight; M_n, number average molecular weight; LMW, low molecular weight; LC, label claim; NMT, not more than; NA, not applicable; AV, acceptance value; HILIC, hydrophilic interaction liquid chromatography; NLT, not less than; ppm, parts per million; USP, United States Pharmacopeia; Ph Eur, European Pharmacopoeia

^a Tested on release only

^b Tested on stability only

The following are taken from Seq. 0040/3.2.P.7., container closure system pdf p. 4 of 6:

Table 3: HTX-011 Co-Packaged Combination Product Kit Configurations

Bupivacaine (mg) / Meloxicam (mg)	NDC	Vial Size (mL)	Cap Color	Drug Product Vial	VVS	LLA	2 mL (3 mL) ^a Syringe	10 mL (12 mL) ^a Syringe	Syringe Tip Cap
60/1.8	47426-304-01	10	(b) (4)	1	1	1	1	0	1
200/6	47426-303-01			1	1	1	0	1	1
300/9	47426-302-02	20		1	1	1	0	1	1
400/12	47426-301-02			1	1	2	0	2	2

Abbreviations: NDC, National Drug Code; VVS, vented vial spike; LLA, Luer lock applicator; (b) (4)

^a The first number indicates the nominal volume of the syringe, and the number in parentheses indicates the maximum volume.

Component	Image	Description
Vented Vial Spike	(b) (4)	The vented vial spike is attached to the medication vial allowing for withdrawal of the medication.
Sterile Syringe		One or two sterile syringes are provided in the kit for withdrawal of the medication and administration.
Luer Lock Applicator		The Luer Lock Applicator is attached to the syringe for use during administration. One or two are provided in the kit depending on the dose.
Sterile Tip Cap		The sterile tip cap is attached to the sterile syringe when the syringe(s) is/are prepared in advance. One or two are provided in the kit depending on the dose.

---END OF REVIEW---

3. APPENDIX

3.1. DOCUMENTS REVIEWED

Sequence	Module
Seq 0040	1, 2, 3

3.2. Appendix

3.2.1. Sterility Review of the syringe tip cap for NDA 211988. This review was performed by David Wolloscheck, CDRH/OPEQ/OHT3/DHT3C/THT3C1. Please see the sterility review memo below.

	DEPARTMENT OF HEALTH & HUMAN SERVICES	Public Health Service Food and Drug Administration
Memorandum		
Sterility Review of an NDA		
Date:	December 9 th , 2019	
To:	Floencia Wilson, Lead Reviewer CDRH/OPEQ/OHT3/DHT3C/THT3C2	
From:	David Wolloscheck, PhD, Senior Staff Fellow CDRH/OPEQ/OHT3/DHT3C/THT3C1	
Re:	NDA 211988. Heron Therapeutics, Inc. Zynrelef	
Recommendation: Acceptable		
 I. SUMMARY There are no outstanding deficiencies related to the sterility, bacterial endotoxin testing, and packaging of the seal tip cap. The Sponsor has provided summary level information for the tip cap consistent with recommendations set in the 2016 FDA guidance <i>Submission and Review of Sterility Information in</i>		

Premarket Notification (510(k)) Submission for Devices Labeled as Sterile. The provided information does not raise concerns regarding the safety of the accessory.

II. SCOPE

The scope of this memorandum is the review of the CR response to deficiency #8 for this submission related to the sterilization, bacterial endotoxin testing, and packaging of the syringe tip cap. The tip cap is a class I exempt device that is reviewed since it is part of the NDA and has not received prior 510(k) clearance. The device is terminally sterilized and intended for single use.

III. BACKGROUND

This is a resubmission of a New Drug Application for Zynrelef by Heron Therapeutics. The product is a drug-device combination and consists of the drug substance and a co-packaged (b) (4) two 510(k) cleared luer lock syringes (b) (4) a Syringe tip cap, and a custom Luer Lock Applicator. The NDA received a CR letter in part due to a lack of sterilization information for the syringe tip cap (CR deficiency #8).

IV. INDICATIONS FOR USE

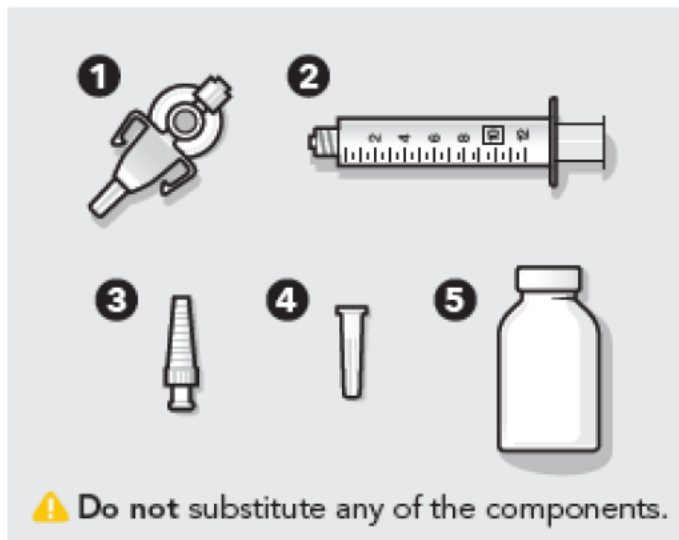
“Management of Postoperative Pain.”

V. DEVICE DESCRIPTION

The device is a syringe tip cap cover. The tip cap is used when the drug is prepared in advanced to avoid contamination of the medication. The following is an excerpt from the IFUs describing the use of the accessory:

For Operating Room Preparation

It is recommended that a 2-person team prepare this product: one sterile person and one non-sterile person. If product is prepared in advance of surgery, a syringe tip cap 4 may be used to cap the syringe until ready for application. Before administration, remove the syringe tip cap and attach the Luer lock applicator 3 .



(b) (4)

(b) (4)

VI. STERILIZATION, PACKAGING, SIMULATED SHIPPING AND DISTRIBUTION, STABILITY (SHELF LIFE), AND PACKAGE INTEGRITY TESTING

The Sponsor provided information regarding sterilization in Module 3.2.R.4 of the NDA.

Table 1 shows the Sterility Check List as part of the sterility review.

Table 1. Sterility Check List

(b) (4)

(b) (4)	N/A
2. A description of the Validation Method for the (b) (4) (not data): (Full citation of an FDA recognized standard is recommended including date (e.g., ANSI/AAMI/ISO 11135:2007)),	ISO 11137-1:2006(R)2013 and ISO 11137-2:2013. (b) (4)
3. Sterility assurance level (SAL): (b) (4)	(b) (4)
4. Is it labeled “Non-pyrogenic”?	Yes
a. If so, a description of the method: (e.g., LAL (<i>Limulus</i> Amebocyte Lysate test))	USP <85> and <161>
b. A statement confirming that endotoxin testing will be conducted on every batch or if not, information regarding the sampling plan used for in-process testing and/or finished product release, as recommended in the FDA guidance, Pyrogen and Endotoxins Testing: Questions and Answers”	Yes
c. Identification of the chosen testing limit	(b) (4) EU/device
d. An explanation supporting the selected endotoxin limit	USP <161>
5. Packaging a. A description of the packaging (not including package integrity test data):	(b) (4)
b. Description of the package test methods	Visual Inspection (ASTM F1886M-16), Dye Penetration (ASTM F1929-15 (b) (4)), Bubble Leak (ASTM F2096-11), Seal Strength (ASTM F88/F88M-15 (b) (4))

A. Sterilization

(b) (4) provided summary level information regarding the sterilization similar to what is normally requested as part of a 510(k) review per the 2016 FDA guidance *Submission and Review of Sterility Information in Premarket Notification (510(k)) Submission for Devices Labeled as Sterile*. The information is summarized in the table above and is acceptable.

B. Endotoxin

Summary information regarding bacterial endotoxin testing was provided (b) (4). The information is consistent with the 2016 FDA sterility guidance and is acceptable (see table above).

C. Packaging

(b) (4) stated that the packaging consists of (b) (4). The following image of the device (b) (4) was provided:

BD Tip Cap in Sterile Barrier System**D. Simulated Shipping and Aging and associated Packaging Integrity Testing**

The Sponsor conducted testing of the packaging after shipping and accelerated aging. The Sponsor stated that the testing was done (b) (4). Please note that this is not acceptable, (b) (4).

(b) (4). However, Heron stated that (b) (4) conducted simulated shipping and subsequent package integrity testing. Hence, this is acceptable. Aging was done (b) (4) with a stated storage temperature (b) (4). Assuming a Q₁₀ value of (b) (4), the conducted aging is acceptable per ASTM F1980-16 *Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices* and is representative of the stated (b) (4) shelf-life. After aging and shipping, the Sponsor conducted a visual

inspection per ASTM F1886M016, Dye Penetration Testing per ASTM F1929-15, Bubble leak testing per ASTM F2096-11, and Seal Strength testing per ASTM F88-15. The Sponsor did not report an acceptance criterion for seal strength testing but compared the strength of the seal at (b) (4) years. The following is a comparison of the average seal strength at the stated timepoints:

Accelerated Age	Results for Each Year	
	Baseline (T=0)	(b) (4)
Average (lb _f /in) (Standard Deviation)		(b) (4)

Abbreviation: lb_f/in, pound force per inch

The reported values for seal strength are consistent with what is typically reported for this type of packaging and is acceptable. Since the seal strength does not appear to decrease over time, the reported results are acceptable.

The Sponsor reported no failures for the visual inspections, dye penetration, and bubble test. Hence, the packaging data is acceptable.

VII. Deficiencies

N/A

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CDRH/OPEQ/OHT3/DHT3C/THT3C1

ICC1900822

NDA (b) (4) Zynrelef (bupivacaine/meloxicam), Administration Kit
Heron Therapeutics, Inc.

The original memo from the CDRH Device Reviewer and the OC Reviewer is uploaded in Salesforce. Please see the link below:

<https://force-dsc.lightning.force.com/lightning/r/Case/500t000000JLZEBA5/view>

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Devices and Radiological Health

Office of Compliance (OC)

Date: March 6, 2019

To: Anika Lalmansingh, RBPM

CC: Ogochukwu Ogoegbunam, RPM, Office, Location,
Office of Combination Product at: combination@fda.gov

From: Florencia Wilson, Lead reviewer, CDRH/ODE/DAGRID/GHDB
Payal Patel, OC Consultant, Office of Health Technology 3

Applicant/Licensure: Heron Therapeutics, Inc

Submission (Type & Number): NDA 211988

Combination Product Name: Zynrelef

Combination Product bupivacaine and meloxicam to be administered via an administration kit

Intended Use: management of postoperative pain

Device Constituent (Type): Administration Kit (vented vial spike, luer lock syringe [3 mL, 12 mL], syringe tip cap, luer lock applicator)

CTS ICCR Number: ICC1800678

SharePoint ICCR Number: ICCR2018-04044

ICCR Instruction (ICCR Form): new NDA

Pre-Approval Facility

Inspection:

CDRH/OC Recommendation: due to the (b) (4) device component being used for this application **we recommend a PAI.**

This portion of the consult for CON1830617 - ICC1800971 (NDA 211988 from Heron Therapeutics, Inc. for HTX-011), is for a **determination of device facility inspection.**

HTX-011 is an extended-release, fixed-dose combination product that contains bupivacaine and low-dose meloxicam. It is a co-packaged combination drug-device product that includes a vial of HTX-011 packaged with devices intended for preparation and delivery of the drug. The primary mode of action of the combination product is based on the drug constituents. It is administered as a single dose that is applied into the surgical site to coat the affected tissues. HTX-011 is applied without a needle using a syringe with an applicator attached.

HTX-011 is assembled in a co-packaged combination product kit with the drug product vial and all components required for preparation and administration of the product. The packaging configurations are determined based on the presentation as outlined in 3.2.P.7). Each HTX-011 vial is labeled and

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Office of Compliance (OC)

packaged in a vial carton. One vial carton is kitted along with a vented vial spike (VVS), Luer lock syringe(s), Luer lock applicator(s) (LLA), and syringe tip cap(s). The applicant states “all components other than the LLA are commercially available, off-the-shelf, CE marked, pharmaceutical delivery support components that are legally marketed, with established usage histories and safety profiles. The VVS and Luer lock syringe are 510(k) cleared, and the sterile tip is a Class I exempt device”. The LLA was designed (b) (4)

(b) (4) The LLA is a device that is manufactured for the combination product kit and included for review and approval in this application, and is manufactured at a contract manufacturing site, (b) (4) (FEI: (b) (4)).

As the LLA is a **component** of the final finished combination product, and (b) (4) is not the final kit assembling manufacturer, a facilities **inspection of this facility is not recommended** for this site. The applicant has identified two (2) facilities that are responsible for the packaging and labeling of co-packaged combination product kit as stated below. The activities for Secondary Packaging conducted at these facilities is listed in 3.2.P.3.3.1.5, (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4) (FEI: (b) (4)) – The previous inspection was conducted (b) (4) and found NAI for a combination product post-approval inspection (b) (4) the firm assembles, packages and labels (b) (4) in accordance with drug and device inspection (following the QSIT inspections). This firm assembles, packages and labels (b) (4) The QSIT inspection covered CAPA and Production and Process Controls (b) (4)

(b) (4) This is similar to the current responsibilities of (b) (4) in this application.

The previous inspection was conducted (b) (4) and found NAI (b) (4) the QSIT inspection was conducted covering CAPA and Production and Process Controls. **A device inspection (b) (4) is not recommended at this time.**

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(b) (4) (FEI: (b) (4)) – The previous inspection was conducted (b) (4) and found NAI for an initial inspection for the site after the firm's relocation. At that time the firm was acting as a primary and secondary packaging facility of finished drug products (b) (4). The drug cGMP portion of that inspection covered Quality, Facility and Equipment, Materials, Packaging and Labeling systems. A device Post-Approval Inspection is recommended for this facility, specifically covering the CAPA (21 CFR 820.100) and Production and Process Controls (21 CFR 820.70) systems.

Let me know if you have any follow up questions, I will continue with the QS review. Please let me know when you need that by and if possible update the consult to reflect that date.

Rationale for PAI recommendation:

(b) (4) (FEI: (b) (4)) the firm responsible for (b) (4)

1. (b) (4)
(b) (4) This inspection was however found VAI, there is no noted follow up for this observation. (b) (4) and due to the (b) (4) device component being used for this application we recommend a PAI.

Additional Comments (April 16, 2019)

On 4/12/19 Yoon Oh from CDER provided us a copy of the FDA 483 Observation for the PAI for NDA 211988 for (b) (4) (FEI: (b) (4)), since the inspection just closed the EIR report has not been provided for review. The investigator noted one observation during the inspection (b) (4)

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(b) (4)

I have no additional concerns regarding this facility at this time and support the Approve Facility recommendation from the investigator. However, I would like to read the final EIR with regards to the follow up on the complaints.

Digital Signature Concurrence Table	
Reviewer	
Team Lead	
Branch Chief	

ATTACHMENT I: Final Risk Assessments

[IQA Review Guide Reference](#)

A. Final Risk Assessment – NDA 211988

- a) **Drug Product: ZYNRELEF™** (Bupivacaine and Meloxicam) solution; 60 mg/1.8 mg, 200 mg/6 mg, 300mg/9mg and 400 mg/12 mg.

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
		H, M, or L		Acceptable or Not Acceptable	
Assay, stability (APIs)	Stability of the drugs (APIs) in solid state	Moderate	(b) (4)	Acceptable	
Physical stability (Drug Product)	Drug(s) in dissolved state	High		Acceptable	
Degradation Products (Drug Product)	Drug(s) in dissolved state, (b) (4) manufacturing	High		Acceptable	
Content uniformity	Highly Viscous solution	Moderate		Acceptable	
Microbial Limits	(b) (4)	High		Acceptable	
In Vitro Release (ER Solution)	Modified In Vitro Release (IVR) methods employed for quality control	Medium		Acceptable	
Extractables and Leachables	(b) (4)	High		Acceptable	

	(b) (4)		(b) (4)		
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Venkateswara
Pavuluri

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Date: 6/18/2020 08:30:52AM

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Recommendation: Complete Response**NDA 211988****Review 1**

Drug Name/Dosage Form	Zynrelef (bupivacaine and meloxicam) Extended Release Solution
Strength	400 mg/12 mg, 200 mg/6 mg, 60 mg/1.8 mg
Route of Administration	(b) (4)
Rx/OTC Dispensed	Rx
Applicant	Heron Therapeutics, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0002	30-OCT-2018	All OPQ Disciplines and CDRH
0007	29-NOV-2018	CDRH
0008	12-DEC-2018	CDRH
0012	08-JAN-2019	Process
0013	10-JAN-2019	CDRH
0015	16-JAN-2019	Process
0017	22-JAN-2019	All OPQ Disciplines
0018	23-JAN-2019	CDRH
0019	24-JAN-2019	Process, CDRH
0020	28-JAN-2019	Process, CDRH
0023	31-JAN-2019	CDRH
0024	06-FEB-2019	Process, CDRH
0027	13-FEB-2019	Drug Product
0028	21-FEB-2019	Process
0030	25-FEB-2019	Drug Product and Process
0031	28-FEB-2019	Drug Product, Biopharm.
0035	14-MAR-2019	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Joe Leginus	Donna Christner
Drug Product	Venkat Pavuluri	Julia Pinto
Process	Yoon Oh	Pei-I Chu
Microbiology	Christine Craig	TBD
Facility	Yoon Oh	Jonathan Swoboda
Biopharmaceutics	Hansong Chen	Kelly Kitchens
Regulatory Business Process Manager	Anika Lalmansingh	N/A
Application Technical Lead	Venkateswara Pavuluri	N/A
Laboratory (OTR)	Xiaofei Liu; Cindy Diem Ngo	Cynthia Sommers, Method Verification Coordinator
ORA Lead	Caryn McNab	Michael Tollon
Environmental	N/A	N/A

Quality Review Data Sheet

[IQA Review Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	11-DEC-2018	
	Type II			Adequate	13-JUN-2019	
	Type III (if applicable)					Adequate information included in submission
	Type III (if applicable)					Adequate information included in submission
	Type III (if applicable)					Adequate information included in submission
	Other 510(k)					510(k) cleared for marketing
	Other 510(k)					510(k) cleared for marketing

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	125927	Basis for NDA 211988
NDA	016964	RLD, MARCAINE™ (bupivacaine HCl) injection, USP
NDA	020938	RLD, MOBIC® (meloxicam) tablets

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			

CDRH	Complete	NOT APPROVABLE	26-MAR-2019	Florencia Wilson
Clinical	NA			
Other (Method Verification by OTR)	Complete	Acceptable	06-MAR-2019	Cynthia Sommers
CDRH OC - Device Facility Inspection: (b) (4) (FEI: (b) (4))	Complete	Approve Facility	16-APR-2019	Payal Patel

Executive Summary

[IQA Review Guide Reference](#)

I. Recommendations and Conclusion on Approvability

Based on evaluation of quality information provided in the NDA original submission with subsequent amendments to date (SN#0002 to #0035) and the recent pre-approval inspection of drug product manufacturing facilities

(b) (4) **NDA 211988 for ZYNRELEF™ (bupivacaine and meloxicam) Extended-release solution is NOT APPROVABLE** from quality (CMC) perspective. The deficiencies are outlined below.

1. Leachables study data is inadequate to support the proposed shelf-life of the drug product.
2. Sterility assurance of the syringe tip cap was established at release and through the end of shelf-life of the component approved under 510(k).
3. Deficiencies identified in facility inspection for (b) (4) (FEI: (b) (4)) manufacturing facility.

II. Summary of Quality Assessments

A. Product Overview

ZYNRELEF™ (bupivacaine and meloxicam) Extended-release solution is a co-packaged combination product consisting of a vial, containing sterile non-aqueous viscous extended-release solution of bupivacaine and meloxicam, in a carton, along with device components required for preparation and administration. ZYNRELEF™ is supplied in three different dose strengths, i.e. 60 mg/1.8 mg, 200 mg/6 mg, or 400 mg/12 mg of bupivacaine base and meloxicam respectively, filled in either a 10 mL or 20 mL (b) (4) clear glass vials, closed with a (b) (4) stopper and secured with an aluminum seal with flip-off cap. Other device components included in the kit for preparation and application of the drug solution include syringe(s), tip cap(s), vented vial spike [VVS], Luer lock applicator(s) [LLA(s)], and Instructions for Use. The syringes are made of (b) (4) barrel and (b) (4) piston; the tip cap and LLAs are made of (b) (4); and VVS are made of (b) (4) materials.

NA

**Total Number of Comparability Protocols (ANDA only)**

Proposed Indication(s) including Intended Patient Population	(b) (4)
Duration of Treatment	One-time use during surgery
Maximum Daily Dose	400 mg Bupivacaine and 12 mg meloxicam

Alternative Methods of Administration	None, Bupivacaine was earlier approved for parenteral use, while meloxicam was only approved for oral use
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B. Quality Assessment Overview

The drug product is a sterile solution for instillation into surgical wound comprising Bupivacaine and Meloxicam. The drug substances are referenced to DMF (b) (4) (Bupivacaine) and DMF (b) (4) (Meloxicam) that were reviewed as adequate to use in the manufacture of the drug product. Bupivacaine has a retest period of (b) (4) months (b) (4) years) and meloxicam has a retest period of (b) (4) months (b) (4) years). (b) (4) is considered a novel excipient, for which the applicant has provided adequate information on synthesis and characterization of impurities and toxicological assessment. The drug product is prepared (b) (4)

(b) (4) In-use compatibility of the various device components with the drug product during preparation and use is adequately tested. **However, enough information is not provided in the submission, to ensure that the tip cap (a 510(k) cleared device component will be provided sterile and will remain sterile throughout its shelf-life and the device is safe for use.**

Upon inspection of the drug manufacturing facility ((b) (4) FEI: (b) (4)), deficiencies were identified, because the (b) (4) study (b) (4) has not been completed. Analytical methods used for monitoring the quality of the drug substances and finished drug product, including tests for sterility and endotoxin content are adequately validated. Suitability of primary container closure system (CCS), clear USP (b) (4) glass vials (b) (4) 20 mm (b) (4) stoppers (b) (4)

(b) (4) is adequately justified through stability testing of the finished drug product. **However, the assessment of leachables entering the drug product, during processing from manufacturing equipment components in contact with drug product and component of primary CCS during shelf storage were not adequately monitored.**

Therefore, the following deficiencies have been identified:

- 1. The testing of leachables (b) (4) during stability testing, without initial test data is not adequate to establish suitability of the CCS, components of the manufacturing equipment used and the shelf-life of drug product.**
- 2. Enough information was not provided in the submission, to ensure that the tip cap will be provided sterile and will remain sterile throughout its shelf-life and the device is safe for use.**

3. Deficiencies identified in facility inspection for (b) (4) (FEI: (b) (4)) manufacturing facility.

C. Special Product Quality Labeling Recommendations (NDA only)

Not applicable for NDA receiving a complete response

D. Final Risk Assessment (see Attachment)

The OPQ deficiencies affecting NDA approval are as noted above. Refer the IQA document attached for discipline specific reviews and list of all deficiencies to be sent to Sponsor.

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BIOPHARMACEUTICS**Product Background:**

NDA: NDA 211988

Drug Product Name / Strength: ZYNRELEF (Bupivacaine and Meloxicam) Extended-Release Solution / 400 mg/12 mg, 200 mg/6 mg, 60 mg/1.8 mg

Route of Administration: Injection

Applicant Name: Heron Therapeutics, Inc.

Review Recommendation: Adequate***Review Summary:***

Heron Therapeutics, Inc. developed ZYNRELEF (Bupivacaine and Meloxicam) Extended-Release Solution and submitted the application under NDA 211988 to seek approval through the 505(b)(2) regulatory pathway. The proposed drug product is indicated for (b) (4)

(b) (4)

The Biopharmaceutics review focuses on the In Vitro Release (IVR) method development, IVR data, IVR acceptance criteria, and Extended Release Claim.

The proposed IVR method was reviewed and found acceptable. The IVR method has some discriminatory power based on the *in vitro* study conducted.

The following acceptance criteria were recommended by the Agency and accepted by the Applicant:

Bupivacaine

6 hours: (b) (4) %

24 hours: (b) (4) %

(b) (4) hours: NLT (b) (4) %

Meloxicam

6 hours: (b) (4) %

30 hours: (b) (4) %

(b) (4) hours: NLT (b) (4) %

From the Biopharmaceutics perspective, this Reviewer concludes that NDA 211988 for ZYNRELEF (Bupivacaine and Meloxicam) Extended-Release Solution is **adequate** for approval.

List Submissions being reviewed (table):

9/21/2018	NDA 211988/Original submission
1/22/2019	eCTD-0017/Response to Biopharmaceutics Information Requests
2/28/2019	eCTD-0031/Response to Biopharmaceutics Information Requests

Highlight Key Outstanding Issues from Last Cycle: None.

Concise Description Outstanding Issues Remaining: None.

BCS Designation

Reviewer's Assessment: N/A since the drug product is an injectable solution.

IVR Method and Acceptance Criteria

Reviewer's Assessment: Adequate

1. Component and composition of Drug Product

Table 1. Composition of HTX-011 Extended-Release Solution

Component	Concentration (% w/w)	Concentration (mg/g)	Concentration (mg/mL)	Function	Reference to quality standard
Bupivacaine base	2.50	25.0	29.25	Active ingredient	Manufacturer
Meloxicam	0.75	0.75	0.88	Active ingredient	USP, Ph Eur
AP 135	62.375	623.75	729.788	Release-controlling agent	Manufacturer
Dimethyl sulfoxide	10.00	100	117	(b) (4)	USP, Ph Eur
Triacetin	25.00	250	292.5		USP, Ph Eur
Maleic acid	0.05	0.5	0.585		NF, Ph Eur
Total	100	1000.00	1170		

Abbreviations: AP135, tri (ethylene glycol) poly(orthoester); USP, United States Pharmacopeia; Ph Eur, European Pharmacopoeia; NF, National Formulary

ZYNRELEF (Bupivacaine and Meloxicam) Extended-Release Solution(HTX-011) is a fixed dose combination product, which contains two active ingredients: bupivacaine and meloxicam. HTX-011 is filled in 10 mL or 20 mL of vial and intended for a single dose local administration into the surgical site. Of the inactive ingredients, AP 135 (tri (ethylene glycol) poly(orthoester)) is a highly viscous polymer, which controls the release of both APIs.

2. In Vitro Release (IVR) method

The Applicant developed the following IVR method for HTX-011 Extended-Release Solution:

Table 2. The proposed IVR method

Apparatus	A rotating forced air incubator with custom-machined inserts
Speed	(b) (4) rpm
Dissolution media	Phosphate-buffered saline (PBS), pH 7.4
Volume	100 mL
Sampling Time Points	(b) (4) hours
Temperature	37 ± 0.5 °C
Proposed acceptance criteria	Bupivacaine 6 hours: (b) (4) % (b) (4) hours: (b) (4) % (b) (4) hours NLT (b) (4) % Meloxicam 6 hours: (b) (4) % 30 hours: (b) (4) % (b) (4) hours NLT (b) (4) %

(b) (4)

(b) (4)

3. IVR method development

The Applicant stated that the IVR method was developed (b) (4)
(b) (4) A full IVR method development report was
included in 3.2.P.2 Pharmaceutical Development.

(b) (4)

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Reviewer's comments

The Applicant used supporting data to demonstrate (b) (4) the IVR method. The proposed IVR method is acceptable.

It is also acceptable not to include additional time points between 6 and 24 hours only because the Applicant provided sufficient data (b) (4)

4. Drug release mechanism

Drug release from the proposed extended release solution might be involved with the following mechanisms: (b) (4)

However, the Applicant stated that the release of both bupivacaine and meloxicam from the solution is mainly (b) (4) due to the following reasons:

(b) (4)

Figure 6. Release Rates in mg/h (Bupivacaine) or µg/h (Meloxicam) (b) (4)
(b) (4) of IVR Method

(b) (4)

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5. Discriminatory power

a. Discriminatory power towards Non-Equivalent Formulations

During the development stage, the Applicant developed two different formulations: HTX-011-56 and HTX-011-49. (b) (4)

The side-to-side comparison between these two formulations are listed in the following table. The results show that these two formulations have significantly different IVR profiles.

Table 5. Composition comparison between HTX-011-56 and HTX-011-49

(b) (4)

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Figure 11. IVR Profiles (b) (4) rpm) for 2 Different Formulations, HTX-011-56 and HTX-011-49 (Top: Bupivacaine; Bottom: Meloxicam)



Reviewer's comments:

AP135 is a release controlling polymer. (b) (4)

(b) (4) based on the calculated similarity factors ($f_2=30.83$ for bupivacaine and $f_2=25.24$ for meloxicam). The results do demonstrate that the IVR method is able to discriminate differences in AP135 amount.

Since the Applicant did not conduct a BE study to compare HTX-011-56 and HTX-011-49; it is not clear if they are not bioequivalent. Therefore, it is unclear if the proposed IVR method is able to reject product that is not bioequivalent to the reference-target drug product.

For discriminatory power study, we expect the meaningful variations for the most relevant critical material attributes, critical formulation variables, and critical process parameters (e.g., ± 10 -20% change to the specified values or ranges for these variables). In this case, the relative change of AP135 in HTX-011-49 is about (b) (4)% compared with that of the target formulation and within the expected variation range. (b) (4). We could not ensure if the change in the amount of AP135 only has a significant impact on IVR profiles.

b. Discriminatory power towards the changes in manufacturing process

During the manufacture of development lots, HTX-011-56 was subjected (b) (4)

(b) (4) The details are listed in Table 6. The data show that the lots manufactured (b) (4) have similar release profiles.

Table 6. (b) (4) Data from Development Lots of HTX-011-56

(b) (4)

Reviewer's comments:

Different lots manufactured (b) (4) have similar IVR profiles based on the calculated similarity factors, $f_2s > 50$. Therefore, the IVR method is not able to discriminate the changes (b) (4)

Figure 12. IVR Profiles for HTX-011-56 Subjected (b) (4) During Manufacture (Top: Bupivacaine; Bottom: Meloxicam)

(b) (4)

C. Discriminatory power towards the changes in viscosity

The Applicant intentionally manufactured the lots with different viscosities (b) (4)

(b) (4) The release data of these lots are listed in Tables 7 and 8.

Table 7. Average % Bupivacaine Released at Each Timepoint as a Function of HTX-011-56 Viscosity (n=6)

(b) (4)

Table 8. Average % Meloxicam Released at Each Timepoint as a Function of Viscosity (n = 6)

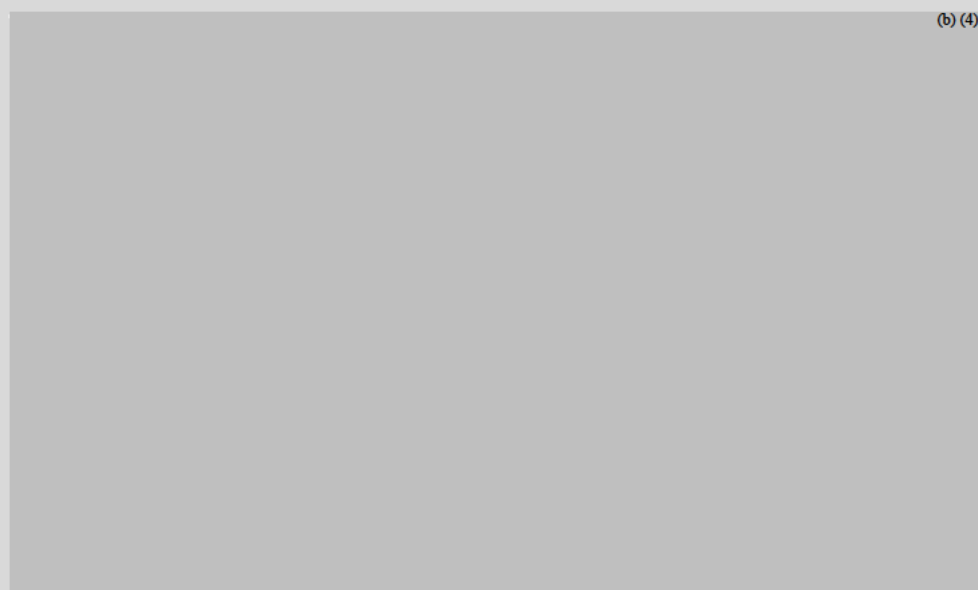
(b) (4)



Figure 13. Bupivacaine IVR profile comparison between the lots with different viscosities



Figure 14. Meloxicam IVR profiles comparison between the lots with different viscosities



Reviewer's comments:

The Applicant set the following viscosity acceptance criteria for their product. (b) (4)

(b) (4)

(b) (4)

The data show that (b) (4)

(b) (4)

(b) (4) the proposed IVR method is not sensitive enough to discriminate the changes in the viscosity of the drug product.

6. IVR data and acceptance criteria

Table 9. Lot Information of clinical batches

Batch number	Bupivacaine/ Meloxicam (mg/mg)	Vial size (mL)	Manufacture date	Use
026301	400/12	20	June 2016	Registration Stability and Clinical Studies 102, 202, 203, 208, 209, 211
026476	200/6	10	Nov 2016	Registration Stability and Clinical Study 301
026568	400/12	20	Jan 2017	Registration Stability, Clinical Studies 209, 211, and 302
026709	400/12	20	May 2017	Clinical Study 302

The Applicant used the proposed IVR method to conduct IVR tests on the above clinical lots; however, these lots were already 12 months to 24 months old when the tests were conducted. The detailed information is listed in Table 10.

Table 10. Age of Clinical Lots at time of IVR testing

Clinical lot number	Age at Time of Testing (months)
026301	24
026476	15
026568	15
026709	12

Table 11. Mean Bupivacaine IVR data of clinical lots

Lot number/Time (h)	(b) (4)
026301	
026476	
026568	
026709	

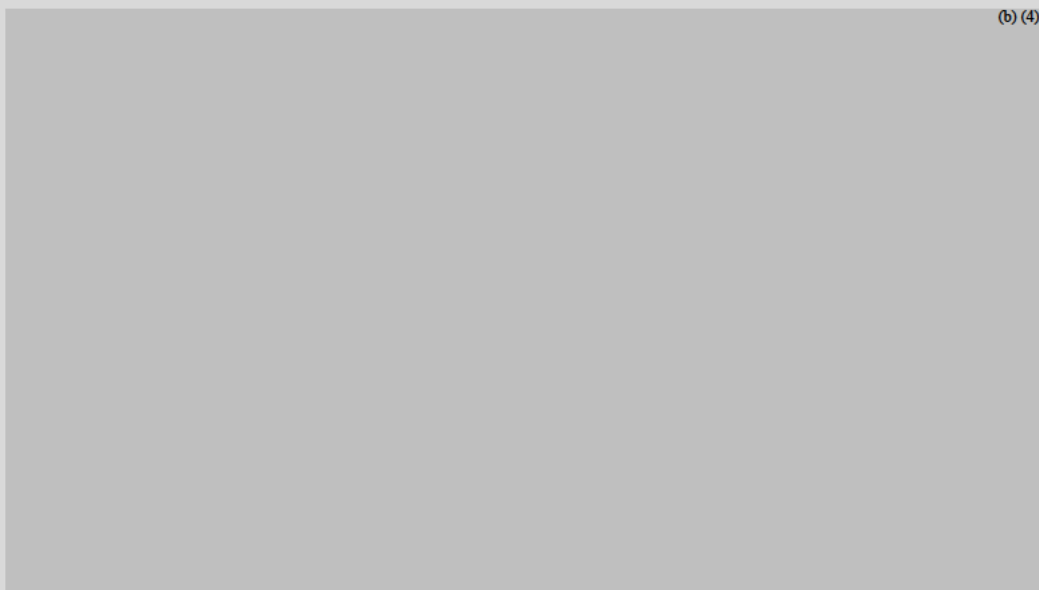
Table 12. Mean Meloxicam IVR data of clinical lots

Lot number/Time (h)	(b) (4)
026301	(b) (4)
026476	
026568	
026709	

Figure 15. Mean Bupivacaine IVR profile comparison of clinical lots



Figure 16. Mean Meloxicam IVR profile comparison of clinical lots



Reviewer's comments:

The complete IVR data for the above clinical batches were provided in Module 3.2.P.5.3, which were generated using the proposed regulatory in vitro release method (i.e. rotation speed = (b) (4) rpm). However, when the in vitro release tests were conducted, these batches were at least 12 months old. The acceptance criteria should be established based on the data of the fresh clinical batches; therefore, the Applicant was requested to provide the complete IVR data of some fresh batches.

In the response to Biopharmaceutics IR 1, the Applicant provided the complete IVR data of 9 validation batches, which were manufactured recently and tested immediately after they were released (Table 13).

Table 13. Lot Information of validation batches

Batch number	Bupivacaine/ Meloxicam (mg/mg)	Vial size (mL)	Manufacture date	Test date
027563	400/12	20	Sep 2018	Oct 2018
027564	400/12	20	Sep 2018	Oct 2018
027565	400/12	20	Sep 2018	Oct 2018
027566	200/6	10	Sep 2018	Oct 2018
027567	200/6	10	Oct 2018	Nov 2018
027568	200/6	10	Oct 2018	Dec 2018
027700	60/1.8	10	Oct 2018	Nov 2018
027701	60/1.8	10	Oct 2018	Nov 2018
027702	60/1.8	10	Oct 2018	Dec 2018

Table 14. Mean Bupivacaine IVR data of validation batches

Lot number/Time (h)	(b) (4)					
027563	17	56	64	85	89	95
027564	16	55	64	84	89	94
027565	15	55	62	84	87	94
027566	15	52	59	82	86	95
027567	16	50	58	80	86	95
027568	15	54	62	85	89	95
027700	14	52	60	83	88	95
027701	15	55	65	85	89	94
027702	16	56	65	87	91	96

Table 15. Mean Meloxicam IVR data of validation batches

Lot number/Time (h)	(b) (4)					
027563	11	46	57	86	92	98
027564	11	45	56	86	93	99
027565	11	45	54	84	89	98
027566	10	41	50	79	84	96

027567	11	40	49	77	84	97
027568	10	44	53	83	88	95
027700	10	42	52	83	89	98
027701	10	45	57	88	93	99
027702	11	46	58	90	96	103

The Applicant initially proposed the following IVR acceptance criteria:

Bupivacaine

6 hours: (b) (4) %

(b) (4) hours: (b) (4) %

(b) (4) hours: NLT (b) (4) %

Meloxicam

6 hours: (b) (4) %

30 hours: (b) (4) %

(b) (4) hours: NLT (b) (4) %

However, the IVR data provided show that the proposed acceptance criteria were inadequate.

Because the IVR data of Batch 026709 are comparable to those of validation batches (Figures 17 and 18), this Reviewer used the Division of Biopharmaceutics Automation tool to analyze its data and recommended the following dissolution acceptance criteria:

Bupivacaine

6 hours: (b) (4) %

24 hours: (b) (4) %

54 hours: NLT (b) (4) %

Meloxicam

6 hours: (b) (4) %

30 hours: (b) (4) %

54 hours: NLT (b) (4) %

The middle specification time point is recommended (b) (4)

(b) (4) Thus, the middle specification time point for bupivacaine was recommended to be 24 hours instead of (b) (4) hours. For the last time point, 54 hours is more appropriate than (b) (4) hours for both bupivacaine and meloxicam, because all exhibit batches have a mean drug release of $\geq$ (b) (4) % at 54 hours.

Figure 17. Mean Bupivacaine IVR profile comparison of clinical Lot 026709 and validation lots

(b) (4)

Figure 18. Mean Meloxicam IVR profile comparison of clinical Lot 026709 and validation lots

(b) (4)

The above recommended IVR acceptance criteria for bupivacaine are appropriate. Based on the data of Clinical Batch 026709 and Validation Batch 027567 (the worst scenario), this Reviewer used the Division of Biopharmaceutics Automation tool to simulate the passing rate of the recommended IVR acceptance criteria at different stages for both bupivacaine and meloxicam. The results show that the passing rates are 100% and 100% at Stage 1 and Stage 2, respectively (Tables 16 and 18).

For meloxicam, the simulation results based on the data of Clinical Batch 026709 show that the passing rates are 100% and 100% at Stage 1 and Stage 2, respectively (Table 17). However, Validation Batch 027567 has only (b) (4)% chance to meet the criteria at Stage 1 (Table 19). Therefore, the recommended acceptance criteria for meloxicam seem stringent.

Table 16. Simulation results based on the bupivacaine IVR data of Clinical Batch 026709

Pass Level 1 (%)	Pass Level 2 (%)	Pass Level 3 (%)	No. of simulations
100.00	100.00	100.00	100

Table 17. Simulation results based on the meloxicam IVR data of Clinical Batch 026709

Pass Level 1 (%)	Pass Level 2 (%)	Pass Level 3 (%)	No. of simulations
100.00	100.00	100.00	100

Table 18. Simulation results based on the bupivacaine IVR data of Validation Batch 027567

Pass Level 1 (%)	Pass Level 2 (%)	Pass Level 3 (%)	No. of simulations
100.00	100.00	100.00	100

Table 19. Simulation results based on the meloxicam IVR data of Validation Batch 027567

Pass Level 1 (%)	Pass Level 2 (%)	Pass Level 3 (%)	No. of simulations
(b) (4)	(b) (4)	100.00	100

If (b) (4) hours is selected as the last time point (i.e. NLT (b) (4)% in (b) (4) hours), both Clinical Batch 026709 and Validation Batch 027567 have a 100% passing rate for the recommended acceptance criteria at Stage 1 (Tables 20 and 21).

Table 20. Simulation results based on the meloxicam IVR data of Clinical Batch 026709

Pass Level 1 (%)	Pass Level 2 (%)	Pass Level 3 (%)	No. of simulations
100.00	100.00	100.00	100

Table 21. Simulation results based on the meloxicam IVR data of Validation Batch 027567

Pass Level 1 (%)	Pass Level 2 (%)	Pass Level 3 (%)	No. of simulations
100.00	100.00	100.00	100

But for consistency, we recommended changing the last time point for Meloxicam from (b) (4) hours to 54 hours. The actual IVR data of Validation Batch 027567 show that it can meet the criteria at Stage 2.

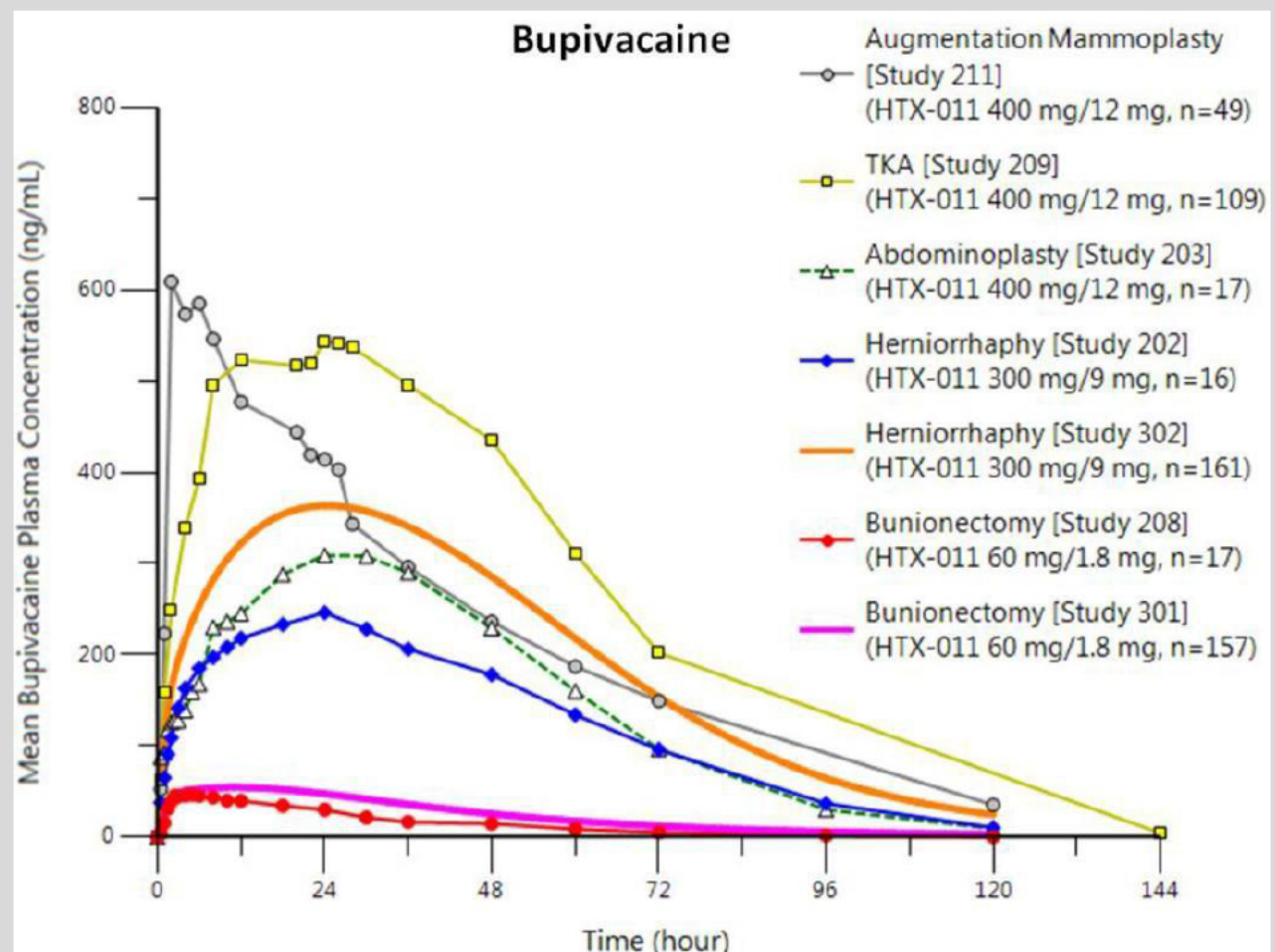
In the response to Biopharmaceutics IR II, the Applicant stated that they accepted the recommended IVR acceptance criteria.

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim**Reviewer's Assessment: Adequate****a. The bioavailability profile established for the drug product rules out the occurrence of any dose dumping**

HTX-011 formulation contains the release controlling agent - AP135, which enables extended release of bupivacaine and meloxicam simultaneously for about 3 days and eliminates the risk of any dose dumping.

Based on the population PK modeling of the bupivacaine and meloxicam plasma concentrations across different surgical procedures, about 38 to 57% of bupivacaine was released during the first 24 hours, and an additional 28 to 33% was released during the second 24 hours after HTX-011 administration. Similarly, about 27 to 41% of meloxicam was released during the first 24 hours, and an additional 23 to 27% during the second day.

Figure 19. Mean Plasma Concentration-Versus-Time Profiles for Bupivacaine Following Instillation of HTX-011 Across Various Surgical Procedures

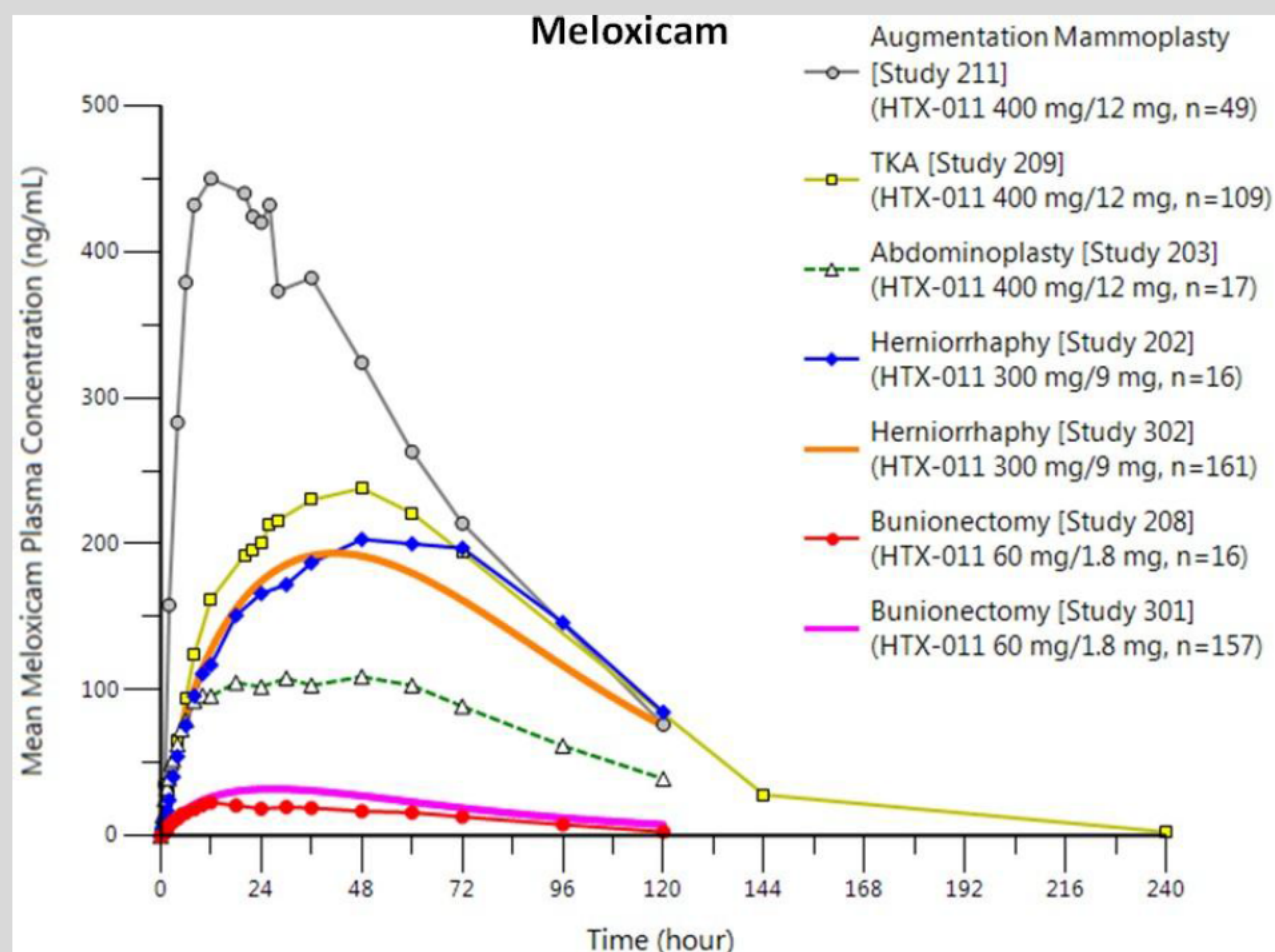


The PK profiles of HTX-011 show that there are two types of bupivacaine concentration-versus-time profiles: one with an earlier T_{max} (about 3 to 4 hours postdose) and shorter concentration plateau and the other with a later T_{max} (approximately 18 to 22 hours postdose) and longer concentration plateau. In contrast, an immediate-release bupivacaine HCl aqueous solution has an early bupivacaine T_{max} (about 0.5 to 1 hour postdose).

The PK profiles of HTX-011 show that meloxicam has a later T_{max} (about 18 to 54 hours postdose) because it has a long half-life.

Administration of HTX-011 with other drugs is not expected to result in dose dumping. In a nonclinical study with minipigs, a single subcutaneous HTX-011 dose was injected into the incision with or without lidocaine. The PK results indicate that no increase in bupivacaine concentration was observed when HTX-011 and lidocaine were co-administered.

Figure 20. Mean Plasma Concentration-Versus-Time Profiles for Meloxicam Following Instillation of HTX-011 Across Various Surgical Procedures



- b. A description of whether the drug product steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed immediate release or to a controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.**

HTX-011 is intended for single dose administration into the surgical site. Multiple dose administration of HTX-011 is not intended and has not been evaluated.

- c. Data supporting that the drug product formulation provides consistent pharmacokinetic performance between individual dosage units.**

PK performance between individual dosage units is not applicable to HTX-011 since it is an extended-release solution intended for single-dose administration into the surgical site.

- d. Data supporting that the drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.**

HTX-011 is intended for single-dose administration into the surgical site to reduce postoperative pain for 72 hours and thus has a less frequent dosing interval compared to the currently marketed reference products. In contrast, the approved immediate-release bupivacaine HCl aqueous solution is administered as a single dose and might be repeated up to once every three hours with total daily dose up to 400 mg.

Meloxicam is available in tablets and capsules for oral use at doses of 7.5 mg/day and 15 mg/day (once daily).

Bridging of Formulations

Reviewer's Assessment: *N/A*

Table 22. Compositions of Clinical HTX-011 Formulations (% w/w)

(b) (4)

There is no change in formulation between clinical batches and commercial batches. HTX-011-56 was selected as the intended commercial formulation and was the only formulation evaluated in the Phase 3 and Phase 2b studies.

List of Deficiencies:

None.

Primary Biopharmaceutics Reviewer Name:

Hansong Chen, PharmD, Ph.D.,

Biopharmaceutics Reviewer

OPQ/ONDP/DB

Secondary Reviewer Name:

Kelly M. Kitchens, Ph.D.

Biopharmaceutics Quality Assessment Lead

OPQ/ONDP/DB

8 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

OFFICE OF DEVICE EVALUATIONDIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**

Date	March 26, 2019
To	Ogochukwu Ogoegbunam, Program Coordinator, OND/ODEII/DAAAP
Requesting Center/Office	CDER/OND
OND Review Division	DAAAP
From	Florencia Wilson CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Sarah Mollo CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for NDA 211988 ICCR2018-04044 ICC1800971
Filing Recommendation	Recommendation Date: Not consulted
Mid-Cycle Recommendation	Recommendation Date: January 29, 2019 CDRH has Information Requests related to the device constituent parts of the combination product - See Section 11.3 for Information Requests
Final Recommendation	Recommendation Date: April 2, 2019 CDRH-ODE: Device Constituent Parts of the Combination Product are Not Approvable - See Section 11 for Complete Response Deficiencies CDRH-OC: Due to the (b) (4) device component being used for this application we recommend a PAI. See Section 13.1.

Digital Signature Concurrence Table

Reviewer	
Team Lead	
Branch Chief	

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2018-04044
ICCR SharePoint Link	ICCR2018-04044
ICC tracking # (Lead)	ICC1800971
Submission Number	NDA 211988
Sponsor	Heron Therapeutics, Inc.
Drug/Biologic	Zynrelef (bupivacaine & meloxicam)
Indications for Use	management of postoperative pain
Device Constituent	Administration Kit (vented vial spike, luer lock syringe [3 mL, 12 mL], syringe tip cap, luer lock applicator)
Related Files	N/A

Table 2. Review Team				
Were other disciplines consulted?			☒ Yes	☐ No
Below is a list of the Discipline Specific ICCR#, ICC# and CON#.				
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	ICCR #	ICC #	CON #
Compliance	Payal Patel	ICCR2018-04044	ICC1800971	CON1830617
Sterility	Katharine Segars	ICCR2018-04044	ICC1800971	CON1830757

Table 3. Important Dates	
Dates of Information Requests	12/22/18
Final Lead Device Review Memo Due	4/2/19
Interim Due Dates	Due Date
Team meetings	12/22/18
Mid-Cycle	1/29/19
Primary Review	4/9/19
PDUFA/GDUFA Due Date	4/30/19

*Of note, words in *italics* are taken directly from the application.

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2. PURPOSE/BACKGROUND

2.1. Scope

Heron Therapeutics, Inc. is requesting approval of the Zynrelef (bupivacaine and meloxicam). The device constituent of the combination product is an administration kit consisting of the drug vial, Vented Via Spike (b) (4) Luer Lock Syringes (2 mL [nominal volume] (3 mL) and 10 [nominal volume] (12 mL), (b) (4), Luer Lock Applicator (custom device) and Syringe tip cap (Class I exempt). The application consists of 3 doses (60mg bupivacaine/1.8mg meloxicam, 200mg bupivacaine/6mg meloxicam, 400mg bupivacaine/12mg meloxicam).

Each of the dose presentation has an administration kit with the following device components:

Bupivacaine (mg)/ Meloxicam (mg)	Vial Size (mL)	Drug product vial	Vented Via Spike (VVS) (b) (4)	Luer Lock Applicator (LLA) (custom device)	2 mL (3mL) Syringe (b) (4)	10 mL (12mL) Syringe (b) (4)	Syringe tip cap (Class I exempt)
60/1.8	10	1	1	1	1	0	1
200/6		1	1	1	0	1	1
400/12	20	1	1	2	0	2	1

CDER/OND has requested the following consult for review of the device constituent of the combination product on 2/21/18:

- Delivery device consults - technical/engineering (e.g., syringes, autoinjectors)
- new NDA

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- Device performance
- Biocompatibility of the patient contacting components
- Release Specifications for the device constituent
- Sterility of the device constituent if applicable
 - CDRH's lead reviewer consulted for sterility review for the luer lock applicator, that is a custom device included in the administration kit for this application.
 - The memo is appended in Section 13.2.
 - The syringe tip cap is a device constituent of the administration kit. The Sponsor stated that this is a sterile Class I device, the sterility of the syringe tip cap will be reviewed by CDRH.

CDRH also is responsible for the OC review for this file. This lead reviewer consulted for the OC review for this application. The memo is appended in Section 13.1.

This review will not cover the following review areas:

- Biocompatibility inclusive of compatibility of the drug with the device materials

- The syringe component (vented vial spike, syringes (2), luer lock applicator and tip cap) in the administration kit is labeled to be a container closure (b) (4) this was brought up to CDER during the Team meeting on 12/20/18. Venkat Pavuluri (DP and ATL) reviewer acknowledged and will perform as part of the drug product review.
- Human Factors

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

Additional Information (3/26/19):

An e-mail correspondence from the RPM (Ogochukwu Ogoegbunam) was received today (3/26/19) indicating that this application will be CRL. A follow-up telephone conversation, today as well, confirmed this information and the reason is due to insufficient data for Non-Clinical and CMC to recommend approval, in addition to the approaching action date of April 30, 2019.

2.2. Prior Interactions

There is no prior interaction with CDER with this file.

2.2.1. Related Files

2.3. Indications for Use

Table 1: Indications for Use

Combination Product	Indications for Use
Zynrelef (bupivacaine and meloxicam)	management of postoperative pain
Vented Via Spike (VVS) (b) (4)	The intended use of this device component (b) (4) (b) (4) (b) (4) intended for use in the preparation and patient administration of cytotoxic medications.
Luer Lock Syringes (3 and 12 mL) (b) (4)	for delivery of the drug product
Luer Lock Applicator (LLA) (custom device included in the application)	The luer lock applicator (LLA) is a device component (b) (4) (b) (4) The distal end of the LLA is tapered for aiming and inserting a viscous drug product into a surgical area; the proximal end is a female Luer lock for connecting to a syringe The sterile LLA is attached to the sterile syringe for use during administration. One or two are provided in the kit, depending on the dose.

Syringe tip cap	The sterile syringe tip cap is attached to the sterile syringe when the syringe(s) is/are prepared. One or two are provided in the kit, depending on the dose.
-----------------	--

Component	Image	Description
Vented Vial Spike	(b) (4)	The vented vial spike is attached to the medication vial allowing for withdrawal of the medication.
Sterile Syringe		One or two sterile syringes are provided in the kit for withdrawal of the medication and administration.
Luer Lock Applicator		The Luer Lock Applicator is attached to the syringe for use during administration. One or two are provided in the kit depending on the dose.
Sterile Tip Cap		The sterile tip cap is attached to the sterile syringe when the syringe(s) is/are prepared in advance. One or two are provided in the kit depending on the dose.

3. ADMINISTRATIVE
3.1. Documents Reviewed

Document Title	Location
Cover Letters	Module 1.2
Statement of right of reference (b) (4) (b) (4)	1.4.2 Statement of Right of references
Reviewer Guide	Sequence 0002/1.2. Cover Letter

Design History File	Module 3.2.R. Regional Information
Device LLA (all documents)	Module 3.2.R. Regional Information
Device (b) (4) (all documents)	Module 3.2.R. Regional Information
Device Kit (all documents)	Module 3.2.R. Regional Information
(b) (4)	(b) (4)
(b) (4)	(b) (4)

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

Administration Kit Device Description:

*the syringe is not the primary container closure, clarified in the IR sent on 12/24/18

Device Characteristic	N/A	Description / Specification	
Syringe Name		Norm-Ject Syringe (b) (4) (2 mL [nominal volume] (3 mL) and 10 [nominal volume] (12 mL)	
Syringe Platform Name (if applicable)	X		
Priming Dose / Volume	X		
Dose accuracy			
		Dose	Specifications
		60 mg bupivacaine/1.8mg meloxicam	NLT (b) (4)mL
		200 mg bupivacaine/6mg meloxicam	NLT (b) (4) mL
		400 mg bupivacaine/12mg meloxicam	NLT (b) (4) mL
Injection Time	X		
Injection Site		Wound site	
Injection tissue and depth of injection		The drug product is applied to the wound site prior to closure of the surgical wound	
Audible / visual feedback		visual	
Cap Removal Force	X		
Activation Force	X		
Visibility of medication container		The container closure is a vial (CDRH does not review)	
Needle Specifications - Length(s) - Gauge(s) - Connection type - ISO 11608-2:2012 - Prestaked	X		
Type of Use (e.g. single use,		Single use, disposable	

disposable, reusable, other)		
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)		Health care provider
Method of actuation	X	
Automated Functions	X	
Residual Medication	X	
Drug Container Type	X	
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)		mL
Environments of use		Healthcare facility
Storage conditions and expiry		Room temperature
Graduation marks / fill lines		510(k) cleared syringes (b) (4) with graduation markings, ± 0.5 mL for the 10 mL (12mL) and ± 0.1 mL for the 2 mL (3 mL) syringe
Preparation and administration (describe all that are applicable) • Warm to room temp prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation steps (e.g., pinch skin, inject through clothing, etc.) • Changing / disposing needles • Etc.		Preparation (b) (4)
Safety Features • Needle safety	X	
Material composition		VVS – (b) (4) material LLA – (b) (4) Syringe – barrel (b) (4), piston (b) (4) Syringe Tip cap – (b) (4)

Taken from 3.2.P.7. pp. 3-6:

**CO-PACKAGED COMBINATION PRODUCT KIT
COMPONENTS**

HTX-011 is assembled in a co-packaged combination product kit with the drug product vial and all components required for preparation and administration of the product (Table 2). The

packaging configurations are determined based on the presentation (Table 3). Each kit also contains the Prescribing Information and Instructions for Use (IFU).

Section 3.2.R contains the documents related to the Design History File for the Luer lock applicator (LLA) and co-packaged kit as well as supportive information for the off-the-shelf device components.

Table 2: HTX-011 Co-Packaged Combination Product Kit Components

Description	Manufacturer	Manufacturer Part Number	510(k) Clearance Number	Shelf Life	Storage Condition
VVS	(b) (4)	011-CS-75	(b) (4)	(b) (4)	Room temperature
2 mL (3 mL)* Luer lock syringe		4020-X00V0			Room temperature, protect against moisture and sunlight
10 mL (12 mL)* Luer lock syringe		4100-X00V0			
Syringe tip cap		305819	Class I exempt device	(b) (4)	Room temperature
LLA		709689	Custom device included in this NDA		Room temperature, protect from moisture (proposed)

Abbreviations: VVS, vented vial spike; LLA, Luer lock applicator; NDA, New Drug Application

* The first number indicates the nominal volume of the syringe, and the number in parentheses indicates the maximum volume.

^b-Refer to Section 3.2.P.8.1.6.

Table 3: HTX-011 Co-Packaged Combination Product Kit Configurations

Bupivacaine (mg) / Meloxicam (mg)	NDC	Vial Size (mL)	Cap Color	Drug Product Vial	VVS	LLA	2 mL (3 mL)* Syringe	10 mL (12 mL)* Syringe	Syringe Tip Cap
60/1.8	47426-304-01	10	(b) (4)	1	1	1	1	0	1
200/6	47426-303-01			1	1	1	0	1	1
400/12	47426-301-02	20		1	1	2	0	2	2

Abbreviations: NDC, National Drug Code; VVS, vented vial spike; LLA, Luer lock applicator

(b) (4)

* The first number indicates the nominal volume of the syringe, and the number in parentheses indicates the maximum volume.

Taken from 3.2.R. Device Kit: Risk management plan:

Component	Image	Description
Vented Vial Spike	(b) (4)	The vented vial spike is attached to the medication vial allowing for withdrawal of the medication.
Sterile Syringe		One or two sterile syringes are provided in the kit for withdrawal of the medication and administration.
Luer Lock Applicator		The Luer Lock Applicator is attached to the syringe for use during administration. One or two are provided in the kit depending on the dose.
Sterile Tip Cap		The sterile tip cap is attached to the sterile syringe when the syringe(s) is/are prepared in advance. One or two are provided in the kit depending on the dose.

Figure 1: HTX-011 Secondary and Tertiary Packaging and Components Unprinted Example



Figure 2: HTX-011 Tertiary Packaging Partially Assembled Unprinted Example



The following are taken from 3.2.R. Regional Information:

VVS:

(b) (4)



Luer Lock Syringes:

3mL:

(b) (4)



12mL:

(b) (4)



Syringe tip cap:

- The Sponsor states that this is a Class I exempt device (b) (4) provided a memo on the shelf life and package integrity summary for Catalog
- a Certificate of compliance (located in 3.2.R Regional Information, Device (b) (4) Tip Cap certificate of compliance) addressing the following:

(b) (4)



LLA

The following is taken from DEVICE: LLA Technical Requirements, 3.2.R., pdf p.2:

3. DESCRIPTION

(b) (4)



The following is taken from DEVICE: LLA Technical Requirements, 3.2.R., pdf p.3:

(b) (4)



(b) (4)

Device Description Recommendation	
The Sponsor Provided Complete Device Description for the Device Constituent	☒
The Sponsor DID NOT Provide Complete Device Description for the Device Constituent	☐
Device Description Information Requests	Section 11.1 Filing IRs - # Section 11.2 74-Day Letter IRs - # Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #
All Information Requests were Resolved over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

5. FILING REVIEW

CDRH performed Filing Review	☐
CDRH was not consulted prior to the Filing Date; therefore, CDRH did not perform a Filing Review	☒

Table 4: Design Control Documentation Check

Design Control Requirement	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		3.2.R. Regional Information
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		3.2.R. Regional Information

Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		3.2.R. Regional Information
--	---	--	-----------------------------

Design Controls Recommendation	
The Sponsor Provided Complete Design Controls for the Device Constituent	☒
The Sponsor DID NOT Provide Complete Design Controls for the Device Constituent	☐
Design Control Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #
All Information Requests were Resolved over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. Summary of Design V&V Attributes

Table 5: Summary of Design V&V Attributes

Design Verification / Validation Attributes		Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing		X		
To-be-marketed device was used in the pivotal clinical trial?		X		
Selectable dose range on device matches the labeled dose range for the medication?				X
Verification methods relevant to specific use conditions as described in design documents and labeling		X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)		X		
Traceability demonstrated for specifications to performance data		X		
Conformance to applicable standards demonstrated	ISO 11608-1:2014 – Needle based injection systems – Requirements and Test Methods			X
	ISO 11608-2:2012 – Needles			X
	ISO 11608-5:2012 – Automated Functions			X
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry		X		
Discipline -Specific Design Verification / Validation adequately addressed	Biocompatibility	X		
	Sterility	X		

Referenced Standards and Guidance Documents

Reference Standard / Guidance	Description / Extent of FDA Recognition	Documentation Adequate	
		Yes	No
See below		X	

The following is taken from DEVICE KIT: V&V Maser Plan, 3.2.R., pdf pp. 5-6 of 14:

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Page 16 of 107

Design Verification Recommendation	
The Sponsor Provided Complete Design Verification for the Device Constituent	☒
The Sponsor DID NOT Provide Complete Design Verification for the Device Constituent	☐
Design Verification Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #
All Information Requests were Resolved over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

7. RISK ANALYSIS

7.1. Risk Analysis Attributes

Risk Analysis Summary

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		

7.2. Summary of Risk Analysis

A risk management report located in 3.2.R. Regional Information, DEVICE KIT: Risk Management Report, per ISO 14971:2007/(R)2012, Medical devices — Application of risk management to medical devices was provided by the Sponsor for the co-packaged combination product kit including the LLA. Please see below:

Risk Management Report for Co-packaged combination product kit:



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(b) (4)

Risk Analysis Recommendation	
The Sponsor provided complete Risk Analysis for the Device Constituent	☒
The Sponsor DID NOT provide There are Complete Response Deficiencies, See Section 13 Risk Analysis for the Device Constituent	☐
Risk Analysis Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #
All Information Requests were Resolved over the course of the review	☒
There are Complete Response Deficiencies, See Section 12	☐

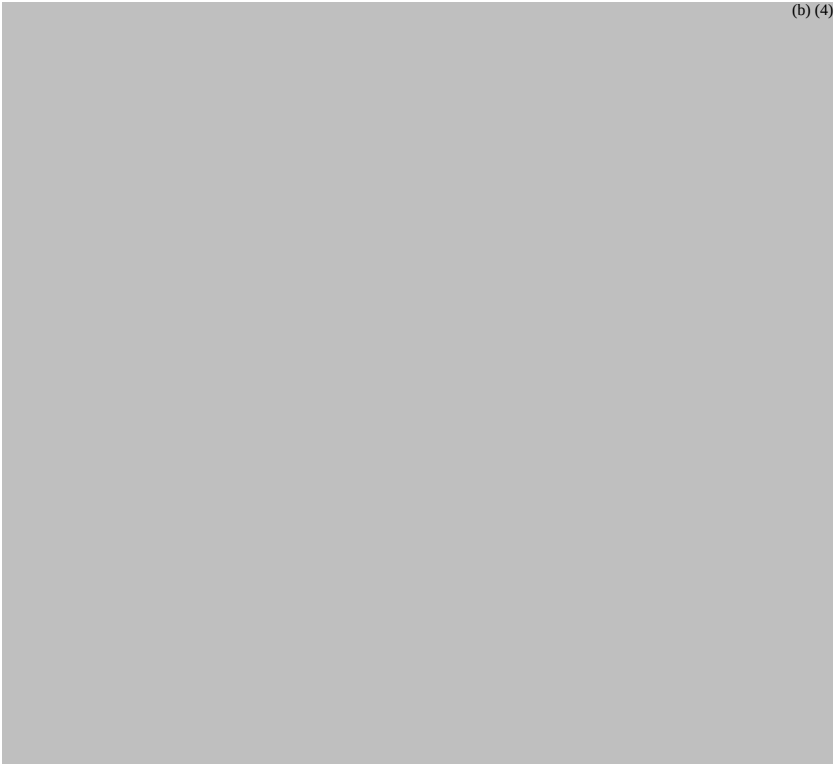
8. LABELING

Administration Kit Labeling Checklist

Attribute	Present		
	Yes	No	N/A

Device Type	Type	X		
	Syringe Size(s)	X		
	Needle Gauge			X
	Needle Length			X
	Quantity			X
Prescription Statement under 801.109(b)(1), except for insulin syringes		X		
Special requirements for insulin syringes as described in 801.403 about mixing insulin, including "For use with U100 insulin only" on the barrel and gradations on the barrel in units;				X
Any instructions for using specialized syringes such as the anti-needlestick devices and cartridge syringes;				X
Any specific drug or biologic use;		X		
Instructions on how to clean and sterilize any reusable components.				X

8.1. Device Labels



Reviewer Comment

The package labeling is acceptable, but the full review is deferred to the lead team, CDER.

8.2. Instructional Labeling

(b) (4)



(b) (4)

6. COMPATIBILITY

(b) (4)

Reviewer Comment

Drug device compatibility was performed

(b) (4)

(b) (4) The acceptability of the compatibility of HTX-011-56 with the device components used for preparation and administration is deferred to CDER.

(b) (4)

An IR will be sent. Please see Section 10.

In review of the provided response received on 2/1/19, where the Sponsor will remove the statement, (b) (4)
(b) (4) This response is adequate.

This IR is RESOLVED.

8.3. Warnings/Precautions/Contraindications

Reviewer Comment

The Sponsor provided Warnings/Precautions/Contraindications in Labeling. Full review is deferred to CDER.

Labeling Recommendation	
The Sponsor provided complete Labeling for the Device Constituent	☒
The Sponsor DID NOT provide complete Labeling for the Device Constituent	☐
Labeling Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #
All Information Requests were Resolved over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

9. DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The following release specifications are included for the device constituent within eCTD Module 3.2.P.5:

Release Specifications

Attribute	Specification	Test Method
Dose Accuracy (extractable volume)	(b) (4)	
Break Loose/Glide Force	(b) (4)	

Module 3.2.P.5. p. 90 (the raw data is provided in p. 91):

Table 81: Summary of Verification for Extractable Volume Testing of HTX-011

Parameter	Acceptance Criteria	Result
Method Use/ Precision	(b) (4)	

Abbreviations: NLT, not less than; NMT, not more than; Std Dev, standard deviation

Reviewer Comment

The release specifications for the EPR is modified based on the provided IR response by the Sponsor.
This is adequate.

Release Specifications Recommendation	
The Sponsor provided complete Release Specifications for the Device Constituent	☒
The Sponsor DID NOT provide complete Release Specifications for the Device Constituent	☐
Release Specifications Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #
All Information Requests were Resolved over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

10.INTERACTIVE REVIEW

10.1. Filing Information Requests

Are there filing review information requests? ☒ No ☐ Yes

This section is not applicable

10.2. 74-Day letter Information Requests

Are there 74-Day Letter information requests? ☐ No ☒ Yes

(b) (4)

The response was provided to Dr. Katharine Segars. The acceptability of the response is deferred to Dr. Segars. The full Sterility memo will be appended in Section 13.2 CDRH Sterility Consult.

Consultant Comments:

(b) (4)
(b) (4)

(b) (4) This deficiency is resolved.

10.3. Mid-Cycle Information Requests

Are there Mid-Cycle review information requests? ☐ No ☒ Yes

The Mid-Cycle Information Requests are follow-up to IRs sent prior to the Mid-Cycle.

10.4. Interactive Review

Are there other interactive review information requests? ☐ No ☒ Yes

The interactive review information requests are follow-up to IRs sent prior to the Mid-Cycle.

11.COMplete Response Deficiencies

1. You provided shelf life and package integrity summary results for the syringe tip cap. However, you did not provide enough information to ensure that the tip cap will be provided sterile and will remain sterile throughout its shelf-life. This information should be provided to ensure that your device is safe for use. Please provide the following:
 - a. A description of the sterilization method (b) (4) as well as the sterilization site;
 - b. In case of (b) (4) sterilization, (b) (4)
 - c. For (b) (4) the maximum levels (b) (4) and an explanation why these levels are acceptable;
 - d. A description of the sterilization validation method with a citation of the relevant standard(s), but not the validation data itself;
 - e. The sterility assurance level;
 - f. Pyrogenicity testing, including a description of the test method, the chosen endotoxin test limit, and your testing frequency. Alternatively, you may provide a scientific justification for why endotoxin testing is not required; and
 - g. A description of the packaging used to maintain the sterility of the device and a description of the test methods, but not the package integrity test data itself. Please note that the Agency recommends seal strength and a package integrity test after accelerated (and/or real time) aging and visual inspection and a package integrity test after simulated shipping and distribution.

12.RECOMMENDATION

12.1. Recommendation to CDER/OND

CDRH is recommending that the device constituent of the combination product is not approvable for the proposed indication based on inadequate information on the syringe tip cap's sterility. See Section 11 for the deficiencies to include in the complete response letter.

12.2. Recommended Post-market commitments/post-market requirements

CDRH has Post-Market commitments/requirements	☐
CDRH does not have Post-Market commitments/requirements	☒

13. Appendix

13.1. CDRH-OC Consult:

Date:	March 6, 2019
To:	Anika Lalmansingh, RBPM
CC:	Ogochukwu Ogoegbunam, RPM, Office, Location, Office of Combination Product at: combination@fda.gov
From:	Florencia Wilson, Lead reviewer, CDRH/ODE/DAGRID/GHDB Payal Patel, OC Consultant, Office of Health Technology 3
Applicant/Licensure:	Heron Therapeutics, Inc
Submission (Type & Number):	NDA 211988
Combination Product Name:	Zynrelef
Combination Product	bupivacaine and meloxicam to be administered via an administration kit
Intended Use:	management of postoperative pain
Device Constituent (Type):	Administration Kit (vented vial spike, luer lock syringe [3 mL, 12 mL], syringe tip cap, luer lock applicator)
CTS ICCR Number:	ICC1800678
SharePoint ICCR Number:	ICCR2018-04044
ICCR Instruction (ICCR Form):	new NDA
Pre-Approval Facility	
Inspection:	
CDRH/OC Recommendation:	due to the (b) (4) device component being used for this application we recommend a PAI.

This portion of the consult for CON1830617 - ICC1800971 (NDA 211988 from Heron Therapeutics, Inc. for HTX-011), is for a **determination of device facility inspection**.

HTX-011 is an extended-release, fixed-dose combination product that contains bupivacaine and low-dose meloxicam. It is a co-packaged combination drug-device product that includes a vial of HTX-011 packaged with devices intended for preparation and delivery of the drug. The primary mode of action of the combination product is based on the drug constituents. It is administered as a single dose that is applied into the surgical site to coat the affected tissues. HTX-011 is applied without a needle using a syringe with an applicator attached.

HTX-011 is assembled in a co-packaged combination product kit with the drug product vial and all components required for preparation and administration of the product. The packaging configurations are determined based on the presentation as outlined in 3.2.P.7). Each HTX-011 vial is labeled and packaged in a vial carton. One vial carton is kitted along with a vented vial spike (VVS), Luer lock syringe(s), Luer lock applicator(s) (LLA), and syringe tip cap(s). The applicant states "all components other than the LLA are commercially available, off-the-shelf, CE marked, pharmaceutical delivery support components that are legally marketed, with established usage histories and safety profiles. The VVS and Luer lock syringe are 510(k) cleared, and the sterile tip is a Class I exempt device". The LLA was designed (b) (4)

(b) (4) The LLA is a device that is manufactured for the combination product kit and included for review and approval in this application, and is manufactured at a contract manufacturing site. (b) (4) (FEI: (b) (4)).

As the LLA is a **component** of the final finished combination product, and (b) (4) is not the final kit assembling manufacturer, a facilities **inspection of this facility is not recommended** for this site. The applicant has identified two (2) facilities that are responsible for the packaging and labeling of co-packaged combination product kit as stated below. The activities for Secondary Packaging conducted at these facilities is listed in 3.2.P.3.3.1.5. (b) (4)

(b) (4)

(b) (4)

(b) (4) (FEI: (b) (4)) – The previous inspection was conducted (b) (4) and found NAI for a combination product post-approval inspection (b) (4) the firm assembles, packages and labels (b) (4) (b) (4). in accordance with drug and device inspection (following the QSIT inspections). This firm assembles, packages and labels (b) (4) The QSIT inspection covered CAPA and Production and Process Controls

(b) (4).

This is similar to the current responsibilities of (b) (4) in this application.

The previous inspection was conducted (b) (4) and found NAI (b) (4) the QSIT inspection was conducted covering CAPA and Production and Process Controls. **A device inspection (b) (4) is not recommended at this time.**

(b) (4) (FEI: (b) (4)) – The previous inspection was conducted (b) (4) and found NAI for an initial inspection for the site after the firm's relocation. At that time the firm was acting as a primary and secondary packaging facility of finished drug products (b) (4) The drug cGMP portion of that inspection covered Quality, Facility and Equipment, Materials, Packaging and Labeling systems. **A device Post-Approval Inspection is recommended for this facility, specifically covering the CAPA (21 CFR 820.100) and Production and Process Controls (21 CFR 820.70) systems.**

Let me know if you have any follow up questions, I will continue with the QS review. Please let me know when you need that by and if possible update the consult to reflect that date.

Rationale for PAI recommendation:

(b) (4) (FEI: (b) (4)) the firm responsible for (b) (4)

1.

(b) (4)

(b) (4) This inspection was however found VAI, there is no noted follow up for this observation (b) (4) due to the (b) (4) device component being used for this application **we recommend a PAI.**

Digital Signature Concurrence Table	
Reviewer	Payal Patel -S 2019.03.18 07:52:09 -04'00'
Team Lead	
Branch Chief	Nikhil Thakur -S3 Digitally signed by Nikhil Thakur -S3 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nikhil Thakur -S3, 0.9.2342.19200300.100.1.1=1300215196 Date: 2019.03.20 11:50:23 -04'00'

13.2. CDRH Sterility Consult:

Sterility Consult Review

Consult Number: CON1830757

Document Number: ICC1800971 for NDA 211988

Applicant: Heron Therapeutics, Inc.

Trade Name: Zynrelef

Consult Request Type: Sterility

Requestor: Florencia Wilson, Nurse Consultant, CDRH\OHT3\DHT3C\THT3C1 (pilot office)
Email: Florencia.wilson@fda.hhs.gov Phone: 240-402-9978

Consultant: Katie Segars, Microbiologist, CDRH\OHT3\DHT3C\THT3C1 (pilot office)
Email: Katharine.segars@fda.hhs.gov Phone: (b) (4)

Date: 02/28/2019

Summary and Conclusion: The Luer Lock Applicator (LLA) is provided single use, sterilized (b) (4). The sponsor provided validation testing to demonstrate that the recommended dose achieves an SAL (b) (4). Additional supporting documents included a dose mapping study, bacterial endotoxin test information, and package integrity testing to support the proposed (b) (4) shelf life. **The sterility information appears to be adequate.**

Background Information: The Intercenter Consult ICC1800971 pertains to the CDER-led drug-device combination product, Zynrelef. A sterility consult was requested by the CDRH lead reviewer, Ms. Florencia Wilson, on 12/26/2018.

Consult Request: The following consult instructions were provided in CTS: “Hi Katie, I will provide you with the documents in a separate e-mail. Thanks, Flo.” The sterilization validation documents for the Luer Lock Applicator were provided via email on 12/27/2018 and subsequent documents were forwarded by the lead reviewer during interactive review.

NOTE: This consult is limited to a review of the sterilization validation information for the luer lock applicator included in the following documents:

- DEVICE_LLA Sterilization Validation Report.pdf
- LLA-t0-report-process-2
- LLA Accelerated Aging One Year Report (Packaging Process 2)
- LLA Accelerated Aging Two Year Report (Package Process 2)
- LLA Accelerated Aging Three Year Report (Package Process 2)
- lla-dose-mapping.pdf
- “Quality Info Amend” provided via email dated 01/10/19
- “Quality Information Amendment – Response to Quality Information Request – Bacterial Endotoxin

Testing for LLA” via email dated 01/22/2019

- “lla-dose-mapping-2019-01-22”

Please note that all comments are taken/summarized from the sponsor’s submission, unless noted as “**Consultant Comments.**”

DEVICE DESCRIPTION

The following device description was provided in the document entitled: “Device_LLA Essential Design Outputs.pdf”

(b) (4)

STERILITY REVIEW

(b) (4)

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(b) (4)

Consultant Comments: The revised (b) (4) study report (b) (4) appears to be consistent with the ISO 11137-3 recommendations. **This deficiency is resolved.**

Digital Signature Concurrence Table	
Reviewer Sign-Off	Katharine Segars, Ph.D.

	Branch Chief Sign-Off		
--	-----------------------	--	--

Date: March 6, 2019

To: Anika Lalmansingh, RBPM

CC: Ogochukwu Ogoegbunam, RPM, Office, Location,
Office of Combination Product at: combination@fda.gov

From: Florencia Wilson, Lead reviewer, CDRH/ODE/DAGRID/GHDB
Payal Patel, OC Consultant, Office of Health Technology 3

Applicant/Licensure: Heron Therapeutics, Inc

Submission (Type & Number): NDA 211988

Combination Product Name: Zynrelef

Combination Product bupivacaine and meloxicam to be administered via an administration kit

Intended Use: management of postoperative pain

Device Constituent (Type): Administration Kit (vented vial spike, luer lock syringe [3 mL, 12 mL], syringe tip cap, luer lock applicator)

CTS ICCR Number: ICC1800678

SharePoint ICCR Number: ICCR2018-04044

ICCR Instruction (ICCR Form): new NDA

Pre-Approval Facility

Inspection:

CDRH/OC Recommendation: due to the (b) (4) device component being used for this application **we recommend a PAI.**

This portion of the consult for CON1830617 - ICC1800971 (NDA 211988 from Heron Therapeutics, Inc. for HTX-011), is for a **determination of device facility inspection.**

HTX-011 is an extended-release, fixed-dose combination product that contains bupivacaine and low-dose meloxicam. It is a co-packaged combination drug-device product that includes a vial of HTX-011 packaged with devices intended for preparation and delivery of the drug. The primary mode of action of the combination product is based on the drug constituents. It is administered as a single dose that is applied into the surgical site to coat the affected tissues. HTX-011 is applied without a needle using a syringe with an applicator attached.

HTX-011 is assembled in a co-packaged combination product kit with the drug product vial and all components required for preparation and administration of the product. The packaging configurations are determined based on the presentation as outlined in 3.2.P.7). Each HTX-011 vial is labeled and

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Devices and Radiological Health

Office of Compliance (OC)

packaged in a vial carton. One vial carton is kitted along with a vented vial spike (VVS), Luer lock syringe(s), Luer lock applicator(s) (LLA), and syringe tip cap(s). The applicant states "all components other than the LLA are commercially available, off-the-shelf, CE marked, pharmaceutical delivery support components that are legally marketed, with established usage histories and safety profiles. The VVS and Luer lock syringe are 510(k) cleared, and the sterile tip is a Class I exempt device". The LLA was designed (b) (4)

(b) (4) The LLA is a device that is manufactured for the combination product kit and included for review and approval in this application, and is manufactured at a contract manufacturing site (b) (4) (FEI: (b) (4)).

As the LLA is a component of the final finished combination product, and (b) (4) is not the final kit assembling manufacturer, a facilities inspection of this facility is not recommended for this site. The applicant has identified two (2) facilities that are responsible for the packaging and labeling of co-packaged combination product kit as stated below. The activities for Secondary Packaging conducted at these facilities is listed in 3.2.P.3.3.1.5 (b) (4)

(b) (4)

(b) (4)

(b) (4) (FEI: (b) (4)) – The previous inspection was conducted (b) (4) and found NAI for a combination product post-approval inspection (b) (4) the firm assembles, packages and labels (b) (4) in accordance with drug and device inspection (following the QSIT inspections). This firm assembles, packages and labels (b) (4) The QSIT inspection covered CAPA and Production and Process Controls (b) (4)

(b) (4) This is similar to the current responsibilities of (b) (4) in this application.

The previous inspection was conducted (b) (4) and found NAI (b) (4) the QSIT inspection was conducted covering CAPA and Production and Process Controls. A device inspection (b) (4) is not recommended at this time.

(b) (4) (FEI: (b) (4)) – The previous inspection was conducted (b) (4) and found NAI for an initial inspection for the site after the firm's relocation. At that time the firm was acting as a primary and secondary packaging facility of finished drug products (b) (4). The drug cGMP portion of that inspection covered Quality, Facility and Equipment, Materials, Packaging and Labeling systems. A device Post-Approval Inspection is recommended for this facility, specifically covering the CAPA (21 CFR 820.100) and Production and Process Controls (21 CFR 820.70) systems.

Let me know if you have any follow up questions, I will continue with the QS review. Please let me know when you need that by and if possible update the consult to reflect that date.

Rationale for PAI recommendation:

(b) (4) (FEI: (b) (4)) the firm responsible for (b) (4)

1. (b) (4)

(b) (4) This inspection was however found VAI, there is no noted follow up for this observation. (b) (4) due to the (b) (4) device component being used for this application we recommend a PAI.

Additional Comments (April 16, 2019)

On 4/12/19 Yoon Oh from CDER provided us a copy of the FDA 483 Observation for the PAI for NDA 211988 for (b) (4) (FEI: (b) (4)), since the inspection just closed the EIR report has not been provided for review. The investigator noted one observation during the inspection (b) (4)

As the supporting EIR report and exhibits were not yet available, Katie Segars (Sterilization Consultant), Florencia Wilson and myself called the investigator for clarification. He stated (b) (4)

I have no additional concerns regarding this facility at this time and support the Approve Facility recommendation from the investigator. However, I would like to read the final EIR with regards to the follow up on the complaints.

Digital Signature Concurrence Table	
Reviewer	
Team Lead	
Branch Chief	

ATTACHMENT I: Final Risk Assessments

[IQA Review Guide Reference](#)

A. Final Risk Assessment – NDA 211988

- a) **Drug Product: ZYNRELEF™** (Bupivacaine and Meloxicam), Extended-release solution; 60 mg/1.8 mg, 200 mg/6 mg and 400 mg/12 mg.

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
		H, M, or L		Acceptable or Not Acceptable	
Assay, stability (APIs)	Stability of the drugs (APIs) in solid state	Moderate	(b) (4)	Acceptable	
Physical stability (Drug Product)	Drug(s) in dissolved state	High		Acceptable	
Degradation Products (Drug Product)	Drug(s) in dissolved state, (b) (4) manufacturing	High		Acceptable	
Content uniformity	Highly Viscous solution	Moderate		Acceptable	
Microbial Limits	(b) (4)	High		Not acceptable	PAI required upon resubmission.
In Vitro Release (ER Solution)	Modified In Vitro Release (IVR) methods employed for quality control	Medium		Acceptable	

			(b) (4)		
Extractables and Leachables	(b) (4)	High		Not Acceptable	Additional testing recommended for resubmission



Venkateswara
Pavuluri

Digitally signed by Venkateswara Pavuluri
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