CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209511Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 209511
Assessment 2

Drug Product Name	Bupivacaine implant
Dosage Form	Collagen implant
Strength	300 mg (3 x 100 mg collagen implant)
Route of Administration	Implantation in surgical wound
Rx/OTC Dispensed	N/A
Applicant	Innocoll Pharmaceuticals Limited
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 44; eCTD 0043	26 Feb 2020	Drug product, microbiology, facilities
Supporting document 47; eCTD 0047	30 Mar 2020	Micro
Supporting document 49; eCTD 0048	24 Apr 20	Drug product
Supporting document 50; eCTD 0049	22 Jun 20	Drug product
Supporting document 51; eCTD 0050	8 Jul 20	Drug product, biopharm
Supporting document 52; eCTD 0051	15 Jul 20	Drug product, biopharm

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	N/A
Drug Product	Valerie Amspacher	Julia Pinto
Manufacturing	Tarun Mehta	N/A
Microbiology	Yan Zheng	Elizabeth Bearr
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

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval of this application. The sponsor has adequately addressed the deficiencies stated in the complete response letter.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This application was originally submitted 31 Oct 2016 but was determined to not be a complete submission and it was not filed. It was resubmitted 2 Feb 2018 (eCTD 0008) and was not approved, a complete response letter was sent 30 Nov 2018. This review is of a resubmission dated 26 Feb 20 (eCTD 0043) in response to the complete response letter.

The sponsor has also included additional drug product specification test information that will be reviewed here.

The sponsor has adequately responded to the deficiencies. We agree with the sponsor's proposed 24 month expiry. We also agree with the sponsor's statement, "XARACOLL should be stored at 20 °C to 25 °C (68 °F to 77°F); excursions permitted between 15 °C and 30 °C (59 °F and 86 °F) [See USP Controlled Room Temperature]."

Regulatory History:
The CMC deficiency in the complete response letter dated 30 Nov 2018:
The leachables assessment you have provided is incomplete. An analytical method for the detection of leachables has not been provided, and therefore, a correlation between the extractables and leachables cannot be made. Leachables testing should be performed on (b) (4)y manufactured produc (b) (4)

(b) (4)

a. From the robust extractables profiles of both primary and secondary packaging, identify and determine the target leachables.
b. Develop methods which can detect these leachables in the drug product.

c. Test 3 batches of drug product at multiple time-points on stability with emphasis on (b) (4) manufactured product that includes ink labeling on individual blisters as planned for commercial product.
We also refer you to USP <1663> and <1664> for additional information.

Proposed Indication(s) including Intended Patient Population	Placement into the surgical site in adults to produce postsurgical local analgesia following open inguinal hernia repair
Duration of Treatment	(b) (4)
Maximum Daily Dose	300 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Choose an item.

N/A

Drug Product: Adequate

The sponsor adequately responded to the deficiency about extractables/leachables. Leachables stability data is provided.

We agree with the sponsor's proposed 24 month expiry. We also agree with the sponsor's statement, "XARACOLL should be stored at 20 °C to 25 °C (68 °F to 77°F); excursions permitted between 15 °C and 30 °C (59 °F and 86 °F) [See USP Controlled Room Temperature]."

Labeling: Adequate

Manufacturing: Adequate

Biopharmaceutics: Adequate

On 2/26/2020, the Applicant submitted an amendment to address the deficiencies in the CR letter. In Module 3.2.P.8.3, the Applicant submitted all stability dissolution data through the proposed expiry period. However, these data were reported as ranges instead of individual values for all time points; therefore, we could not ensure if the batches on which Stage 2 Testing was conducted meet the approved dissolution criteria.
In the response to Biopharmaceutics IRs, the Applicant submitted all of the requested dissolution data, including individual values, which show

that all batches meet the approved dissolution acceptance criteria at Stage 1 or Stage 2.

Microbiology (if applicable): Adequate

The product presentation, container closure system, manufacturing site, (b) (4) validation data, manufacturing process (b) (4) (b) (4)), product release specification and testing methods for sterility and endotoxins testing remain unchanged, and were reviewed and found adequate in N209511MR01 on 10/05/2018.

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Active	22 Aug 2018	

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

Document	Application Number	Description
IND	77127	
NDA	016964	
NDA	(b) (4)	

2. CONSULTS

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

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Valerie Amspacher

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R REGIONAL INFORMATION

Environmental

Assessment: Adequate
See original review in Panorama dated 24 Oct 2018.

Methods Validation or Verification Package

Assessment: N/A

Comparability Protocols

Assessment: N/A

Post-Approval Commitments

Assessment: *N/A*

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

The PI complies with all statutory/regulatory requirements and is consistent with guidance recommendations from a product quality perspective.

According to the draft guidance "Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format" implant is an acceptable dosage form term. The word implant will be used in the official name of the drug product per email discussion with David Claffey and Swapan De 11 Oct 2018.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments

Product Title in Highlights		
Proprietary name	Yes	Yes
Established name(s)	Yes, need to remove (b) (4)	Product title should be (bupivacaine HCl implants)
Route(s) of administration	Yes	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Yes	Maybe equivalency statement should be included here
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	Maybe equivalency statement should be included here
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Should include the salt, bupivacaine hydrochloride	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Missing	Needs to be added, 5 cm white square, sterile
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
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.	N/A	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	
Dosage form(s) and route(s) of administration	Yes	Need to remove (b) (4) (b) (4)
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Yes – equivalency statements present	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	Maybe remove "purified Type I" not sure if this is needed or promotional
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.	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Yes	
Pharmacological/ therapeutic class	No	Not present
Chemical name, structural formula, molecular weight	No, Missing structural formula, molecular weight	Not present
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"		Are the comments under 11.2 needed or promotional?

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	emove (b) (4)
Strength(s) in metric system	Yes	Add 300 mg equivalency statement
Available units (e.g., bottles of 100 tablets)	Yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	No	5 cm white square, sterile
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

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.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

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		

2.0 PATIENT LABELING

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

This label will be on each single pouch which will contain 3 implants.

Item	Assessor's Comments about Container Labeling	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes, need to remove (b) (4) (b) (4)	
Dosage strength	Yes, have equivalency statement for 100 mg but need to add equivalency statement for 300 mg	
Route of administration	Yes	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	have equivalency statement for 100 mg but need to add equivalency statement for 300 mg	
Net contents (e.g. tablet count)	Yes	
"Rx only" displayed on the principal display	Yes	
NDC number	Yes	
Lot number and expiration date	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	

Bar code	Yes	

Item	Assessor's Comments about Container Labeling	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	N/A	
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.	N/A	

Assessment of Carton and Container Labeling: Adequate
The immediate container label complies with all statutory/regulatory requirements and is consistent with guidance recommendation from a Quality perspective.

The carton labeling complies with all regulatory requirements from a Quality perspective.

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Julia Pinto

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BIOPHARMACEUTICS

IQA Review Guide Reference

Product Background:

NDA: NDA 209511-ORIG-1-RESUB-44

Drug Product Name / Strength: XARACOLL (bupivacaine HCl collagen-matrix; INL-001)/300 mg (3 x 100 mg implants)

Route of Administration: Implants

Applicant Name: Innocoll Pharmaceuticals

Review Recommendation: **Adequate**

Review Summary:

Innocoll Pharmaceuticals developed XARACOLL (bupivacaine HCl collagen-matrix; INL-001)/300 mg (3 x 100 mg implants). It is indicated for placement into the surgical site in adults to produce postsurgical local analgesia following open inguinal hernia repair. NDA 209511 was originally submitted on October 31, 2016. However, a Refuse to File (RTF) letter was issued to this NDA on December 23, 2016 by the Agency because the Applicant failed to sufficiently bridge the clinical formulation and commercial formulation.

On 2/2/2018, the Applicant resubmitted this NDA but a CR was issued on 11/28/2018. During that review cycle, this NDA was deemed adequate from a Biopharmaceutics perspective.

On 2/26/2020, the Applicant submitted an amendment to address the deficiencies in the CR letter. In Module 3.2.P.8.3, the Applicant submitted all stability dissolution data through the proposed expiry period. However, these data were reported as ranges instead of individual values for all time points; therefore, we could not ensure if the batches on which Stage 2 Testing was conducted meet the approved dissolution criteria.

In the response to Biopharmaceutics IRs, the Applicant submitted all of the requested dissolution data, which show that all batches meet the approved dissolution acceptance criteria at Stage 1 or Stage 2.

Conclusion and Recommendation:

From a Biopharmaceutics perspective, NDA 209511-ORIG-1-RESUB-44 for XARACOLL (bupivacaine HCl collagen-matrix; INL-001)/300 mg (3 x 100 mg implants) is adequate.

List Submissions being reviewed (table):

2/26/2020	eCTD-0043/NDA 209511727 resubmission
7/8/2020	eCTD-0050/Response to Biopharmaceutics Information Request
7/15/2020	eCTD-0051/Response to Biopharmaceutics Information Request

Highlight Key Outstanding Issues from Last Cycle: None.

Concise Description Outstanding Issues Remaining: None.

Stability dissolution data and Acceptance Criteria

Reviewer's Assessment: ***{Adequate}***

1. Approved dissolution method and acceptance criteria

During the last cycle of review, the following dissolution method and acceptance criteria were approved:

Table 1. Approved dissolution method and acceptance criteria

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
USP Type II (Paddle) with customized sinkers	50 rpm	pH 6.8 Phosphate buffer, 37 ± 0.5 °C	500 mL	0.5 (b) (4) 2 h (b) (4) 6 h: NL (b) (4)

2. Stability dissolution data

The Applicant provided a significant amount of new stability data in this resubmission. However, there are many dissolution failures on stability at Stage 1. Specifically, those batches failed to meet the approved dissolution acceptance criteria at Stage 1 at many stability time points, and the Applicant conducted Stage 2 testing and reported that all of them meet the criteria at Stage 2.

However, the Applicant reported dissolution ranges instead of individual dissolution data; therefore, we could not confirm whether those batches truly meet the acceptance criteria at Stage 2.

In the response to Biopharmaceutics IRs (see Appendix for details), the Applicant submitted all of the requested individual dissolution data, which show that all batches failed at Stage 1 meet the approved dissolution acceptance criteria at Stage 2, which is shown in Table 2 below:

Table 2. Lots that failed at Stage 1 meet the approved dissolution criteria at Stage 2

Lot Number	Lot use	Stability condition	Status at Stage 1	Status at Stage 2
17022302	Tech transfer lot	25°C/60%RH	(b) (4)	Pass at all time points at Stage 2
17022302	Tech transfer lot	40°C/75% RH		Pass at two time points at Stage 2
17032302	Tech transfer lot	25°C/60%RH		Pass at two time points at Stage 2
17032302	Tech transfer lot	40°C/75% RH		Pass at all time points at Stage 2
17010603	Tech transfer lot	25°C/60%RH		Pass at Stage 2
17112407	Process validation lot	25°C/60% RH		Pass at all time points at Stage 2
17112407	Process validation lot	40°C/75% RH		Pass at all time points at Stage 2
18022611	Secondary lots leachable stability	40°C/75% RH		Pass at all time points at Stage 2
19001902	Primary lots leachable stability	25°C/60% RH		Pass at all time points at Stage 2
19001902	Primary lots leachable stability	40°C/75% RH		Pass at Stage 2

19011802	Primary lots leachable stability	40°C/75% RH	(b) (4)	Pass at Stage 2

List of Deficiencies:

None.

Primary Biopharmaceutics Reviewer Name and Date:

Hansong Chen, PharmD, Ph.D.

OPQ/ONDP/Division of Biopharmaceutics

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

Okpo Eradiri, Ph.D.

OPQ/ONDP/Division of Biopharmaceutics

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	209511
Assessment Cycle Number	02
Drug Product Name/ Strength	XARACOLL® (Bupivacaine hydrochloride collagen matrix implants) / 300 mg (3×100 mg collagen matrices).
Route of Administration	Surgical implantation
Applicant Name	Innocoll Pharmaceuticals
Therapeutic Classification/ OND Division	OND/ON/DAAP
Manufacturing Site	Syntacoll GmbH (the manufacturing/packaging/labelin (b) (4) (b) (4) site) Donaustraße 24/Auf dem Gries 75, 93342 Saal/Donau, Germany
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
CR Resubmission	02/26/2020
Response to IR	03/30/2020

List Submissions being assessed (table):

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: NDA209511 was originally submitted on 02/02/2018. NDA209511 was reviewed and found adequate in N209511MR01 on 10/05/2018. A complete response letter (CRL) was issued on 11/30/2018 due to non-micro deficiencies. Resubmission dated 02/26/2020 is provided in response to the CRL. Submission dated 03/30/2020 is provided in response to the IR dated 03/19/2020.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents: N/A

Note to reviewer:
NDA209511 was reviewed and found adequate in N209511MR01 on 10/05/2018. Resubmission dated 02/26/2020 is provided in response to the CRL dated 11/30/2018. Resubmission addresses quality deficiencies including extractable/leachable assessment. The product presentation, container closure system, manufacturing site (b) (4) validation data, manufacturing process (b) (4) product release specification and testing methods for sterility and endotoxins testing remain unchanged, and were reviewed and found adequate in N209511MR01 on 10/05/2018.

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The acceptance criteria were satisfied in all test time points.

Acceptable

Primary Microbiology Assessor Name and Date: Yan Zheng, Ph.D. 04/07/2020

Secondary Assessor Name and Date (and Secondary Summary, as needed): Elizabeth Bearr, Ph.D., Acting Q.A.L. 04/07/2020

Yan Zheng

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Elizabeth Bearr

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Valerie Amspacher

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/s/

VALERIE R AMSPACHER
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Recommendation: Complete Response
See end of the executive summary for deficiency that will be sent to sponsor.

NDA 209511
Review # 1

Drug Name/Dosage Form	XARACOLL (bupivacaine HCl collagen-matrix implants)Implants
Strength	300 mg (3 x 100 mg implants)
Route of Administration	Implantation
Rx/OTC Dispensed	Rx
Applicant	Innocoll Pharmaceuticals
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA (SD#01)	10/31/2016	OPQ
Resubmission NDA (SD#09)	02/02/2018	OPQ
Amendment (SD#14)	03/30/2018	Micro,
Amendment (SD#16)	05/07/2018	Micro,
Amendment (SD #18)	06/01/2018	Biopharm
Amendment (SD#22)	06/28/2018	Process, Biopharm
Amendment (SD#25)	07/10/2018	Drug Product,
Amendment (SD#30)	08/07/2018	Drug Product,
Amendment (SD#31)	08/16/2018	Drug Substance, Process, Micro, Drug product, Biopharm
Amendment (SD#32)	09/14/2018	Drug Product,
Amendment (SD#33)	09/20/2018	Drug Product
Amendment (SD#34)	09/27/2018	Micro,
Amendment (SD#37)	10/04/2018	Micro,

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Debasis Ghosh	OPQ/ONDP/DNDPAPI/BII
Drug Product	Valerie Amspacher	OPQ/ONDP/DNDPII/BIV
Process	Tarun Mehta	OPQ/OPF/DPAII/BVI
Microbiology	Elizabeth Bearr	OPQ/OPF/DMA/BI
Facility	Christina Capacci-Daniel	OPQ/OPF/DIA/BII

Biopharmaceutics	Sandra Suarez/Haritha Mandula	OPQ/ONDP/DB/BII
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Debasis Ghosh	OPQ/ONDP/DNDPII/BIV
Laboratory (OTR)		
ORA Lead	Caryn McNabb/Michael Tollon	
Environmental Analysis (EA)	In accordance with 21 CFR 25.30, the applicant claimed a categorical exclusion from the requirement for an Environmental Assessment. (see Sec 1.12.14)	ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)		Adequate	08/22/2018	No review needed at this time.
	Type III *(if applicable)*					No Type III Drug Master Files (DMFs) are referenced in this application.
	Type IV *(if applicable)*					No Type IV Drug Master Files (DMFs) are referenced in this application.
	Other					NA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	77127	Bupivacaine Collagen Matrix Sponge (INNOCOLL)
RLD	NDA 016964	Marcaine (bupivacaine HCl) Injection (HOSPIRA)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH	Biocompatibility of Collagen Matrix Component of Xaracoll	Biocompatibility test report support the collagen component of the Xaracoll.	03/08/2018	Lixin Liu/Cynthia Chang

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided inadequate CMC information to assure quality and safety of the product for the intended use. More specifically, the applicant has provided an incomplete leachable assessment. The leachables from the primary packaging materials may potentially compromise quality of the product when manufactured and packaged using the proposed manufacturing process. While the drug substance (DNDAPI/ONDP), process and facility (OPF), and biopharmaceutics (DBP/ONDP) disciplines have recommended the NDA for approval, the drug product team (ONDP), in conjunction with the PT team, recommend a CR due to the lack of an adequate leachable assessment that includes a validated method which failed to ensure the quality & safety of the product for the intended use. Therefore, from the OPQ perspective, this NDA is NOT recommended for Approval. The Agency will provide a Complete Response letter indicating the deficiencies.

II. Summary of Quality Assessments

A. Product Overview

Xaracoll® (bupivacaine HCl collagen-matrix implants) containing 300 mg (3 x 100 mg) is a single-use product intended to be administered during surgery through placement within multiple layers at the surgical site for post-surgical analgesia following (b) (4)

The application has been re-submitted under 505(b)(2) of FD & C Act. The Listed Drug is Marcaine™0.25% infiltration (bupivacaine HCl 175 mg) was approved under NDA 016964. The application was originally submitted on 31-Oct-2016. The application received RTF (Refuse-to-File) status on 23-Dec-2016 due to regulatory, CMC, non-clinical, CDRH and other issues. In this re-submission, the applicant provided updated CMC & other information including response to those deficiencies.

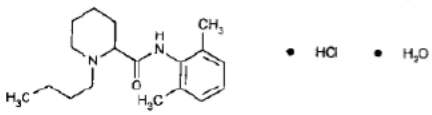
Proposed Indication(s) including Intended Patient Population	XARACOLL is a collagen-matrix implant of bupivacaine indicated for placement into the surgical site to produce postsurgical analgesia following (b) (4) It is not being studied for use in patients younger than 18 years of age.
Duration of Treatment	XARACOLL is intended for single-dose administration
Maximum Daily Dose	The recommended dose is 300 mg bupivacaine HCl (three bupivacaine HCl collagen-matrix implants, each containing 100 mg of bupivacaine HCl)

Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

The drug substance, bupivacaine hydrochloride, is a local anesthetic which can produce moderate to prolonged anesthesia. The drug substance is chemically known as 1-butyl-*N*-(2,6-dimethylphenyl)-2-piperidine carboxamide hydrochloride monohydrate. It has the following chemical structure, molecular formula and molecular weight:



Molecular formula

$C_{18}H_{28}N_2O \cdot HCl \cdot H_2O$

Relative molecular mass

342.90	monohydrate
324.89	anhydrous
288.43	free base anhydrous

It is a white (b) (4) crystalline powder with high melting point. It is soluble in water. (b) (4) (b) (4) All CMC information regarding drug substance has been referenced to DMF (b) (4) The Applicant provided a letter of authorization from the DMF holder to use the information contained in the DMF for the evaluation of the NDA. Based on last DMF review (08/22/2018), the DMF (b) (4) is adequate. Although, the CMC information in the DMF includes impurity information, the sponsor provided structures of four identified process/ degradation impurities including the information on their origin, fate and controls in the NDA. The drug substance is a USP and Ph. Eur. monographed product. The proposed specification and tests are consistent with the compendial standards.

The **drug substance review team** concluded that adequate information is provided in the application and in the Type II DMF (b) (4) to ensure identity, strength, purity and quality of drug substance. Based on the stability data, as provided in the DMF (b) (4), the **proposed retest date o** (b) **months** when stored (b) (4)

(b) (4) is adequate (See Drug Substance Review by Debasis Ghosh and Donna Christner in Panorama for additional information).

The **Facility reviewer** (OPF) has made acceptable recommendations for drug substance manufacturing and testing sites based on inspectional history (See Facility review by Christina Capacci-Daniel in panorama for additional information).

Drug Product:

The drug product, Xaracoll (bupivacaine HCl collagen-matrix implants) 300 mg is supplied as three sterile surgical implants (5 cm x 5 cm x 0.5 cm), each containing 100 mg of bupivacaine HCl and 75 mg of Type I purified collagen in individually sealed blisters. Type I purified collagen serves as an inert delivery system and releases the bupivacaine through dissolution and diffusion from the porous matrix. The implant consists of purified type I bovine collagen (b) (4) (b) (4) (b) (4) The applicant intends to store Xaracoll at 20-25 C (68-77 F), excursions permitted between 15-30°C (59-86°F). A shelf life of 24 months from the date of manufacturing is proposed.

Based on the assessment by drug product review team, the proposed **shelf life of 24 months when stored in the proposed container closure system at room temperature can be granted.**

The **Biopharmaceutics Team (**ONDP) assessed the multi-point dissolution profile comparison for the Phase 3 lots and commercial lot. Based on the assessment, the team concluded that the quality of the product is acceptable despite changes in the manufacturing process during the development of the product. The bridging issues have been adequately addressed. From biopharmaceutics perspective, the application is recommended for **approval** (see Biopharmaceutics review by Kalpana Paudel and Kelly Kitchens in panorama).

The **Process** Review Team (OPF) indicated that the commercial batch formula reflects the proposed composition, the commercial batch record, and the commercial scale. (b) (4) of the drug substance are in the formulation. The Team concluded that the applicant has provided adequate information to address drug product manufacturing, process and controls issues. The NDA is **approvable**

from process perspective. (See Process Review by Tarun Mehta and Ubrani Venkataram in panorama for additional information).

The **Microbiology** review team stated that the submission is recommended for **approval** on the basis of sterility assurance (see Microbiology review by Yan Zheng and Elizabeth Bearr).

The **Facility reviewer (OPF)** has made **acceptable** recommendations for **drug product** manufacturing and testing sites based on inspectional history (See Facility review by Christina Capacci-Daniel in panorama for additional information).

The **Facility reviewer (CDRH)** recommended VAI (Voluntary Action Indicated). However, the final classification has been deferred to CDER. According to CDER Facility reviewer (Christina Capacci-Daniel) VAI for device coverage is an **acceptable** recommendation (email dated 09/28/2018) (also see review memo provided by Arabella (Bella) Pelina in panorama).

Biocompatibility of collagen matrix component of Xaracoll was assessed by Lixin Liu of **CDRH** following an Inter-center consult request from CDER (ICCR2018-03014). The CDRH team provided following recommendations:
*"The reviewed **biocompatibility test reports support that the collagen component of the Xaracoll combination product** is non-cytotoxic, non-irritant, non-sensitive, non-pyrogenic, non-genotoxic and non-toxic in short-term condition. Therefore, I recommend no deficiencies be issued to the sponsor on the reviewed biocompatibility test reports. However, to fully demonstrate that the collagen component is biocompatible and is safe for clinical use, I defer to CDER non-clinical review group to evaluate the local tissue response (implantation study) and longer term systemic toxicity (subacute/Sub-chronic toxicity), the toxicological information of raw materials/chemicals used in the manufacture process, and extractable/leachables in the final product to capture the full and complete manufacturing process of the finished product."*

Based on the assessment of CMC information by **drug product review team**, except the following deficiency, the applicant provided adequate CMC information to ensure the quality of drug product for the intended use. While evaluating the compatibility of primary container closure system (blister package), the drug product reviewer identified an incomplete leachable assessment with primary container closure system. It has been noted that the sponsor did not submit an analytical method for the leachables. The review team indicated that leachable assessment is critical due to the proposed drug product manufacturing process. In this proces (b) (4) (b) (4) We note that the sponsor recommended the extractables study of the secondary packaging (b) (4) (b) (4) and this would have been acceptable if leachables data on the primary packaging had been available. The complete response will be

due to the lack of leachables data at several timepoints throughout stability including (b) (4) manufactured product. Based on this deficiency, drug product review team recommended a 'Complete Response'. The deficiency and information needed to resolve the deficiency are reproduced from drug product review:

An incomplete leachables assessment has been provided. An analytical method for the detection of leachables has not been provided and therefore a correlation between the extractables and leachables cannot be made. Leachables testing should be performed on (b) (4) ***manufactured produc*** (b) (4) (b) (4)

In order to resolve this deficiency:

a) From the robust extractables profiles of both primary and secondary packaging, identify and determine the target leachables

b) Develop methods which can detect these leachables in the drug product.

c) Test 3 batches of drug product at multiple time-points on stability with emphasis on (b) (4) ***manufactured product that includes ink labeling on individual blisters as planned for commercial product.***

d) We refer you to USP <1663> and <1664>.

Based on the Labeling review by drug product review team, the labels (package inserts, container and cartons) comply with all regulatory requirements from a CMC perspective (see Labeling review by Valerie Amspacher and Julia Pinto in panorama)

Based on assessment by drug product review team, the claim of categorical exclusion for **environmental assessment is acceptable** (see drug product review by Valerie Amspacher and Julia Pinto in panorama)

C. **Final Risk Assessment**

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	-	-
Physical stability (API)	• Formulation • Raw materials	L	-	-	-

	• Process parameters • Scale/equipment • Site				
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	-	-
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	-	-
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	-	-

*Risk ranking applies to product attribute/CQA
**For example, post marketing commitment, knowledge management post approval, etc.

Deficiency to be sent to the Sponsor:

An incomplete leachables assessment has been provided. An analytical method for the detection of leachables has not been provided and therefore a correlation between the extractables and leachables cannot be made. Leachables testing should be performed on (b) (4) manufactured product (b) (4) (b) (4)

In order to resolve this deficiency:
a.From the robust extractables profiles of both primary and secondary packaging, identify and determine the target leachables.
b.Develop methods which can detect these leachables in the drug product.
c.Test 3 batches of drug product at multiple timepoints on stability with emphasis on (b) (4) manufactured product that includes ink labeling on individual blisters as planned for commercial product.
d.We refer you to USP <1663> and <1664>.

Valerie Amspacher

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Date: 10/23/2018 05:07:27PM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

Julia Pinto

Digitally signed by Julia Pinto
Date: 10/23/2018 05:47:50PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

NDA 209511
Table of Contents

Post-Approval Commitments

Reviewer's Assessment:

Lifecycle Management Considerations

Reviewer's Assessment: N/A

LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Yes
Dosage form, route of administration	Yes
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Yes

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	N/A

3. ***Section 3 Dosage Forms and Strengths***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Yes
Strengths: in metric system	Yes
Active moiety expression of strength with equivalence statement (if applicable)	Yes
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Yes

4. ***Section 11 Description***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Yes
Dosage form and route of administration	Yes
Active moiety expression of strength with equivalence statement (if applicable)	Yes
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Yes
Statement of being sterile (if applicable)	Yes
Pharmacological/ therapeutic class	Yes
Chemical name, structural formula, molecular weight	Yes
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Yes
Available units (e.g., bottles of 100 tablets)	Yes
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes
Special handling (e.g., protect from light)	N/A
Storage conditions	Yes
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Yes

Reviewer's Assessment of Package Insert: Adequate
if the Prescribing Information complies with all regulatory requirements from a CMC perspective.

II. Labels:

1. ***Container and Carton Labels***

Label on outer packaging of 3 blisters

Item	Information provided in the container label (*individual blister)*	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Yes *(Yes)*	Yes
Dosage strength	Yes *(Yes)* equivalence statement present - bupivacaine HCl 100 mg (equivalent to 88.8 mg bupivacaine)	Yes - equivalence statement present - bupivacaine HCl 100 mg (equivalent to 88.8 mg bupivacaine)
Net contents	Yes	Yes
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Yes	Yes
Lot number and expiration date (21 CFR 201.17)	Yes	Yes
Storage conditions	Yes	Yes
Bar code (21CFR 201.25)	Yes	Yes
Name of manufacturer/distributor	Yes	Yes
And others, if space is available	N/A	N/A

Reviewer's Assessment of Labels: Adequate.

The labels comply with all regulatory requirements from a CMC perspective

The inked label on the 3 individual collagen containing blisters will be treated as "drug packaged in a container too small or otherwise unable to accommodate a label with sufficient space to bear the information required for compliance with section 502(e)(1) 21" which according to CFR 201.10 only needs to have brand and generic name, lot number, manufacturer. The inked label on the blisters meets this standard.

Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 10/23/2018 05:01:01PM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

Julia Pinto

Digitally signed by Julia Pinto
Date: 10/23/2018 05:48:31PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

TPLC EIR Review Memorandum

Template

Applies To: CDRH/ Office of Product Evaluation and Quality (OPEQ)

Date Effective: 06/29/2018

Use FEEDBACK✓CDRH to provide comments on this document (include Doc # 03600)

Date:	September 27, 2018
From:	Bella Pelina, CSO, CDRH/OC/DMQ/POND
Through:	Matthew Krueger, Chief, CDRH/OC/DMQ/POND
To:	Steven Kinsley, CDER/OPQ/OPRO/DRBPMI/RBPMBI, WO75 RM 4668, Steven.Kinsley@fda.hhs.gov Julia Pinto, CDER/OPQ/ONDP/DNDPII/NDPBIV, WO21 RM 2506, Julia.Pinto@fda.hhs.gov Office of Combination Products at Combination@fda.gov **RPM:** Ayanna Augustus, CDER/OND/ODEII/DAAAP, WO22 RM 3175, Ayanna.Augustus@fda.hhs.gov
Device(s) Covered:	XARACOLL® (bupivacaine HCl collagen-matrix implants) 300 mg
Firm Name:	Innocoll Pharmaceuticals
Firm Address:	Monksland Business Park, Unit 9, Block D, Athlone Co. Roscommon Ireland W37K30
Inspection Site:	Syntacoll GmbH, Saal A.d. Donau, Bavaria, Germany 93342 FEI: 3005133617
Inspection Date(s):	6/25/2018 – 6/29/2018
Firm Response Date:	7/12/2018
Investigator(s):	Tenzin Jangchup, IOG & Adaliz Santaliz-Cruz, IOG
ORA Recommendation:	VAI
CDRH Decision:	NAI for QS regulation

I. Purpose and Type of Inspection

The purpose for this inspection was a pre-approval inspection for NDA 209511.

The current inspection was conducted per CP 7346.832: Pre-Approval Inspections (b) (4) and (b) (4), for devices.

II. Background Information

Manufacturer

(b) (4) . Syntacoll GmbH is a wholly owned subsidiary of Innocoll Pharmaceuticals Limite (b) (4)

For the subject combination product, Syntacoll is the manufacturer of the bupivacaine matrix including extraction and purification of the collagen raw materials. Syntacoll currently manufactures and packages collagen-based drugs and medical device (b) (4)

Product Description

XARACOLL (bupivacaine HCL collagen-matrix implants) 300mg is indicated for postsurgical analgesia – more specifically, the delivery of bupivacaine hydrochloride (HCl) directly to the surgical site to reduce both the incisional and deep visceral pain associate with surgery.

XARACOLL will be provided as 3 sterile surgical implants (5 cm x 5 cm (b) (4) cm) composed of purified biodegradable Type I bovine-collagen matrix as the drug delivery system.

Each implant contains 100mg of the drug substance bupivacaine hydrochloride (HCl) and is individually packaged into a 50 x 50 mm (inner dimension (b) (4) blister (b) (4)) of 7 mm height that is sealed (b) (4). The blister is considered primary packaging (b) (4) (b) (4) The pouch is considered secondary packaging. The pouch will be (b) (4), with primary labeling being applied to one side of the pouch. The pouch will be then placed in a white cardboard clipboard carton (170 x 25 x 287 mm).

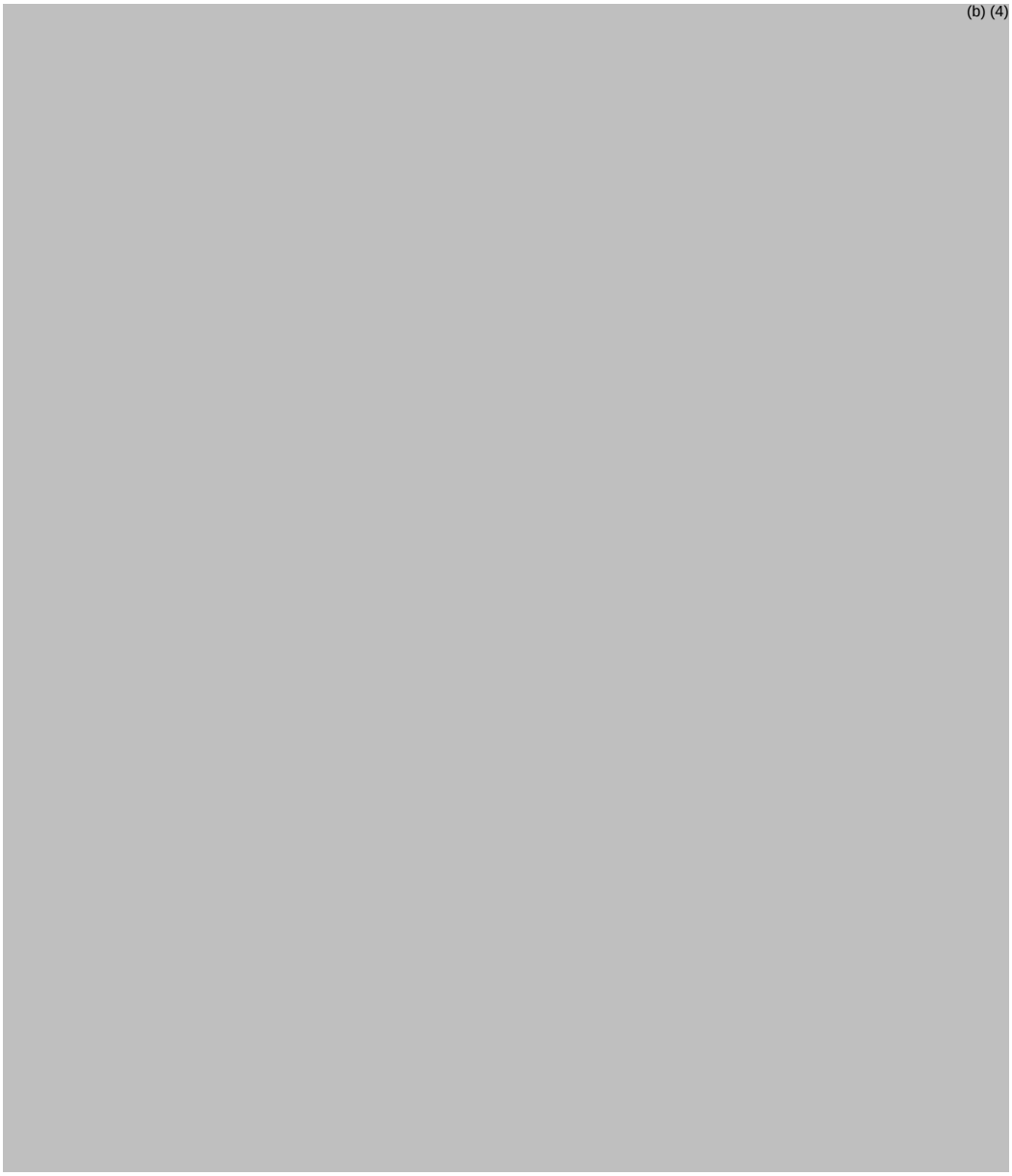
III. Regulatory History

There is no regulatory history; this is the firm's initial inspection.

IV. Quality System Review

The review of the EIR, exhibits, and the FDA form 483, and the firm's response for compliance with the QS regulation has been completed. The results of the evaluation follow below and are organized starting with the most serious violations.

(b) (4)



(b) (4)

[redacted]

V. Observations Pertaining to Other Regulations

There are no observations pertaining to other regulations.

VI. Nonsupportable Observations

There are no non-supportable FDA 483 observations.

VII. Compliance Decision

Based on the review of the documentation provided, the CDRH Office of Compliance has determined that this inspection meets the criteria of a Situation II, in Compliance Program, CP 7382.845, Part V, dated February 02, 2011.

Situation II was met because there is minimal probability that the establishment will product nonconforming and/or defective medical devices and the inspection is being classified NAI.

VIII. Recommendation

CDRH recommends that the observations cited be supported under the 21 CFR 211 regulations rather than the 21 CFR 820 regulations based on 21 CFR 4 because, though Observations 3 & 4 were cited under 21 CFR 820 regulations in the FDA 483, the firm may be operating under a CGMP system based on 21 CFR 211. Based on this recommendation, the inspection would be reclassified NAI for 21 CFR 820 device regulations for the EIR date (b) (4) However, since the observations may be potential violations under the 21 CFR 211 operating system, it may be VAI for 21 CFR 211 regulations. The final classification will be deferred to the lead center, CDER.

Reviewer: _____

signature

Team Lead/SME: _____

signature

Team Management Concurrence: _____

signature

BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 209511 Resub-9

Drug Product Name / Strength: XARACOLL (bupivacaine HCl collagen-matrix; INL-001)/ 300 mg (3 x 100 mg implants)

Route of Administration: Implants

Applicant Name: Innocoll Pharmaceuticals

Review Recommendation: **ADEQUATE**

Review Summary:

NDA 209511 for Xaracoll implant was originally submitted on October 31, 2016. The drug product underwent several manufacturing changes through the development program. Multiple formulation modifications (b) (4) (b) (4) were made to the drug dered substantial. Thus, although the proposed formulation was tested in the pivotal Phase 3 clinical studies (INN-CB-014 and INN-CB-016), the pharmacokinetic (PK) profile for this formulation was not available. The PK data (Pivotal PK study: INN-CB-013) obtained with the prior formulation cannot be applied to the commercial formulation. The future manufacturing changes being proposed to the commercial formulation was also considered major and the Applicant did not provide any data to support the bridging between formulations. Therefore, a Refuse to File (RTF) letter was issued on December 23, 2016 by the Agency. The Applicant was asked to conduct a BA/BE study using the final formulation for Xaracoll implant in the action letter.

In the current submission, the Applicant submitted the data of a new PK study (INN-CB-022) using drug product (lot 15041002) manufactured in the same clinical facility using the same collagen (b) (4) and manufactured in an identical manner to the Phase 3 lot. This study characterized the PK of the INL-001 product used in the pivotal Phase 3 studies and provided a PK comparison relative to the listed drug (LD), Marcaine™ 0.25% infiltration (bupivacaine HCl 175 mg). This study will be reviewed by Clinical Pharmacology team.

However, there has been manufacturing process optimization since completion of the repeat PK study (INN-CB-022), in preparation for future commercial manufacturing. In the current submission, the Applicant has provided multiple-point dissolution profile comparison using the Similarity Factor (f2) for the Phase 3 lot and commercial lots to confirm the lack of impact of these changes as per the FDA request during the Type B pre-NDA Meeting held on 31 July 2017 (10 August 2017 meeting minutes). f2 values are more than 50 for the three batches compared. The Applicant's data is, hence, found to be acceptable and the bridging issue between the phase 3 formulation and commercial formulation has been adequately addressed.

Additionally, the dissolution method and acceptance criteria are found to be acceptable.

From Biopharmaceutics perspective, NDA 209511 is recommended for approval.

List Submissions being reviewed (table): Dissolution method and acceptance criteria; Formulation bridging

Application 209511 - Sequence 0008 - 0008 (9) 02/02/2018 ORIG-1 /Multiple Categories/Subcategories

Application 209511 - Sequence 0017 - 0017 (18) 06/01/2018 ORIG-1 /Quality/Response To Information Request

Application 209511 - Sequence 0021 - 0021 (22) 06/28/2018 ORIG-1 /Quality/Response To Information Request

Application 209511 - Sequence 0030 - 0030 (31) 08/16/2018 ORIG-1 /Quality/Response To Information Request

Highlight Key Outstanding Issues from Last Cycle: The Applicant was asked to conduct a new PK study with INL-001 using drug product manufactured in the same way as that used for the Phase 3 study and to also bridge Phase 3 formulation to final commercial formulation.

Concise Description Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment: N/A

Solubility: N/A

Permeability: N/A

Dissolution: See below.

Background

The proposed drug product, XARACOLL (bupivacaine HCl collagen-matrix) implant is a combination product consisting of one active moiety, bupivacaine (INL-001), and a drug delivery component consisting solely of highly purified, resorbable Type 1 bovine collagen. It is a single use surgical implant composed of three collagen matrices. The dosage is 300 mg (3 x 100 mg collagen-matrix implants, equivalent to 266.4 mg bupivacaine) and the proposed indication is placement into the surgical site to produce postsurgical analgesia (b) (4)

The active ingredient, INL-001, bupivacaine, is the same as that of the listed drug, Marcaine, but the drug product is a unique dosage form based on Innocoll's proprietary COLLARX® technology.

COLLARX technology results in a highly purified, porous, biocompatible, biodegradable, and bioresorbable collagen matrix that releases the locally acting bupivacaine over time in the surgical wound. After placement of INL-001 at the site of the surgical wound, the drug release mechanism involves absorption of liquid from the wound site, which results in dissolution and diffusion of bupivacaine from the porous (b) (4) collagen matrix.

NDA 209511 for Xaracoll implant was originally submitted on October 31, 2016. However, a RTF letter was issued on December 23, 2016. The RTF letter had several CMC deficiencies, including the following major deficiency related to bridging:

The manufacturing changes implemented to the formulation tested in the pivotal pharmacokinetic (PK) study INN-CB-013 are considered substantial changes, requiring in vivo bioequivalency data. Although the proposed commercial formulation was tested in the pivotal Phase 3 studies, the PK profile for the final commercial formulation is not available and you have not provided any data to support the scientific bridge.

You must conduct a BA/BE study with the final formulation. These data will serve as a reference for multiple regulatory purposes involving your proposed drug product.

Following the RTF letter, a Type A meeting was held on February 23, 2017 to clarify/ discuss the RTF issues. In the meeting minutes dated 03/27/2017, the Sponsor stated that they will repeat the BA/BE study.

Current Submission

The Applicant resubmitted the NDA on February 2, 2018, Sequence No. 0008 to provide response to the RTF letter.

In the current submission (resubmission 9), the Applicant conducted a new PK study (INN-CB-022) with INL-001, using drug product (lot 15041002) manufactured in the same clinical facility using the same collagen (b) (4) and manufactured in an identical manner to the Phase 3 lot. This study characterized the pharmacokinetics of the INL-001 product used in the pivotal Phase 3 studies and provided a PK comparison relative to the listed drug (LD), Marcaine™ 0.25% infiltration (bupivacaine HCl 175 mg). The results from this study are summarized in Section 2.7.2 and the complete study report is provided in Section 5.3.1.2, INN-CB-022. This study will be reviewed by Clinical Pharmacology team.

A brief summary of manufacturing changes that occurred during development is provided in Table 1 (Section 2.3, Item 11).

Table 1: Summary of Manufacturing Changes during Development of INL-001

(b) (4)

During the Type B pre-NDA Meeting held on 31 July 2017 (10 August 2017 meeting minutes), the Applicant requested Agency concurrence that process optimization changes made after manufacturing the Phase 3 lots for manufacturing the commercial lots would not be considered significant changes. The FDA requested a multiple-point dissolution profile comparison for the Phase 3 and commercial lots to confirm the lack of impact of these changes, using the Similarity Factor (f2) calculation with an acceptance criterion of f2 >50 to demonstrate similarity.

In response to the FDA's request, a new dissolution study (ER-QC0051-01) was performed to compare the dissolution profiles of INL-001 by using the Phase 3 and commercial lots (see the section below).

Dissolution comparison for Phase 3 batch and the commercial batch

Dissolution studies were performed a (b) (4) (b) (4) (b) (4) The dissolution was performed in accordance with method QC6-11-00 and samples were assayed using the routine HPLC assay method QC6-009-01.

Three lots were evaluated in this study.

1. Lot 15041002 was used in the new PK study (INN-CB-022 (b) (4) (b) (4)
2. Lot 17032302 was manufactured in the (b) (4) (b) (4)
3. Finally, Lot 17051707 is representative of the **final commercial product** (b) (4) (b) (4)

Table 3 presents the mean values (± standard deviation [SD]) of % release of bupivacaine from the INL-001 collagen matrix over time in the various pH settings of the three tested lots.

Table 3. Dissolution Profiles of INL-001 with Three Lots Tested at pH (b) (4) 6.8, an (b) (4)

pH in PBS Time (minutes)	Lot Number 15041002 % Release (Mean ± SD)	 17032302 % Release (Mean ± SD)	 17051707 % Release (Mean ± SD)
(b) (4)			
pH 6.8			
15	40.3 ± 2.5	37.6 ± 1.2	39.0 ± 1.2
30	53.5 ± 3.0	47.8 ± 1.6	52.5 ± 1.4
60	65.9 ± 4.4	58.1 ± 1.9	64.6 ± 2.6
120	77.1 ± 4.6	69.9 ± 2.5	75.9 ± 4.0
360	95.7 ± 5.1	89.8 ± 1.9	93.3 ± 3.8
(b) (4)			

PBS = phosphate buffered saline; SD = standard deviation.
Data source: Summary Report ER-QC0051-01

Table 4. Similarity Analysis of Dissolution Profiles Among Lots

pH in PBS Statistic	Statistical Analysis 15041002 vs 17032302	 15041002 vs 17051707	 17032302 vs 17051707
(b) (4)			
pH 6.8			
f1 (<15)	8.8	2.2	7.3
f2 (>50)	60.4	86.9	65.6
(b) (4)			

f1 = dissimilarity factor; f2 = similarity factor; PBS = phosphate buffered saline; vs = versus.
Data source: Summary Report ER-QC0051-01

Figure 1. Dissolution Profiles (Mean ± SD % Release) of INL-001 with Three Lots Tested at pH (b) (4) 6.8, an (b) (4)

A: Tested at pH (b) (4) in PBS

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

(b) (4)

The Applicant provided all the raw data in document ERQC-000051. However, the dissolution was found to be performed only with n=8 units. The details on manufacturing and testing dates were also not available. An information request (IR) was, therefore, communicated to the Applicant (See below in list of deficiencies: Information Request 1) to submit complete comparative dissolution profile data (individual, mean, %RSD, mean profile) for **n=12** implants/batch.

The Applicant provided response to the IR comment on 6/28/2018. The batch information and dates of testing are provided below. All three lots of product were full-scale (b) (4) kg) lots, 100 mg strength, manufactured b (b) (4)

Drug product batch number	Date of manufacture	Use
Clinical Lot		
15041002	12-Feb-2015	Nonclinical study (b) (4) 134509; Clinical study INN-CB-022; Stability program SP-QC-0043.
(b) (4)		
17032302	03-Mar-2017	Tech transfer lot (put on stability SP-QC-0059).
(b) (4)		
17051707	08-Aug-2017	Process validation lot (put on stability SP-QC-0066).

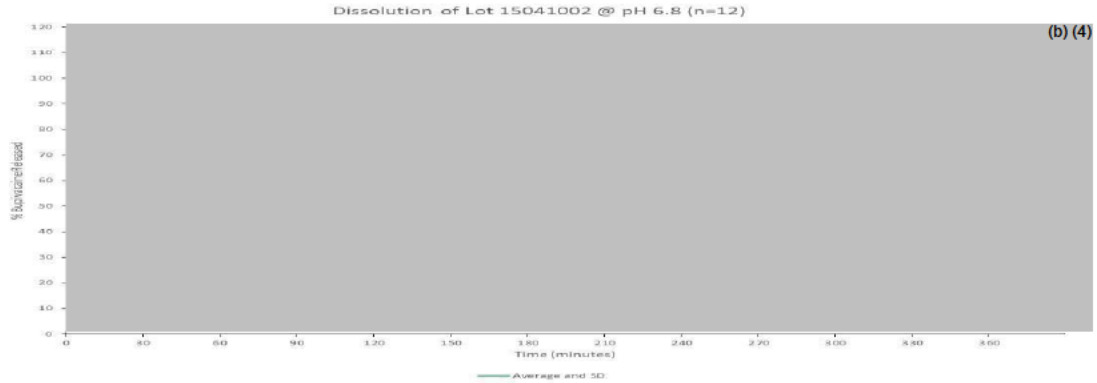
Drug product batch number	pH	Date of Testing (initial n=8 samples)	Date of Testing (new n=4 samples)
Clinical Lot			
15041002	(b) (4)	01-02Sep2017	22May2018
	6.8	08-17Mar2017 [1]	
	(b) (4)	06-14Sep2017	14-15May2018
			(b) (4)
17032302	(b) (4)	01-02Sep2017	22May2018
	6.8	08Oct2017	11May2018
	(b) (4)	06-15Sep2017	14-15May2018
			(b) (4)
17051707	(b) (4)	04Oct2017	07May2018
	6.8	07Oct2017	08May2018
	(b) (4)	14-15Sep2017	14-15May2018

[1] 12 samples were originally tested for this lot for other studies/purposes and was not specifically repeated for this study

The Applicant has provided all raw data and graph for each lot for all three pH condition in 1.11.4 Multi Module Information Amendment. However, dissolution profile as well as average and standard deviation in only the QC media (pH 6.8) are shown below.

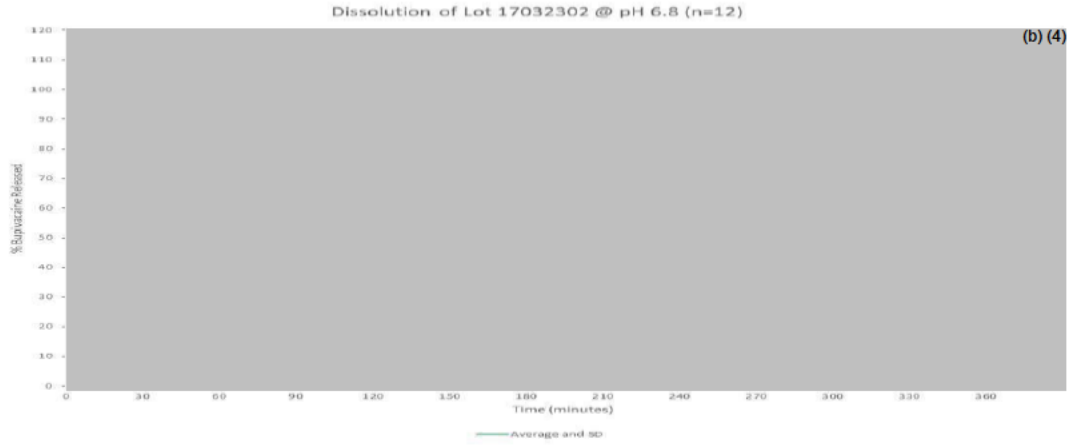
Dissolution Profile of Lot 15041002 @ pH 6.8

Time (minutes)	% Bupivacaine Released	Average	SD	% RSD
15	(b) (4)	39.6	2.4	6.1%
30		53.5	2.7	5.1%
60		66.5	4.1	6.1%
120		78.6	4.8	6.0%
360		96.8	4.8	4.9%



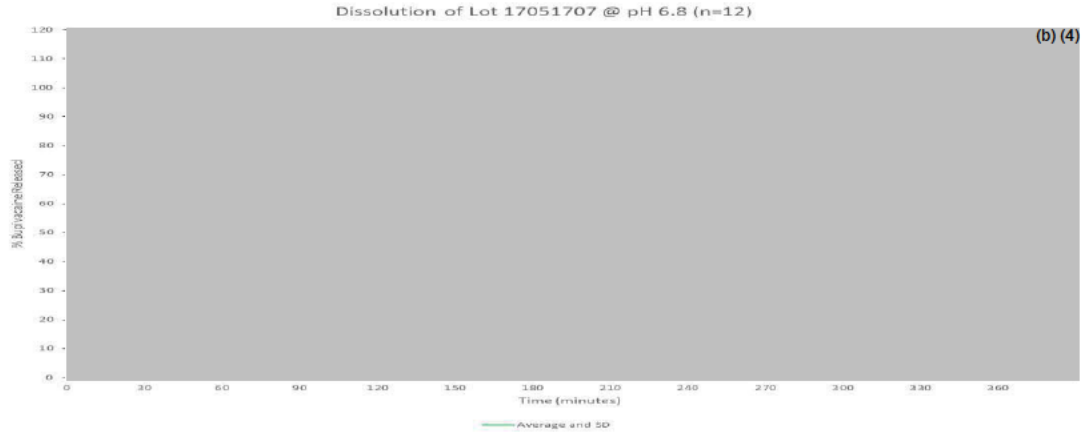
Dissolution Profile of Lot 17022302 @ pH 6.8

Time (minutes)	% Bupivacaine Released	Average	SD	% RSD
15	(b) (4)	36.9	1.4	3.8%
30		47.7	1.3	2.7%
60		58.3	1.5	2.6%
120		69.3	2.3	3.4%
360		88.7	2.4	2.7%



Dissolution Profile of Lot 17051707 @ pH 6.8

Time (minutes)	% Bupivacaine Released	Average	SD	% RSD
15	(b) (4)	37.0	3.0	8.2%
30		51.0	2.6	5.1%
60		63.6	3.1	4.9%
120		74.7	4.7	6.2%
360		91.9	4.5	4.9%



The similarity factor (f2) was calculated by this Reviewer for all 3 batches in pH 6.8 dissolution media. The f2 values between all 3 batches were more than 50 (see table below).

Lot No.	f2
Lot 15041002 vs. Lot 17022302	57.01
Lot 15041002 vs. Lot 17051707	72.37
Lot 17022302 vs. Lot 17051707	69.45

The f2 values indicate similarity between the dissolution profiles of the Phase 3 lot and commercial lots. The Applicant's response is thus acceptable.

In-Vitro Dissolution Method and Acceptance Criteria

The following dissolution method and acceptance criteria are proposed as a quality control tool for release and during stability testing:

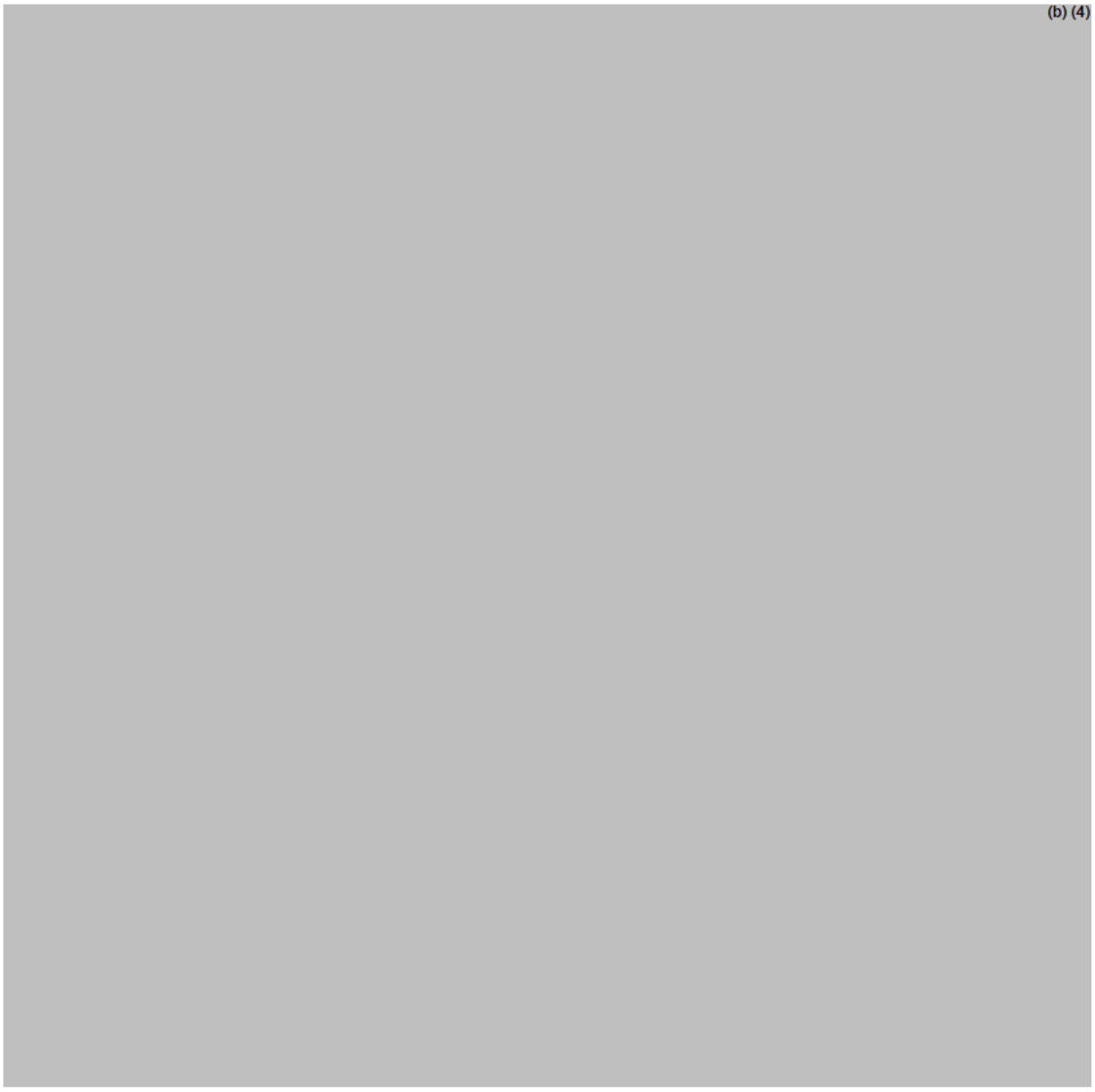
Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Proposed acceptance Criteria
Bupivacaine	Collagen implant	II (paddle) with customized sinkers	50	Phosphate buffer saline (PBS) pH 6.8	500, 37 °C ± 0.5 °C	30 min (b) (4) 120 mi 360min: NL (b) (4)

However, dissolution method development report was not found in the submission. In response to an IR (See details in list of deficiencies: Information Request 2), the Applicant provided the requested information. A summary of the information is provided below.

Dissolution method development

(b) (4)

(b) (4)

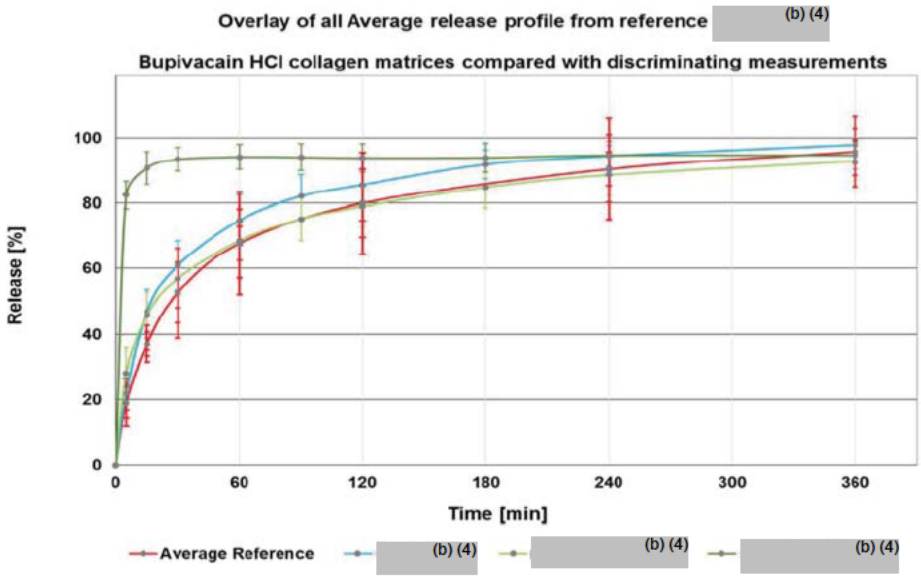


Discriminating ability of the dissolution method

A discussion of the release mechanism and discriminating ability of the dissolution method is provided in section 3.2.P.2.1 Introduction. The discriminating ability of the dissolution method was demonstrated by comparison of dissolution profiles of the drug product manufactured under target conditions vs. those of drug products intentionally manufactured to create (b) (4) defects (b) (4) (Figure

(b) (4)

Average of all reference release profiles from (b) (4) Bupivacaine HCl collagen matrices with 1 x standard deviation (SD), 2 x SD and 3 x SD. Overlaid with the data from discrimination study.



f1 and f2 test for (b) (4) Bupivacaine HCl collagen matrices against reference average

	f1	*f2*
(b) (4)	14.6	53.4
	6.8	61.3
	146.0	13.5

Based on the data provided, it can be concluded that the dissolution method is discriminating toward (b) (4) defects.

The Applicant has provided explanation of why (b) (4) defects are important for Xaracoll implants. The Applicant noted that while Xaracoll is a modified release product, the drug release

(b) (4)

(b) (4)

Dissolution acceptance criteria

In the Justification of Specifications, the Applicant mentioned that a total of 12 different XARACOLL batches from 2010 to the present were evaluated using the improved dissolution methodology to set the specification. Since no data was located in the submission, the Applicant was requested to provide complete dissolution data for these 12 batches (individual, mean, %RSD, mean profile, n=12/batch). An IR was, therefore, communicated to the Applicant (See below in list of deficiencies: Information Request 1). The Applicant provided response to the IR comment on 06/01/2018 and submitted complete dissolution data for all the batches in 1.11.1 Quality Information Amendment. Information for each lot included in the dissolution testing is provided in Table below.

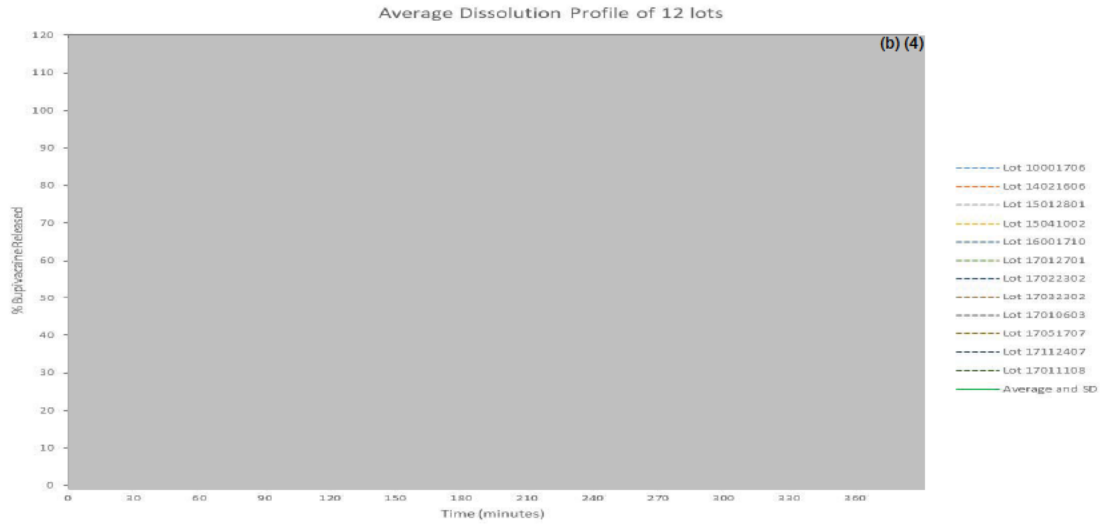
Drug Product Lots Tested

Drug product batch number	Date of manufacture	Date of Testing (2017)	Use
Clinical Lots			
10001706	21-Jun-2010	09Feb - 13Aug	Nonclinical studies (b) (4) 134501, (b) (4) 134502; Clinical study INN-CB-010.
14021606	20-Jun-2014	09Feb - 15Oct	Nonclinical studies (b) (4) 134506, (b) (4) 134508; Clinical study INN-CB-013; Stability program SP-QC-0039.
15012801	11-Feb-2015	09Feb - 13Oct	Clinical studies INN-CB-014, INN-CB-016; Stability program SP-QC-0043.
15041002	12-Feb-2015	03Mar - 26May	Nonclinical study (b) (4) 134509; Clinical study INN-CB-022; Stability program SP-QC-0043.

Drug product batch number	Date of manufacture	Date of Testing (2017)	Use
(b) (4)			
16001710	19-Oct-2016	09Feb - 15May	Tech transfer lot
17012701	07-Feb-2017	10May – 20Jul	Tech transfer lot
17022302	01-Mar-2017	10May – 13Oct	Tech transfer lot (put on stability SP-QC-0059).
17032302	03-Mar-2017	10May – 15Oct	Tech transfer lot (put on stability SP-QC-0059).
17010603	14-Mar-2017	16May – 01Jun	Tech transfer lot (put on stability SP-QC-0059).
(b) (4)			
(final process)			
17051707	08-Aug-2017	07Oct – 10Oct	Process validation lot (put on stability SP-QC-0066).
17112407	10-Aug-2017	09Oct – 15Oct	Process validation lot (put on stability SP-QC-0066).
17011108	16-Aug-2017	09Oct – 15Oct	Process validation lot (put on stability SP-QC-0066).

Average Dissolution Profile of All 12 Lots

	% Bupivacaine Released														
Time (minutes)	Lot 10001706	Lot 14021606	Lot 15012801	Lot 15041002	Lot 16001710	Lot 17012701	Lot 17022302	Lot 17032302	Lot 17010603	Lot 17051707	Lot 17112407	Lot 17011108	Average	SD	%RSD
15	(b) (4)												39.5	2.5	6.3 %
30													**51.6**	**2.4**	**4.7 %**
45													58.4	2.5	4.4 %
60													63.3	2.7	4.2 %
90													70.1	3.0	4.3 %
120													**75.0**	**3.3**	**4.4 %**
180													81.9	3.4	4.2 %
240													87.0	3.5	4.0 %
360													**93.5**	**3.0**	**3.2 %**



Based on all data, the Applicant's proposed drug release acceptance criteria for bupivacaine implant is acceptable.

Dissolution of stability batches

On 7/31/2018, Drug Product Reviewer, Dr. Valerie Amspacher, brought to our attention that registration batches 14021606, 15012801, 15041002 stored at 25 °C ± 2 °C/60 % ± 5 % RH for 24 months did not meet the current dissolution acceptance criteria i.e. 30 min: (b) (4); 120 min: (b) (4); and 360 min: NLT (b) (4) as shown in the tables below.

Table 8 Stability results for Xaracoll batch 14021606 at 25 °C ± 2 °C/60 % ± 5 % RH (study code SP-QC0039)

Test	Specification	Initial	3 mo.	6 mo.	9 mo.	12 mo.	18 mo.	24 mo.
Appearance	White to off-white porous sponge	Complies	Complies	Complies	Complies	Complies	Complies	Complies
(b) (4)	NMT (b) (4) %	(b) (4)						
	(b) (4)							
Bupivacaine identity	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Bupivacaine content/assay	(b) (4)							
Related compound (b) (4) (HPLC)	NMT (b) (4) %							
Related compounds (GC)	Any single impurity NMT (b) (4) % Total impurities NMT (b) (4) %							
Dissolution[1]	T 30 min: NMT (b) (4) T 120 min: NLT T 360 min: NLT							
Bacterial endotoxins	NMT (b) (4) EU/implant							
Sterility	Sterile	Sterile	-	-	-	Sterile	-	Sterile
Package integrity (outer pouch)[2]	NMT (b) (4) any single value)							
Peel strength (outer pouch)[3]	NLT (b) (4) N							

[1] Range of six individual samples / specification according to valid version at time point of testing
[2] Highest value of five individual samples
[3] Lowest value of five individual samples

Table 11 Stability results for Xaracoll batch 15012801 at 25 °C ± 2 °C/60 % ± 5 % RH (study code SP-QC0043)

Test	Specification	Initial	3 mo.	6 mo.	9 mo.	12 mo.	18 mo.	24 mo.
Appearance	White to off-white porous sponge	Complies	Complies	Complies	Complies	Complies	Complies	Complies
(b) (4)	NMT (b) (4) %							(b) (4)
								(b) (4)
Bupivacaine identity	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Bupivacaine content/assay								(b) (4)
Related compound (b) (4) (HPLC)	NMT (b) (4) %							(b) (4)
Related compounds (GC)	Any single impurity NMT (b) (4) % Total impurities NMT (b) (4)							
Dissolution[1]	T 30 min: NMT (b) (4) T 120 min: NLT T 360 min: NLT							
Bacterial endotoxins	NMT (b) (4) EU/implant							
Sterility	Sterile	Sterile	-	-	-	Sterile	-	Sterile
Package integrity (outer pouch)[2]	NMT (b) (4) (any single value)							(b) (4)
Peel strength (outer pouch)[3]	NLT (b) (4) N							

[1] Range of six individual samples / specification according to valid version at time point of testing
[2] Highest value of five individual samples
[3] Lowest value of five individual samples
[4] Specification in place at the time only required average of 6 samples to meet specification

Table 14 Stability results for Xaracoll batch 15041002 at 25 °C ± 2 °C/60 % ± 5 % RH (study code SP-QC0043)

Test	Specification	Initial	3 mo.	6 mo.	9 mo.	12 mo.	18 mo.	24 mo.
Appearance	White to off-white porous sponge	Complies	Complies	Complies	Complies	Complies	Complies	Complies
(b) (4)	NMT (b) (4) %							(b) (4)
								(b) (4)
Bupivacaine identity	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Bupivacaine content/assay								(b) (4)
Related compound (b) (4) (HPLC)	NMT (b) (4) %							(b) (4)
Related compounds (GC)	Any single impurity NMT (b) (4) % Total impurities NMT (b) (4)							
Dissolution[1]	T 30 min: NMT (b) (4) T 120 min: NLT T 360 min: NLT							
Bacterial endotoxins	NMT (b) (4) EU/implant							
Sterility	Sterile	Sterile	-	-	-	Sterile	-	Sterile
Package integrity (outer pouch)[3]	NMT (b) (4) (any single value)							(b) (4)
Peel strength (outer pouch)[4]	NLT (b) (4) N							

[1] Range of six individual samples / specification according to valid version at time point of testing
[2] Results pending
[3] Highest value of five individual samples
[4] Lowest value of five individual samples

On 8/2/2018, an IR was communicated to the Applicant to explain these failures and discuss corrective actions to avert such dissolution failures (see List of deficiencies: IR 2 below).

In a response provided on 08/16/2018, the Applicant noted that the dissolution method historically demonstrated significant variability, but no changes were deemed necessary as the results met the

specifications in place at the time. They noted that this is the case for all the stability data shown in section 3.2. P.8.3.

(b) (4)

The Applicant also noted that a total of 12 different XARACOLL batches (n=12) from 2010 to the present were evaluated using the improved dissolution methodology. These data were submitted earlier in response to a deficiency (see List of deficiencies: IR 1 below) and the summary is presented in the review section *Dissolution acceptance criteria*. This included the lots referenced in this stability-related IR with lot 14021606 tested at a minimum of 32 months of age and lots 15012801 and 15041002 being at or beyond the proposed 24-month shelf life. The individual data of each batch is presented below.

Figure 2: Dissolution Profile of Lot 14021606

Time (minutes)	% Bupivacaine Released	Average	SD	%RSD
15	(b) (4)	37.1	2.0	5.3 %
30		49.6	2.3	4.5 %
45		57.9	3.2	5.5 %
60		64.4	3.7	5.8 %
90		73.1	4.1	5.6 %
120		79.2	4.0	5.1 %
180		86.8	3.9	4.5 %
240		92.4	3.7	4.0 %
360		98.3	3.6	3.6 %

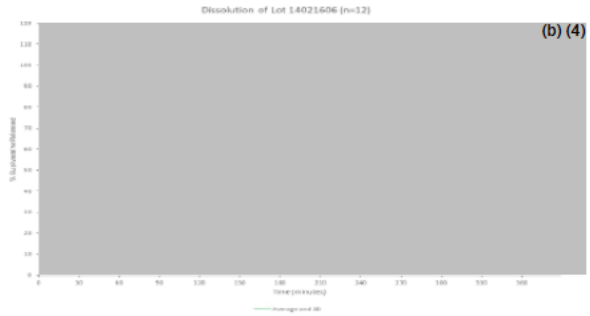
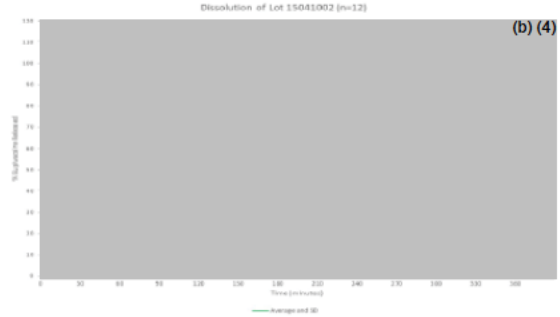


Figure 3: Dissolution Profile of Lot 15012801

Time (minutes)	% Bupivacaine Released	Average	SD	%RSD
15	(b) (4)	37.8	4.9	12.9 %
30		52.2	5.2	10.0 %
45		60.6	5.5	9.1 %
60		67.1	6.0	9.0 %
90		75.0	7.7	10.2 %
120		80.7	8.5	10.5 %
180		87.7	8.7	10.0 %
240		92.5	8.5	9.2 %
300		98.2	8.1	8.5 %

Figure 4: Dissolution Profile of Lot 15041002

Time (minutes)	% Bupivacaine Released	Average	SD	%RSD
15	(b) (4)	59.4	2.5	8.2 %
30		53.6	3.0	5.6 %
45		61.6	4.5	7.3 %
60		66.5	5.1	7.7 %
90		73.4	5.9	8.1 %
120		78.1	6.3	8.1 %
180		84.7	6.3	7.4 %
240		89.9	6.3	7.0 %
300		95.6	5.4	5.6 %



As can be seen from the data, all three batches comply with the current dissolution acceptance criteria at or even beyond the proposed 24-month shelf life. Thus, the risk is low, and the batches meet the current dissolution acceptance criteria during the shelf-life. Hence, the Applicant's justification is acceptable.

Comparative in vitro/in vivo studies

The Applicant has also conducted in vitro dissolution study using INL-001 implants from the same batch (Lot 14021606) as that used in an in vivo release rate study (b) (4) 134508) in beagle dogs and the PK clinical study (INN-CB-013).

Figure 2 shows the percentage of bupivacaine release in vitro from the INL-001 implant over time. Approximately 60% of the bupivacaine was released from the matrices after 1 h (60 min), 80% was released after 2 h (120 min), and complete release of drug occurred at about 450 minutes (the following figure incorrectly marks complete release as occurring at 24 hours).

Figure 2. Mean Bupivacaine Release Profile from INL-001 (Lot 14021606)

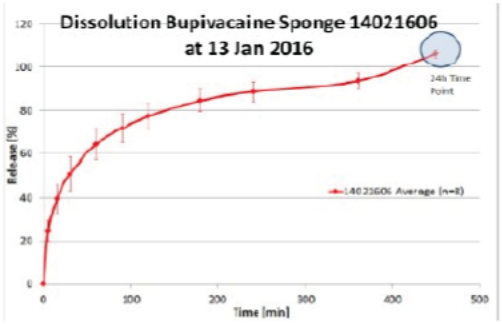
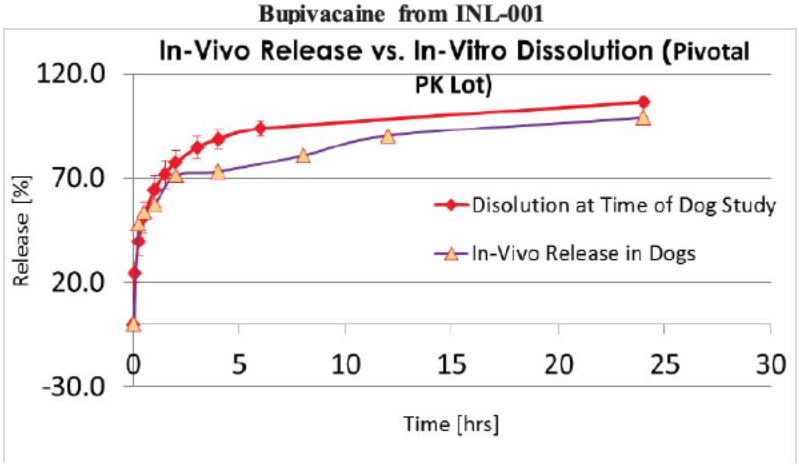


Figure 3 presents the in vivo release data compared to the in vitro dissolution data. In Vivo Release of Bupivacaine from INL-001 collagen-matrix (study (b) (4)134508) was evaluated following surgical placement into the subcutaneous tissue of Beagle dogs. Residual INL-001 implant material was retrieved at various time points after surgical implantation and evaluated for bupivacaine levels. The in vitro dissolution profile of bupivacaine from the matrix was similar to that observed in vivo. Approximately 57.4% of the bupivacaine was released from the matrix after 1 hour (60 min), 80.8% was released after 8 hours, and 99.0% was released at 24 hours following implantation in dogs.

Figure 3. In Vivo Release of Bupivacaine from INL-001 versus In Vitro Dissolution of Bupivacaine from INL-001



List of Deficiencies:

Information Request 1 (submitted on April 17, 2018)

The following deficiencies were communicated to the Applicant during first (filing) review cycle.

1. You have provided dissolution data for n=8 implants for 3 batches (Lot 15041002, Lot 17032302, Lot 17051707) in *Summary of Biopharmaceutic Studies and Associated Analytical Methods*. We request that you submit complete comparative dissolution profile data (individual, mean, %RSD, mean profile) for **n=12** implants/batch and complete batch information (batch no. and batch manufacturing date, site, size, and the dates of dissolution testing) for all the three lots.

2. In the Justification of Specifications, you mentioned that a total of 12 different XARACOLL batches from 2010 to the present were evaluated using the improved dissolution methodology. Provide complete dissolution data for these 12 batches (individual, mean, %RSD, mean profile, n=12/batch). Also provide complete batch information (batch no. and batch manufacturing date, site, size, and the dates of dissolution testing) for all lots. If you have already provided this data, advise us where the information can be found in the submission.

The Applicant provided responses to the IR comments #2 and #1 on 6/1/2018 and 6/28/2018, respectively. The summary response to each deficiency is provided below.

Reviewer's comment for IR 1

As requested, the Applicant provided in vitro dissolution data for n=12 implants for 3 batches (Lot 15041002, Lot 17032302, Lot 17051707). The data are presented in section *Dissolution comparison for Phase 3 batch and the commercial batch* above. The Applicant's response is acceptable.

Reviewer's comment for IR 2

As requested, the Applicant provided complete in vitro dissolution data for 12 batches. The data are presented in section *Dissolution acceptance criteria* above. The Applicant's response is acceptable.

Information Request 2 (submitted on July 26, 2018 for IR #1 and August 3, 2018 for IR #2)

The following deficiencies were communicated to the Applicant during second review cycle.

1. We could not locate the dissolution method development report. Submit the dissolution method development report with the following information:

a. Solubility data for the drug substance over the physiologic pH range.

b. Detailed description of the dissolution method being proposed for the evaluation of your product, and the developmental parameters (i.e., selection of the apparatus, in vitro dissolution media, rotation speed, pH, assay, sink conditions, etc.) supporting the selection of the proposed dissolution method as the optimal test for your product. Clearly specify the testing conditions used for each test. We recommend the use of at least twelve samples per testing variable.

c. Data demonstrating the discriminating ability of your proposed dissolution method. In general, ensure the testing conducted to demonstrate the discriminating ability of the selected dissolution method compares the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) 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). Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., f2 values) comparing the test and reference drug products. In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent to the reference-target drug product.

Reviewer's comment

The Applicant provided all the requested information on 08/16/2018. A summary of the information is provided in the review section *Dissolution method development* above. The Applicant's response is acceptable.

2. All registration batches are expected to meet the dissolution specification in your stability program through your proposed expiry period. Dissolution failures were observed for batches 14021606, 15012801, 15041002 stored at 25 °C ± 2 °C/60 % ± 5 % RH for 24 months at the S1 stage of testing (n=6 individual samples). Explain these failures and discuss corrective actions to avert such dissolution failures.

Reviewer's comment

The Applicant provided the justification on 08/16/2018 that is summarized in the review section *Dissolution of stability batches* above. The Applicant's response is acceptable.

Primary Biopharmaceutics Reviewer Name and Date: Kalpana Paudel, Ph.D. 07/10/2018; 09/21/2018

***Secondary Reviewer Name and Date*:**
Kelly M. Kitchens, Ph.D., September 26, 2018

Kalpana Paudel

Digitally signed by Kalpana Paudel
Date: 10/05/2018 10:57:57AM
GUID: 562e1e15002f200f35c6ccac959cdb34

Kelly Kitchens

Digitally signed by Kelly Kitchens
Date: 10/05/2018 12:18:47PM
GUID: 508da6fd0002849b46320c175775bdfa

MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA: 209511

Drug Product Name / Strength: XARACOLL® (Bupivacaine hydrochloride collagen matrix implants) /300mg (3×100 mg collagen matrices).

Route of Administration: Surgical implantation

Applicant Name: Innocoll Pharmaceuticals

Manufacturing Site:
Syntacoll GmbH (the manufacturing/packaging/labelin (b) (4) site)
Donaustraβe 24/Auf dem Gries 75, 93342 Saal/Donau, Germany

(b) (4)

Method of Sterilization (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary: The submission is **recommended** for approval on the basis of sterility assurance.

List Submissions Being Reviewed: 02/02/2018; 03/30/2018; 05/07/2018; 08/16/2018; 09/27/2018; 10/04/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: This is an eCTD submission. 02/02/2018 is a resubmission after RTF; 03/30/2018 submission is an amendment for the drug labeling; 05/07/2018 submission is the response to the Agency's information request dated 04/17/2018; 08/16/2018 submission is the response to the Agency's information request dated 07/26/2018;

09/27/2018 submission is the response to the Agency's information request dated 09/13/2018; 10/04/2018 submission is the response to the Agency's information request dated 10/02/2018.

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

No review was conducted on the drug substance as the drug substance is non-sterile.

P.1 Description of the Composition of the Drug Product

- **Description of drug product** –XARACOLL® is a white to off-white drug/device combination product composed of a collagen matrix as the device component and the anesthetic bupivacaine HCl as the drug substance component. The product is a single use surgical implant. Each 5×5×0.5 cm (100mg bupivacaine HCl) implant is filled in a 5×5×1.5 cm (b) (4) (PETG) blister, and sealed (b) (4). Three individual blisters are packaged in a (b) (4) triplet carrier, and sealed in (b) (4) pouch.
- **Drug product composition** –
  The composition of the bulk dispersion (b) (4) (b) (4)t, is as following:

Component	Quality standard	Quantity
		% w/w (bulk formulation) (b) (4)
Bupivacaine HCl monohydrate[1]	USP/Ph. Eur.	(b) (4)
Type I purified bovine collagen[2]	(b) (4)	
		(b) (4)
Total	100.0	(b) (4)
		(b) (4)

Table is reproduced from the submission.

- **Description of container closure system** –
  The container closure system for XARACOLL® consists of a primary container closure system (triplet carrier for single blisters) and a secondary pouch.
  Primary container:

Component	Description	Supplier
Blister	63.2 mm×63.2mm×15mm (outer size) (b) (4) blister	

(b) (4)

Secondary container:

Component	Description	Supplier
Triplet blister carrier frame	214 mm×83mm×17mm (outer size) (b) (4) (b) (4)	(b) (4)
Pouch	220 mm ×280 mm (b) (4): (b) (4)	

The product is placed in the secondary package (pouch), which contains (b) (4) (b) (4). The product (b) (4) (b) (4) (b) (4)

Reviewer's Assessment: ***Adequate***

The product description is acceptable.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity (3.2.P.2.5, Microbiological attributes, p4-13)

(b) (4)

The container closure integrity tests for the secondary package include:

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The routine sterility testing method is acceptable.

P.7 Container Closure

Summary table of the container closure system proposed—see P.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

XARACOLL® is stored at 20-25°C. The shelf life is 24 months from the date of manufacturing (3.2.P.8.1, p6).
Product specifications listed in 3.2.P.5.1 are used for both release and stability. The stability testing schedule is described in Section P 8.3.

Testing (3.2.P.8.1, p5-6)	Test method	Acceptance criteria
Sterility	USP <71>	Sterile
Endotoxins	USP <85>	NMT (b) (4)/implant
Pressure decay (CCIT) (outer pouch)	P 2.5 CCIT	NMT (b) (4) mbar (commercial batches); NMT (b) (4) mbar (clinical batches)
Seal strength (CCIT) (outer pouch)	P 2.5 CCIT	NLT (b) (4)

Reviewer's Assessment: ***Adequate***

The stability summary is acceptable.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

A minimum of one batch of XARACOLL® will be included each year in a stability study. The batch will be placed at long term condition (25±2°C/60±5% RH) and tests (sterility, endotoxins, and CCIT tests) are performed at 0, 12, 24, 36, 48, and 60 months. Test methods and acceptance criteria are described in P 5.2 (endotoxins and sterility test) and P.2.5 (CCIT test).

Reviewer's Assessment: ***Adequate***

The post-approval stability protocol and stability commitment are acceptable.

P.8.3 Stability Data

Stability testing (sterility, endotoxins, seal strength, pressure decay) are performed for the following batches at the indicated frequency:

	Condition	Temperature/humidity	Frequency	Available data
Clinical lots 10001706, 10011706, 10021706	Long term condition	25±2°C/60±5% RH	0,48,60 months	60 months
	Accelerate condition	40±2°C/75±5% RH	0, 6 months	6 months
Clinical lots 14021606,	Long term condition	25±2°C/60±5% RH	0,12,24 months	24 months

15012801, 15041002	Intermediate condition	30±2°C/65±5% RH	0,12,24 months	12 or 24 months
	Accelerate condition	40±2°C/75±5% RH	0, 3, 6, 12 months	6 or 12 months
Clinical scale lots 17022302, 17032302, 17010603	Long term condition	25±2°C/60±5% RH	0, 12, 24,36,48,60 months	0 months
	Accelerate condition	40±2°C/75±5% RH	0, 1, 3, 6 months	1 months

(b) (4)

(b) (4)

No stability data is available for commercial scale lots 17051707, 17112407, 17011108 that are manufactured in commercial facility (3.2.P.8.3, p1).

The acceptance criteria were satisfied in all test time points (3.2.P.8.3, p2-27).

Reviewer's Assessment: ***Adequate***

The provided stability data is acceptable.

A Appendices

A.2 Adventitious Agents Safety Evaluation

XARACOLL is a combination product using collagen matrix as the device component. The manufacture of the (b) (4)

(b) (4)

Reviewer's Assessment: ***Adequate***

The adventitious agent safety evaluation is acceptable.

A.2.1 Materials of Biological Origin (3.2.A.2, p1-2)

(b) (4)

(b) (4)

Information request (April 23, 2018):

(b) (4)

Applicant's response (May 7, 2018):

(b) (4)

Notes to reviewer:

(b) (4)

Reviewer's Assessment: ***Adequate***

The provided official BSE/TSE statement is acceptable.

A.2.2 Testing at Appropriate Stages of Production

(b) (4)

(b) (4)

Reviewer's Assessment: ***Adequate***

The approaches to control viral contamination is acceptable.

(b) (4)

(b) (4)

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Comparability Protocols-N/A

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

2.A. Package Insert

The product is a single-dose, sterile implant. It is stored at 20-25°C and the expiration date is labeled (1.14.1.1, p1).
Route of administration: this implant should be placed in 2 or 3 layers of the surgical site (1.14.1.3, p1).

(b) (4)

Applicant's response (May 7, 2018):
The applicant states that there is no significant risk of contamination of the primary packaging after removal from the outer pouch.
The secondary container (pouch) is prepared for entry into the surgical area using standard practices. Once within the controlled environment of the surgical suite, the secondary pouch may be peeled opened and the product may be removed from the primary container closure system for use.
After the secondary pouch is opened, the product should be used during the prescribed procedure (b) (4)
(b) (4).
Product label states that "do not use XARACOLL if the packaging has been compromised" (see notes to reviewer).

Notes to reviewer:
The product label states that "do not use XARACOLL if the packaging has been compromised", it does not explicitly state that (b) (4)
(b) (4)

(b) (4) This concern has been communicated to the labeling reviewer. No clarification will be requested from quality microbiology.

Reviewer's Assessment: ***Adequate***

The package insert is acceptable.

Primary Microbiology Reviewer Name and Date:
Yan Zheng, Ph.D. 10/05/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Elizabeth Bearr, Ph.D. 10/05/2018

Yan Zheng

Digitally signed by Yan Zheng
Date: 10/05/2018 04:20:36PM
GUID: 58ca9ce301e697996a209b08cf0d70b6

Elizabeth Bearr

Digitally signed by Elizabeth Bearr
Date: 10/05/2018 04:20:27PM
GUID: 55370d1e00cfd67fc04d8bfbedbf3096