

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209511Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: August 12, 2020

To: Renee Petit-Scott, M.D.
Clinical Reviewer
Division of Anesthesia, Addiction Medicine and Pain Medicine (DAAP)

Allison Meyer, Regulatory Project Manager, (DAAP)

Lisa Basham, Associate Director for Labeling, (DAAP)

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for XARACOLL® (bupivacaine HCl) implant

NDA: 209511

In response to DAAP's consult request dated August 12, 2020, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for XARACOLL® (bupivacaine HCl) implant.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAAP on August 10, 2020 and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 30, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Koung Lee at (240) 402-8686 or Koung.lee@fda.hhs.gov.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 24, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 209511
Product Name and Strength:	Xaracoll (bupivacaine HCl collagen-matrix implants) implant, 100 mg
Applicant/Sponsor Name:	Innocoll Pharmaceuticals
OSE RCM #:	201602968
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

As part of their Class 2 Resubmission, Innocoll submitted the revised container label, pouch labeling and carton labeling received on February 26, 2020 for Xaracoll. The revisions are in response to recommendations that we made during a previous label and labeling review.^a The Applicant also submitted the proposed Prescribing Information (PI) and additional four-pack and ten-pack carton labeling. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the labels and labeling for Xaracoll (Appendix A) to determine if they are acceptable from a medication error perspective.

2 REGULATORY HISTORY

Innocoll submitted their original NDA on October 31, 2016. On December 23, 2016, a Refuse to File (RTF) Letter was issued for NDA 209511 due to product quality, nonclinical, clinical pharmacology, biocompatibility, and regulatory deficiencies. On February 2, 2018, Innocoll submitted a complete response to the deficiencies included in the RTF letter. We reviewed the container label, pouch labeling, carton labeling and PI and identified areas of vulnerability that may lead to medication errors. Our recommendations for the container label, pouch labeling

^a Johnson, C. Label and Labeling Review for Xaracoll (NDA 209511). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 31. RCM No.: 2018-2968.

and carton labeling were sent to Innocoll and Innocoll submitted revised labels and labeling which incorporated our recommendations. However, on November 30, 2018, a Complete Response (CR) Letter was issued for NDA 209511 due to product quality and nonclinical deficiencies. Thus, on February 26, 2020, Innocoll submitted their complete response to the deficiencies included in the CR letter as a Class 2 resubmission. In their resubmission, they also included additional packaging configurations, a four-pack carton labeling and a ten-pack carton labeling. The resubmitted and newly proposed labeling are the subjects of this review.

Furthermore, we refer to our previous label and labeling review for recommendations for the PI.^b We note that the proposed PI that was submitted for this resubmission includes revisions that were not part of the PI that we reviewed during the previous review cycle. However, the revisions do not affect our previous recommendations.

3 CONCLUSION

In addition to the recommendations for the PI included in our previous review, we have identified one additional recommendation for the proposed PI. We provide our rationale for concern and recommendation to address this concern in Section 4 below.

4 RECOMMENDATION FOR DAAP

Prescribing Information (PI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The Dosage Forms and Strengths section and the How Supplied/Storage and Handling section of the Full Prescribing Information does not include information related to the color of the implants. Furthermore, the Dosage Forms and Strengths section does not include the dimensions of the implants.	Per 21 CFR 201.57(c)(4)(ii) and 201.57(c)(17), these sections should include all of the appropriate information to facilitate identification of the dosage form.	Add the color (white to off-white) to the Dosage Forms and Strengths section and How Supplied/Storage and Handling sections. Furthermore, add the dimensions of the implant (approximately 5 cm x 5 cm x 0.5 cm) to the Dosage Forms and Strengths section.

^b Johnson, C. Label and Labeling Review for Xaracoll (NDA 209511). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 31. RCM No.: 2018-2968.

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Intercenter consult request from CDER – ICCR2018-03014
Biocompatibility review
Application: NDA 209511
CDRH consult number: CON1814016

To: Allison Meyer
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP

From: Lixin Liu, Ph.D., Biologist
CDRH/ODE/DSD/PRSB2

Date: August 3, 2018

Product: Xaracoll (bupivacaine collagen matrix implant)

Sponsor: Innocoll Pharmaceuticals

Consult: biocompatibility of collagen matrix component of Xaracoll

Introduction

The sponsor, Innocoll Pharmaceuticals, submitted an NDA for their drug/device combination product, Xaracoll (bupivacaine collagen matrix implant) (NDA 209511) for review by CDER/FDA. I conducted an intercenter consultative filing review of the biocompatibility testing of the collagen matrix, the device component of Xaracoll, provided in the NDA. As the sponsor did not provide any biocompatibility information of the collagen matrix of XARACOLL, I recommended Non-Filing of this NDA, and recommended the sponsor to provide the biocompatibility information of the collagen component of XARACOLL. The Refuse to File (RTF) letter was issued which included a request to address biocompatibility concerns on the final combination product as a permanent implant (deficiency #12 of the RTF letter). The sponsor submitted response to the RTF letter, which included the biocompatibility testing on the XARACOLL combination product and the collagen component of XARACOLL. The sponsor also provided a cytotoxicity testing on XARACOLL interactively. My review of the cytotoxicity testing report determined that the results of the provided cytotoxicity testing inadequate to support the safety of the subject product and consequently requested the sponsor to repeat the cytotoxicity testing in FDA's 74-day letter. The sponsor submitted response to the 74-day letter, which included new cytotoxicity testing on the XARACOLL combination product, the collagen component of XARACOLL and the bupivacaine component of XARACOLL. The project manager, Allison Meyer, has requested an intercenter consultative review of biocompatibility of the collagen matrix component of Xaracoll that sponsor provided in their response to the RTF letter and the 74-day letter. As I do not have access to DARRAS, the CDER submission database, my review and comments are limited to the information provided by Allison Meyer and the NDA 209511 submission provided by CDER during the review of the NDA submission. Please refer to section "Review scope of current consult request" for biocompatibility test reports that I have reviewed.

Recommendation

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/Subchronic 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.

Product Summary

XARACOLL® (bupivacaine collagen implant) is a surgical implant composed of a (b) (4) purified resorbable Type I bovine collagen matrix. Each implant (5 × 5 × 0.5 cm) contains 100.0 mg of uniformly distributed bupivacaine HCl (equivalent to 88.8 mg bupivacaine as the free base) and is designed to provide controlled drug release via dissolution and diffusion from the porous (b) (4) matrix. (b) (4)

(b) (4) The composition of the drug product is provided in Table 1.

Table 1 Composition of XARACOLL

Component	Quality standard	Quantity per matrix	Function
Bovine type I collagen, purified	Ph.Eur. monograph 5.2.8	75 mg	Drug delivery system
Bupivacaine HCl	USP	100 mg	Drug substance

(b) (4)

XARACOLL product manufacturing process

XARACOLL is prepared by (b) (4)

(b) (4)

(b) (4) The 3 implants in an

(b) (4) sterile pouch are then labeled and packed into an outer (b) (4) carton for commercial distribution.

Reviewer comments

The provided manufacturing information is limited.

(b) (4)

(b) (4)

(b) (4) ***I defer to CDER reviewer to determine if the toxicology risk assessment is adequate.***

Intended use/indication for use

Use of XARACOLL is intended to produce local anesthetic concentrations at the surgical site and can be implanted at different layers within the surgical cavity. This local anesthetic administration also reduces systemic bupivacaine absorption so that the drug's most serious potential systemic toxicities, namely central nervous system and cardiovascular system toxicity, are minimized.

Summary of previous biocompatibility review for NDA 209511

- The sponsor stated that XARACOLL is a surgical implant which is intended to produce local anesthetic concentrations at the surgical site. The product can be implanted at different layers within the surgical cavity. The sponsor did not identify the biocompatibility contact classification (the nature and duration of contact) of the collagen matrix component of XARACOLL.
- Given the properties and intended use of the product, the aforementioned considerations and data needs are applicable regardless of whether the implant is considered a permanent implant or a prolonged implant: cytotoxicity, sensitization, irritation, acute systemic toxicity, subacute/subchronic toxicity, implantation, material-mediated pyrogenicity, genotoxicity, chronic toxicity and carcinogenicity according to CDRH's 2016 Biocompatibility Guidance "Use of International Standard ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management" for consideration of biocompatibility evaluation endpoints (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM348890.pdf>). The biocompatibility testing should be conducted on the final, sterilized product containing both the bupivacaine and collagen matrix. If testing of the final, finished version of the XARACOLL product results in any negative biocompatibility outcomes, sponsor should determine the reason for failure, including investigation of which of the product components contributed to failed biocompatibility testing.
- The sponsor proposed a chemical characterization of the product to address the chronic toxicity and carcinogenicity concerns. This may be an acceptable alternative approach. Provide toxicological information of raw materials/chemicals used in the manufacture process as well as the residues/leachables in the final product (e.g., Certificates of analysis (CoA), Material safety data sheets (MSDS)). Conduct a toxicology risk assessment as specified in ISO 10993-17, e.g., LD50's, NOAEL, LOAEL, etc., with a worst case comparison of a patient's exposure (i.e., consider the maximum product size and multiple product application) to known toxicity values. The acceptability of these data will be determined during the review of the resubmission.
- The sponsor conducted a rabbit pyrogenicity study on XARACOLL resulting in premature death of the test animal, and contacted the agency to propose not to repeat the rabbit pyrogenicity testing. The sponsor provided justification that the premature death of the animal is due to bupivacaine overdose

through intravenous injection; CDER review concluded that sponsor's justification is acceptable. To mitigate the risk of the presence of pyrogens in the Xaracoll final product, I requested the sponsor to repeat the rabbit pyrogenicity testing on the collagen matrix component without bupivacaine (the placebo sponge) and provide toxicological information of raw materials/chemicals used in the bupivacaine manufacture process and evaluate their pyrogenicity, to capture the full and complete manufacturing process of the finished product (for detailed information, please refer to consult memo for ICCR2017-01101).

- The sponsor did not provide cytotoxicity testing in their response to the RTF letter; they provided cytotoxicity testing report on XARACOLL interactively. The review of the testing report showed a mild cytotoxic effect of XARACOLL extracts (grade 2), and the test article preparation methods are not acceptable. Therefore, I requested the sponsor to repeat the cytotoxicity testing in FDA's 74-day letter (for detailed information, please refer to consult memo for ICCR2018-02464).

Review scope of current consult request

The review for current consult request is limited to the biocompatibility of the collagen matrix component of Xaracoll that sponsor provided in their response to the RTF letter and the 74-day letter. After discussed with Dr. Gary Bond, preclinical reviewer of CDER/OND/DAAAP, I will review the following testing reports in bold, and defer to Dr. Gary Bond to review the rest of the biocompatibility testing reports.

biocompatibility endpoint	Test article	Study #	Reviewer notes (Lixin Liu)
cytotoxicity	combination product, collagen matrix and bupivacaine	GLP-2018-0182	CDRH review
Sensitization	combination product	T1261_300	CDRH review
Irritation	combination product	T1251_800	CDRH review
Acute systemic toxicity	both combination product and collagen matrix	T0625_500/S; T0625_500	CDRH review
pyrogenicity	both combination product and collagen matrix	TU010_807; TU010_807-repeat	CDRH review
Implantation and subacute/subchronic systemic toxicity	combination product		Sponsor provided animal toxicity studies in response to deficiency 9. This approach is acceptable. I defer to CDER non-clinical review group to review.
Genotoxicity (AMES)	both combination product and Bupivacaine	AE26TM.502ICH (b) (4) V0023_311	Bupivacaine - not related to CDRH request; defer to CDER non-clinical review group to review. Combination product: CDRH review
Genotoxicity (Mouse Lymphoma Assay)	both combination product and Bupivacaine	AE26TM.704ICH (b) (4) V0573_200	Bupivacaine - not related to CDRH request; defer to CDER non-clinical review group to review. Combination product: CDRH review
Genotoxicity (Micronucleus Assay)	Bupivacaine	AE32HH.125M012ICH (b) (4)	Not related to CDRH request; defer to CDER non-clinical review group to review.
chronic systemic toxicity and carcinogenicity	Does not provide testing report; risk assessment	n/a	Sponsor provided extractable/leachable analysis and toxicology risk assessment in response to deficiency 10. This approach is acceptable. I defer to CDER non-clinical review group to review.

Biocompatibility test reports review

Cytotoxicity – MEM elution assay (report number: GLP-2018-0182)

Study title: Elution cytotoxicity test (ISO 10993-5 method) of Bupivacaine HCl Collagen - Matrix Implant

Testing facility: (b) (4)

Study purpose: This study was conducted in order to assess the possible cytotoxicity of extracts of a bupivacaine HCL collagen-matrix and a placebo collagen matrix without bupivacaine HCL.

Compliance statement: the testing is conducted in accordance with ISO 10993-5, ISO 10993-12 and 21 CFR Part 58.

Test articles:

1. Bupivacaine HCL Collagen - Matrix Implant: Lot Identification: 17011108 (T18-1235) (provided by the sponsor)
2. Placebo Collagen Matrix: Lot Identification: 18000202 (T18-1236) (also named as “Sponsor Control Article”, provided by the sponsor)
3. Bupivacaine HCL (0.25% Sensorcaine): Lot Identification: 6118316 (T18-1526) (also named as “Active Ingredient Control Article”, provided by the sponsor)

Control articles:

1. Positive control: Sterile Latex Rubber
2. Negative control: Sterile USP High Density Polyethylene Reference Standard

Test Article Preparation and Extraction:

Extracts of the test article, sponsor control article, and standard controls were prepared in accordance with ISO 10993-12:2012 using Complete MEM (MEM supplemented with 10% fetal bovine serum and an antibiotic-antimycotic solution). The test article, 5 cm x 5 cm x 0.5 cm Bupivacaine HCL collagen-matrix implant, yielding a surface area of 60 cm², were extracted employing the 3 cm²/ml surface area to extract volume ratio (60 cm²/20 ml), in accordance with the ISO 10993-12 procedure for Absorbents and Hydrocolloids. The absorption capacity of the test article was determined to be 3.8 ml, and was added to the standard 20 ml extraction volume as indicated above. The sponsor control article was prepared similarly to the test article. The active ingredient control was prepared employing a 1:2 dilution (equal volumes) of 0.25% Sensorcaine and 2X Complete MEM to yield a 1.25 mg/ml solution of Bupivacaine HCL in 1X Complete MEM. The standard positive control was prepared employing the 0.2 gm/ml preparation ratio. The standard negative control was prepared employing the 3 cm²/ml preparation ratio.

The test article and control preparations were incubated for 24 ± 2 hours at 37 ± 1 °C in a humidified incubator. At the end of the extraction period, the extract preparations were shaken or agitated and aseptically decanted into dry, sterile Type I glass vessels. The extracts were not filtered, centrifuged, or otherwise processed, and were immediately used for testing.

Reviewer comments

- *The test article preparation and extraction is consistent with the extraction conditions and methods recommended in ISO 10993-12.*
- *The testing report also reported extract/Sample observations. Since the sponsor conducted an investigational study 2018-RES-039 to investigate the pH measurement after the extractions, the consultant will comment on the extract/Sample observations in the report 2018-RES-039 below.*

Methods:

L929 cells were grown until an approximately 80% confluent monolayer existed. The medium was carefully removed from each monolayer. The undiluted test extract and dilutions (1:4, 1:16, 1:64, and 1:256) were evaluated in triplicate. The active ingredient control dilutions, as well as, the positive, negative, sponsor, and blank controls were also processed in triplicate. All plates were incubated at 37 ± 1 °C in a humidified atmosphere containing 5 ± 1 % CO₂ in air for 48 ± 2 hours. Following incubation, the plates were examined microscopically to determine qualitative morphological reactivity using the following grading system:

<u>Grade</u>	<u>Reactivity</u>	<u>Conditions of all Cultures</u>
0	None	Discrete intracytoplasmic granules; no cell lysis, no reduction of cell growth.
1	Slight	Not more than 20% of the cells are round, loosely attached and without intracytoplasmic granules or show changes in morphology; occasional lysed cells are present; only slight growth inhibition observable.
2	Mild	Not more than 50% of the cells are round, devoid of intracytoplasmic granules, no extensive cell lysis; not more than 50% growth inhibition observable.
3	Moderate	Not more than 70% of the cell layers contain rounded cells or are lysed; cell layers not completely destroyed, but more than 50% growth inhibition observable.
4	Severe	Nearly complete or complete destruction of the cell layers.

The test article meets the requirements of the test if the response to the test article is not greater than grade 2 (mildly reactive). The achievement of a grade greater than 2 is considered a cytotoxic effect.

Results:

Results are presented in Table I of this report.

- The negative control showed no response (grade 0) and the positive control elicited severe reactivity (grade 4), therefore suitability of the test system was confirmed.
- The Sponsor Control (Placebo Collagen Matrix lacking bupivacaine HCL) did not induce cytotoxicity (grade 0).
- The test article, extract of Bupivacaine HCL Collagen - Matrix Implant induced severe cytotoxicity (grade 4) at a neat extracts, and a dilution of 1:4, slight cytotoxicity (grade 1) at a dilution of 1:16, no cytotoxicity (grade 0) at a dilution of 1:64 and 1:256.

- The active ingredient control, Bupivacaine HCL (0.25% Sensorcaine), elicited severe cytotoxicity at a dilution 1:2 and 1:8 (0.031 % bupivacaine HCL) and no cytotoxicity at a dilution 1:32 (0.008% bupivacaine HCL) and 1:128 (0.002% bupivacaine HCL)

ELUTION CYTOTOXICITY TEST (ISO METHOD)

Cytotoxicity Results

Sample Identification	Dilution (Extract Concentration); Nominal Bupivacaine Concentration (mg/mL)*	Extract Observations (color; transparency; pH**)	Grade Plate #1, 2, 3	Reactivity
Test Article: Bupivacaine HCl Collagen – Matrix Implant, Lot Identification: 17011108 (T18-1235)	Neat (100% Extract); 5 mg/mL Bupivacaine	Orange tinted; Cloudy; pH 8-9	4, 4, 4	Severe
	1:4 (25% Extract); 1.25 mg/mL Bupivacaine	Slight orange tinted; Transparent; pH 8-9	4, 4, 4	Severe
	1:16 (6.25% Extract); 0.31 mg/mL Bupivacaine	Reddish colored, Transparent; pH 8-9	1, 1, 1	Slight
	1:64 (1.56% Extract); 0.078 mg/mL Bupivacaine	Reddish colored, Transparent; pH 8-9	0, 0, 0	None
	1:256 (0.39% Extract); 0.020 mg/mL Bupivacaine	Reddish colored, Transparent; pH 8-9	0, 0, 0	None
Sponsor Control: Placebo Collagen Matrix, Lot Identification: 18000202 (T18-1236)	Neat (100% Extract); 0 mg/mL Bupivacaine	Reddish colored, Transparent; pH 8-9	0, 0, 0	None
Active Ingredient Control: Bupivacaine HCl (0.25% Sensorcaine), Lot Identification: 6118316 (T18-1526)	1:2 Dilution (0.125% Bupivacaine HCl); 1.25 mg/mL Bupivacaine	Reddish colored, Precipitate present; pH 7-8	4, 4, 4	Severe
	1:8 Dilution (0.031% Bupivacaine HCl); 0.31 mg/mL Bupivacaine	Reddish colored, Less precipitate present; pH 7-8	4, 4, 4	Severe
	1:32 Dilution (0.008% Bupivacaine HCl); 0.078 mg/mL Bupivacaine	Reddish colored, Very sparse precipitate present; pH 7-8	0, 0, 0	None
	1:128 Dilution (0.002% Bupivacaine HCl); 0.020 mg/mL Bupivacaine	Reddish colored, No precipitate present; pH 7-8	0, 0, 0	None
Negative Control	undiluted	Reddish colored, Transparent, N/A	0, 0, 0	None
Positive Control	undiluted	Reddish colored; Cloudy, N/A	4, 4, 4	Severe
Blank	undiluted	Reddish colored, Transparent; N/A	Normal, Healthy Cells	

*For the Bupivacaine HCl Collagen Matrix Implant the concentrations were calculated by assuming that all bupivacaine HCl in the matrix (100 mg) was extracted into 20 mL of extraction media. Calculations for 0.25% Sensorcaine were based on the stated bupivacaine HCL concentration on the label.

**See Page 4 Note.

N/A: Not Applicable; pH not taken since the standard controls exhibited anticipated extract observations/typical responses.

The results / conclusions relate only to the items tested. This test report shall not be reproduced except in full, without written approval of the laboratory.

End of Report

Conclusion:

The observed cytotoxicity of the Bupivacaine HCL Collagen - Matrix Implant extract is consistent with bupivacaine HCL cytotoxicity since it was not observed with the sponsor control Placebo Collagen Matrix lacking bupivacaine HCL, and since the nominal bupivacaine concentration response for the Bupivacaine HCL Collagen - Matrix Implant extract was similar to, although less cytotoxic than, that observed for the active ingredient control, Bupivacaine HCL (0.25% Sensorcaine) dilutions.

Sponsor's justification on the cytotoxic effect of XARACOLL combination product:

In this study, in addition to the standard positive and negative controls, 3 test articles were included: bupivacaine HCL collagen-matrix (XARACOLL), collagen-matrix alone (no bupivacaine) and aqueous bupivacaine HCL (Sensorcaine® injection, 0.25%, Fresenius Kabi USA, LLC). Sensorcaine is an FDA-approved generic drug, therapeutically equivalent to the XARACOLL NDA Reference Listed Drug, Marcaine® (Hospira, Inc.).

The collagen-matrix alone (no bupivacaine) was not cytotoxic (Grade 0 reactivity). Bupivacaine, the active ingredient in XARACOLL, is known to be cytotoxic (Bentov 2016; Harris 2009). Both aqueous bupivacaine HCL and the bupivacaine collagen-matrix extract were cytotoxic at higher concentrations but not at lower concentrations. The nominal bupivacaine concentration response for the XARACOLL extract was similar to, or less cytotoxic than, that observed for the bupivacaine control extract. The conclusion of this study is that the observed cytotoxicity profile of XARACOLL is due to the active ingredient, bupivacaine HCL, which has known cytotoxicity, and not the collagen-matrix, which exhibited no cytotoxicity.

Despite its known cytotoxicity profile, bupivacaine has been FDA-approved for several decades and has a long history of well-tolerated use for surgical site infiltration to provide post-operative pain relief. A literature search of the overall safety profile of bupivacaine when used for infiltration into the surgical site in soft tissue surgeries was summarized in Appendix A of the Summary of Clinical Safety. The safety profile of XARACOLL from the clinical development program is consistent with the known safety profile of bupivacaine and Innocoll Pharmaceuticals considers that this new cytotoxicity study supports the safe use of XARACOLL for placement into the surgical site to produce postsurgical analgesia following soft tissue surgeries.

Reviewer comments

- *The experiment is well-designed to test the extract of test articles with appropriate positive and negative controls. The consultant has no concerns on the results and conclusion. The consultant agrees with the sponsor that, XARACOLL combination product is cytotoxic and the cytotoxic effect of XARACOLL is attributed to the drug component, bupivacaine HCL, but not to the device component, collagen-matrix.*
- *The sponsor also stated that it is known that bupivacaine is cytotoxic, but it has been FDA-approved and has a long history of safe use. The consultant defers to CDER reviewer to comment on the cytotoxic effect of the bupivacaine component of XARACOLL combination product.*

Investigational study (report number: 2018-RES-039)

In FDA's 74-day letter, the agency requested the following test article preparation methods for extraction in the cytotoxicity testing: "Describe the condition of the test extract (e.g., color, presence of any particles), and describe any changes in the extraction solvent (pre- and post-extraction) and explain the source of these changes (e.g., test article degradation).

In the provided cytotoxicity testing report (report number: GLP-2018-0182), the sponsor documented the changes of the test extracts, such as color, pH, presence of any particles). In the cytotoxicity testing, the sponsor found that the MEM prior to extraction was reddish-colored due to the presence of phenol red, a pH indicator. The MEM changes color based on changes to the pH. In addition to the recording of the color of the MEM after extraction in the study, pH was measured after the extractions were performed using indicator strips that change color based on the pH and the color on the strip was compared to a chart on the strip container to determine a pH range. The MEM containing XARACOLL was noted to be orange color, indicating that the extract was acidic, but the pH strip reading was between 8-9. Because of this discrepancy, an investigation was opened and investigational study 2018-RES-039 was conducted after completion of study GLP-2018-0182.

Study title: ELUTION CYTOTOXICITY EXTRACTION EVALUATION FOR GLP-2018-0182

Testing facility: (b) (4)

Study purpose: To investigate the apparent inconsistency between the pH as indicated by the phenol red in the media, and those recorded using pH test strips. This was done by repeating the extractions performed in GLP-2018-0182 and including measurement of pH using a pH meter. This evaluation is being performed as part of Laboratory Investigation Report (LI R) 18-043. This study falls outside the scope of GLP Regulations.

Test articles:

1. Bupivacaine HCL Collagen - Matrix Implant: Lot Identification: 17011108 (T18-1235) (provided by the sponsor)
2. Placebo Collagen Matrix: Lot Identification: 18000202 (T18-1236) (also named as "Sponsor Control Article", provided by the sponsor)
3. Bupivacaine HCL (0.25% Sensorcaine): Lot Identification: 6118316 (T18-1526) (also named as "Active Ingredient Control Article", provided by the sponsor)

Control articles:

1. Positive control: Sterile Latex Rubber
2. Negative control: Sterile USP High Density Polyethylene Reference Standard

Reviewer comments

The test articles and control articles are same as those in the cytotoxicity testing GLP-2018-0182.

Test Article Preparation and Extraction: The extraction preparation was performed in an identical manner as the procedure used for Study Number GLP-2018-0182

Methods: pH of each extract and dilution was determined using pH 0-14 Universal indicator strips (mfr / lot / exp: EMO Millipore MColorphast / HC577678 / 02-28-2020) and a pH meter (Eqpt 448) for comparison purposes.

Results and discussion:

The pH recordings from the pH meter align with the medium extraction color and are considered more accurate than the readings associated with the pH 0-14 Universal indicator strips. Therefore, the root cause of the discrepancy between the medium color and pH indicator strips in the original study can be attributed to the pH indicator strips and the subjectivity related to evaluating the strips using the associated color chart.

The neat XARACOLL extract was noted to be cloudy. In study GLP-2018-0182, the higher concentration aqueous bupivacaine extracts were noted to have some precipitate present. Given this, and that the extract with the placebo collagen matrix was transparent as were the Bupivacaine HCl Collagen-Matrix extracts with lower bupivacaine concentrations, the cloudiness in the neat extract of the Bupivacaine HCl Collagen-Matrix likely represents precipitation of bupivacaine HCl. This conclusion is supported by GLP study V0573-200, "Genotoxicity Dose Range Finding Study in a Definitive Mouse Lymphoma Assay". In that study, particulates were noted when XARACOLL was extracted in RPMI0. These particulates were analyzed by infrared spectroscopy and the infrared spectrum of the particulates was found to most closely match that of bupivacaine (see Appendix 8 in study V0573-200).

**Elution Cytotoxicity Extraction Evaluation
Results**

Sample Identification	Dilution (Extract Concentration); Nominal Bupivacaine Concentration (mg/mL)*	Extract Observations		2018-RES-039 pH Determinations	
		GLP-2018-0182	2018-RES-039	Indicator Strips	pH Meter
Test Article: Bupivacaine HCl Collagen – Matrix Implant, Lot Identification: 17011108 (T18-1235)	Neat (100% Extract); 5 mg/mL Bupivacaine	Orange tinted; Cloudy; pH 8-9	Orange colored; Cloudy	7-8	6.94
	1:4 (25% Extract); 1.25 mg/mL Bupivacaine	Slight orange tinted; Transparent; pH 8-9	Very slight orangish tint; Slightly cloudy	7-8	7.49
	1:16 (6.25% Extract); 0.31 mg/mL Bupivacaine	Reddish colored, Transparent; pH 8-9	Reddish colored, Transparent	7-8	7.62
	1:64 (1.56% Extract); 0.078 mg/mL Bupivacaine	Reddish colored, Transparent; pH 8-9	Reddish colored, Transparent	7-8	7.69
	1:256 (0.39% Extract); 0.020 mg/mL Bupivacaine	Reddish colored, Transparent; pH 8-9	Reddish colored, Transparent	7-8	7.68
Sponsor Control: Placebo Collagen Matrix, Lot Identification: 18000202 (T18-1236)	Neat (100% Extract); 0 mg/mL Bupivacaine	Reddish colored, Transparent; pH 8-9	Reddish colored, Transparent	7-8	7.42
Active Ingredient Control: Bupivacaine HCl (0.25% Sensorcaine), Lot Identification: 6118316 (T18-1526)	1:2 Dilution (0.125% Bupivacaine HCl); 1.25 mg/mL Bupivacaine	Reddish colored, Precipitate present; pH 7-8	Orange colored, Transparent; No Precipitate present	8-9	7.13
	1:8 Dilution (0.031% Bupivacaine HCl); 0.31 mg/mL Bupivacaine	Reddish colored, Less precipitate present; pH 7-8	Reddish colored, Transparent	8-9	7.62
	1:32 Dilution (0.008% Bupivacaine HCl); 0.078 mg/mL Bupivacaine	Reddish colored, Very sparse precipitate present; pH 7-8	Reddish colored, Transparent	8-9	7.71
	1:128 Dilution (0.002% Bupivacaine HCl); 0.020 mg/mL Bupivacaine	Reddish colored, No precipitate present; pH 7-8	Reddish colored, Transparent	8-9	7.79
Negative Control	undiluted	Reddish colored, Transparent,	Reddish colored, Transparent	N/A	N/A
Positive Control	undiluted	Reddish colored; Cloudy,	Reddish colored; Cloudy	N/A	N/A
Blank	undiluted	Reddish colored, Transparent	Reddish colored, Transparent	8-9	7.35

Reviewer comments

The justification on the condition of the test extract and the changes in the extraction solvent is adequate. Please also see reviewer's comments in Mouse Lymphoma Assay below.

Intracutaneous reactivity – 72 hours in rabbits (report number: T1251 800)**Study title:** ISO Intracutaneous Study in Rabbits**Testing facility:** (b) (4)**Study purpose:** to evaluate the local dermal irritation of a test article extract following intracutaneous injection in rabbits.**Compliance statement:** the testing is conducted in accordance with ISO 10993-10 and 21 CFR Part 58.**Test articles:****Table 1: Test Article**

Name:	Collagen Sponge with Drug Coating
Identification:	15041002
Stability Testing:	In progress (per sponsor)
Expiration Date:	Stable for duration of intended testing (per sponsor)
Strength, Purity and Composition:	Strength: 100mg/sponge; Purity N/A; Composition: Collagen sponge, bupivacaine coating
Physical Description of the Test Article:	Collagen sponges coated with bupivacaine
Storage Conditions:	Room Temperature

Control articles/Extraction vehicles:**Table 2: Control Articles/Extraction Vehicles**

Name:	0.9% sodium chloride USP solution (SC) Sesame oil, NF (SO)
Stability Testing:	Marketed products; stability characterized by labeling
Strength, Purity, Composition or Other Characteristics:	SC: Purity: Meets requirements of USP Sodium Chloride for Injection and is certified as USP Grade; Composition: 0.9% NaCl ± (b) (4), balance is water; sodium chloride CAS No.: 7647-14-5/water CAS No.: 7732-18-5 SO: Purity: Meets the requirements of National Formulary. Composition: CAS No.: 8008-74-0

Test and Control Article Preparation: The test article and the control blank (extraction vehicle without the test article) were subjected to the extraction conditions as described below. The extracts were continuously agitated during extraction.

Table 3: Extraction

Vehicle	Extraction Ratio	Article Amount	Volume of Vehicle	Extraction Condition
SC	60 cm ² :27 mL	56.8 cm ²	26 mL	37°C for 72 hours
SO	60 cm ² :28 mL	56.8 cm ²	27 mL	37°C for 72 hours

The following table contains a description of the test and control article extract conditions.

Table 4: Condition of Extracts

Vehicle	Time Observed	Extract	Condition of Extracts		
			Color	Clarity	Particulates
SC	Before Extraction	Test	Colorless	Clear	None
		Control	Colorless	Clear	None
	After Extraction	Test	Colorless	Clear	None
		Control	Colorless	Clear	None
	Prior to Use	Test	Colorless	Clear	None
		Control	Colorless	Clear	None
SO	Before Extraction	Test	Colorless	Clear	None
		Control	Colorless	Clear	None
	After Extraction	Test	Colorless	Clear	None
		Control	Colorless	Clear	None
	Prior to Use	Test	Colorless	Clear	None
		Control	Colorless	Clear	None

The test article remained visually unchanged following the extraction process. The extracts were maintained at ambient temperature for less than 4 hours before use. The extracts were not centrifuged, filtered, or otherwise altered prior to dosing.

Reviewer comments

The report did not state whether the test article preparation and extraction is in compliance with ISO 10993-12. However, the consultant believes that the methods in current study are consistent with the extraction conditions and methods in the cytotoxicity study GLP-2018-0182. No concern.

Methods: Three male rabbits were tested in this study. A 0.2 mL dose of the appropriate test article extract was injected by the intracutaneous route into five separate sites on the right side of the back of each animal. Similarly, the corresponding control was injected on the left side of the back of each animal. Injections were spaced approximately 2 cm apart. The injection sites were observed immediately after injection. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection. Reactions were scored on a 0 to 4 basis. Any reactions at the injection sites were also noted. The reactions were evaluated according to the following subjective rating scale:

Table 5: Test Scoring

Score	Erythema (ER)	Edema (ED)
0	No erythema	No edema
1	Very slight erythema (barely perceptible)	Very slight edema (barely perceptible)
2	Well-defined erythema	Well-defined edema (edges of area well-defined by definite raising)
3	Moderate erythema	Moderate edema (raised approximately 1 mm)
4	Severe erythema (beet redness) to eschar formation preventing grading of erythema	Severe edema (raised more than 1 mm, and extending beyond exposure area)

The erythema and edema site scores for the test article and control extracts for each animal at each scoring interval were calculated by adding the erythema and edema scores together. The mean score of each individual animal (test and control) was calculated by totaling all of the individual site scores for each animal and dividing by 15 (3 scoring time points x 5 test or control sites). The overall mean for each test article extract and control extract was calculated by adding the mean score for all three animals together and dividing by 3. The difference between the overall mean score of the test article extract and corresponding control extract was calculated by subtracting the overall mean score for the control extract from the overall mean score for the test article extract. If the overall mean score of the test article extract was less than the overall mean score of the corresponding control extract, 0.0 was reported. The requirements of the test were met if the difference between the test extract overall mean score and corresponding control overall mean score was 1.0 or less.

Results: All injection sites appeared normal immediately following injection. The overall mean difference for the extracts is summarized below:

Table 6: Mean Erythema and Edema Scores

Extract	Overall Test Group Mean	Overall Control Group Mean	Overall Mean Difference (Test - Control)
SC	0.0	0.0	0.0
SO	0.5	0.3	0.2

Conclusion: The test article extract met the requirements of the test since the difference between each test article extract overall mean score and corresponding control extract overall mean score was 0.0 and 0.2 for the SC and SO test article extracts, respectively.

Reviewer comments

The consultant has no concern on the test methods and test results. The XARACOLL combination product is non-irritant for this 3-day intracutaneous study.

Sensitization - guinea pig maximization study (report number: T1261_300)

Study title: ISO Guinea Pig Maximization Sensitization Test

Testing facility:

(b) (4)

Study purpose: to evaluate the potential of the test article extract to cause delayed dermal contact sensitization in the guinea pig maximization test.

Compliance statement: the testing is conducted in accordance with ISO 10993-10 and 21 CFR Part 58.

Test articles:

Table 1: Test Article

Name:	Collagen Sponge with Drug Coating
Identification:	15041002
Stability Testing:	In progress (per sponsor)
Expiration Date:	Stable for duration of intended testing (per sponsor)
Strength, Purity and Composition:	Strength: 100mg/sponge; Purity: See Appendix 4; Composition: Collagen sponge, bupivacaine coating
Physical Description of the Test Article:	Collagen sponges coated with bupivacaine
Storage Conditions:	Room Temperature

Control articles:

Table 2: Control Articles

Name:	0.9% sodium chloride USP solution (SC) Sesame oil, NF (SO)
Stability Testing:	Marketed products, stability characterized by labeling
Strength, Purity, Composition or Other Characteristics:	SC: Purity: Meets requirements of USP Sodium Chloride for Injection and is certified as USP Grade; Composition: 0.9% NaCl ± (b) (4), balance is water; sodium chloride CAS No.: 7647-14-5/water CAS No.: 7732-18-5 SO: Purity: Meets the requirements of National Formulary. Composition: CAS No.: 8008-74-0

Test and Control Article Preparation: The test article extract and the vehicle control (extraction vehicle without the test article) were prepared fresh for each phase of testing and subjected to the extraction conditions as described in Table 4. The extracts were continuously agitated during extraction.

Table 4: Extraction
Vehicle: SC

Testing Phase	Treatment Group	Extraction Ratio	Article Amount	Volume of Vehicle	Extraction Condition
Induction I	Test	60 cm ³ :27 mL	56.8 cm ²	26 mL	37°C for 72 hours
	Control	NA	NA	30 mL	37°C for 72 hours
Induction II	Test	60 cm ³ :27 mL	56.8 cm ²	26 mL	37°C for 72 hours
	Control	NA	NA	10 mL	37°C for 72 hours
Challenge	Test	60 cm ³ :27 mL	56.8 cm ²	26 mL	37°C for 72 hours
	Control	NA	NA	10 mL	37°C for 72 hours

Vehicle: SO

Testing Phase	Treatment Group	Extraction Ratio	Article Amount	Volume of Vehicle	Extraction Condition
Induction I	Test	60 cm ³ :28 mL	56.8 cm ²	27 mL	37°C for 72 hours
	Control	NA	NA	30 mL	37°C for 72 hours
Induction II	Test	60 cm ³ :28 mL	56.8 cm ²	27 mL	37°C for 72 hours
	Control	NA	NA	10 mL	37°C for 72 hours
Challenge	Test	60 cm ³ :28 mL	56.8 cm ²	27 mL	37°C for 72 hours
	Control	NA	NA	10 mL	37°C for 72 hours

NA = Not Applicable

The following table contains a description of the test and control article extract conditions.

Table 5: Condition of SC Extracts

Treatment Group	Time Observed	Testing Phase	Condition of Extracts		
			Color	Clarity	Particulates
Test	Before Extraction	Induction I	Colorless	Clear	None
		Induction II	Colorless	Clear	None
		Challenge	Colorless	Clear	None
	After Extraction	Induction I	Colorless	Clear	None
		Induction II	Colorless	Clear	Many, fine, white
		Challenge	Colorless	Clear	Few, fine, white
	Prior to Use	Induction I	Colorless	Clear	None
		Induction II	Colorless	Clear	Many, fine, white
		Challenge	Colorless	Clear	Few, fine, white
Control	Before Extraction	Induction I	Colorless	Clear	None
		Induction II	Colorless	Clear	None
		Challenge	Colorless	Clear	None
	After Extraction	Induction I	Colorless	Clear	None
		Induction II	Colorless	Clear	None
		Challenge	Colorless	Clear	None
	Prior to Use	Induction I	Colorless	Clear	None
		Induction II	Colorless	Clear	None
		Challenge	Colorless	Clear	None

Table 6: Condition of SO Extracts

Treatment Group	Time Observed	Testing Phase	Condition of Extracts		
			Color	Clarity	Particulates
Test	Before Extraction	Induction I	Colorless	Clear	None
		Induction II	Colorless	Clear	None
		Challenge	Colorless	Clear	None
	After Extraction	Induction I	Colorless	Clear	None
		Induction II	Colorless	Clear	None
		Challenge	Colorless	Clear	None
	Prior to Use	Induction I	Colorless	Clear	None
		Induction II	Colorless	Clear	None
		Challenge	Colorless	Clear	None
Control	Before Extraction	Induction I	Colorless	Clear	None
		Induction II	Colorless	Clear	None
		Challenge	Colorless	Clear	None
	After Extraction	Induction I	Colorless	Clear	None
		Induction II	Colorless	Clear	None
		Challenge	Colorless	Clear	None
	Prior to Use	Induction I	Colorless	Clear	None
		Induction II	Colorless	Clear	None
		Challenge	Colorless	Clear	None

The test article remained visually unchanged following the extraction process. The extracts were maintained at ambient temperature for less than 8 hours before use. The extracts were not centrifuged, filtered, or otherwise altered prior to dosing.

Reviewer comments

The report did not state whether the test article preparation and extraction is in compliance with ISO 10993-12. However, the consultant believes that the methods in current study are consistent with the extraction conditions and methods in the cytotoxicity study GLP-2018-0182. No concern.

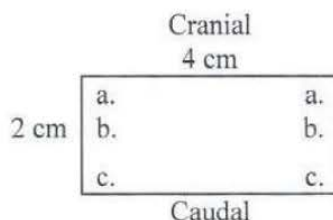
Methods:

Induction I: the guinea pigs were assigned to a treatment group as shown below.

Table 7: Treatment Group Assignment

Vehicle	Treatment Group	Number of Animals
SC	Test	10
	Control	5
SO	Test	10
	Control	5

The test animals were injected with the test article extract and the control animals were injected with the vehicle control. Three rows of intradermal injections (two injections per row) were given to each animal within an approximate 2 cm x 4 cm boundary of the fur clipped area as illustrated below:



Control Animals:

- a. 0.1 mL of 50:50 (v/v) mixture of FCA and the chosen vehicle
- b. 0.1 mL of vehicle
- c. 0.1 mL of a 1:1 mixture of the 50:50 (v/v) vehicle/FCA mixture and the vehicle

Test Animals:

- a. 0.1 mL of 50:50 (v/v) mixture of FCA and the chosen vehicle
- b. 0.1 mL of test extract
- c. 0.1 mL of a 1:1 mixture of the 50:50 (v/v) vehicle/FCA mixture and the test extract

Induction II: At 6 days (± 1 day) after completion of the Induction I injection, the dorsoscapular region (same area as used during Induction I) of each animal was treated with a 10% SLS suspension in petrolatum sufficient to coat the skin. At 24 hours (± 2 hours) any remaining SLS residue was gently removed. An approximate 2 cm x 4 cm section of filter paper, saturated with 0.3 mL of freshly prepared test article extract, was then topically applied to the previously injected sites of the test animals. The control animals were similarly patched with the appropriate vehicle control. Each patch was secured with a nonreactive tape and the trunk of each animal was wrapped with an elastic bandage. At 48 hours, the bandages and patches were removed.

Challenge: At 14 days (± 1 day) after completion of Induction II, nonwoven cotton disks contained in a Hill Top Chamber® were saturated with 0.3 mL of the test article extract or vehicle control. The test extract was applied to the right flank of each animal and the control vehicle was applied to the left flank of each animal. The trunk of each animal was wrapped with an elastic bandage to maintain well-occluded sites. At 24 hours, the wraps and Hill Top Chambers were removed. Any residue remaining at the sites was removed.

Observations for dermal reactions were conducted at 24 and 48 hours after challenge patch removal. The sites were wiped with 35% isopropyl alcohol to facilitate scoring. Dermal reactions were scored in accordance with the criteria shown below:

Table 8: Test Scoring

Patch Test Reaction	Grading Scale
No visible change	0
Discrete or patchy erythema	1
Moderate and confluent erythema	2
Intense erythema and swelling	3

The responses from the challenge phase were compared within the test animal group and between test and control conditions. In the final analysis of data, consideration was given to the overall pattern, intensity, duration and character of reactions of the test as compared to the control conditions. The control conditions are (1) the control vehicle on the test animals, (2) the test on the control animals, and (3) the control vehicle on the control animals. Statistical manipulation of data was not applicable to this study. Grades of 1 or greater observed in the test group generally indicated sensitization, provided that grades of less than 1 were observed on the control animals. If grades of 1 or greater were noted on control animals, then the reactions of test animals that exceeded the most severe control reaction were considered to be due to sensitization.

Results: No evidence of sensitization was observed. Individual results of dermal scoring for the challenge phase are presented in Appendix 2.

Appendix 2 - Dermal Reactions Following Challenge Exposure

SC Group

Treatment Group	Animal Number	Dermal Reactions			
		24 Hour Score		48 Hour Score	
		Control Site	Test Extract Site	Control Site	Test Extract Site
Test	5451	0	0	0	0
	5452	0	0	0	0
	5453	0	0	0	0
	5454	0	0	0	0
	5455	0	0	0	0
	5456	0	0	0	0
	5457	0	0	0	0
	5458	0	0	0	0
	5459	0	0	0	0
	5460	0	0	0	0
Control	5461	0	0	0	0
	5462	0	0	0	0
	5463	0	0	0	0
	5464	0	0	0	0
	5465	0	0	0	0

Appendix 2 (continued) - Dermal Reactions Following Challenge Exposure

SO Group

Treatment Group	Animal Number	Dermal Reactions			
		24 Hour Score		48 Hour Score	
		Control Site	Test Extract Site	Control Site	Test Extract Site
Test	5466	0	0	0	0
	5467	0	0	0	0
	5468	0	0	0	0
	5469	0	0	0	0
	5740	0	0	0	0
	5471	0	0	0	0
	5472	0	0	0	0
	5473	0	0	0	0
	5474	0	0	0	0
	5475	0	0	0	0
Control	5476	0	0	0	0
	5477	0	0	0	0
	5478	0	0	0	0
	5479	0	0	0	0
	5480	0	0	0	0

Conclusion: The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The test article was not considered a sensitizer in the guinea pig maximization test.

Periodic positive control study: The susceptibility of the Hartley guinea pig strain to a known sensitizing agent, 1-chloro-2,4-dinitrobenzene (DNCB), has been substantiated at (b) (4) with this method under lab number 17T_23175_01 completed on April 26, 2017 (Appendix 3).

Reviewer comments

The consultant has no concern on the test methods and test results. The study does not include a concurrent positive control; however, the test report includes results of historic positive control conducted within 3 months of the study. The XARACOLL combination product is not considered a sensitizer.

USP rabbit pyrogenicity study, Material mediated (report number: TU010 807)

Sponsor submitted two rabbit pyrogenicity studies with same report number, TU010_807. The test articles are identified as “Collagen Sponge with Drug Coating” (Test article identification: 15041002) and “Xaracoll Collagen Sponge Only” (Test article identification: 15020502), respectively.

Reviewer comments

The consultant found that the same report with test article “Collagen Sponge with Drug Coating” has been provided by the sponsor to the agency interactively on May 31, 2017, and

the consultant has provided a consult on that report. For detailed information, please see consult memo for ICCR2017-01101. Briefly, the sponsor conducted a rabbit pyrogenicity study on XARACOLL resulting in premature death of the test animal. The sponsor then contacted the agency and stated that “the premature death of the animal was considered most likely due to bupivacaine overdose” and proposed not to conduct the rabbit pyrogenicity study. After reviewed the testing report, and discussed with CDER reviewer on LD50 value of bupivacaine in animal, the consultant believes that sponsor’s justification that the premature death of the animal is due to bupivacaine overdose through intravenous injection is scientific reasonable. However, the consultant requested the sponsor to repeat the rabbit pyrogenicity testing on the collagen matrix component without bupivacaine (the placebo sponge), and provide toxicological information of raw materials/chemicals used in the manufacture process and evaluate their pyrogenicity, to capture the full and complete manufacturing process of the finished product.

USP rabbit pyrogenicity study with test article as “Xaracoll Collagen Sponge Only”

Study title: USP Rabbit Pyrogen Study, Material Mediated

Testing facility: (b) (4)

Purpose: to determine whether an extract of the test article induced a pyrogenic response following intravenous injection in rabbits.

Test guidelines: USP, General Chapter <151>, Pyrogen Test and 21 CFR 58

Test article:

Table 1: Test Article

Name:	Xaracoll Collagen Sponge Only
Identification:	15020502
Stability Testing:	In progress (per sponsor)
Expiration Date:	Stable for duration of intended testing (per sponsor)
Strength, Purity and Composition:	Strength: not applicable because no active ingredients are used to formulate a concentration; Purity: not applicable because the test article does not contain an active ingredient; Composition: Type 1 bovine collagen
Physical Description of the Test Article:	White sponge material containing type 1 bovine collagen
Storage Conditions:	Room Temperature

Animal: rabbit, New Zealand White

Test article preparation: The test article was subjected to the extraction conditions as described below. The extract was continuously agitated during extraction.

Table 3: Extraction

Vehicle	Extraction Ratio	Article Amount	Volume of Vehicle	Extraction Condition
SNPS	*60 cm ² :27 mL	498.6 cm ²	224 mL	37°C for 72 hours

Table 4: Condition of Extract

Vehicle	Time Observed	Extract	Condition of Extract		
			Color	Clarity	Particulates
SNPS	Before Extraction	Test	Colorless	Clear	None
	After Extraction	Test	Colorless	Clear	None
	Prior to Use	Test	Colorless	Clear	None

Reviewer comments

The extraction vehicle and extraction condition are appropriate. The condition of the test extract appears normal both before and after extraction. I have no concern.

Test procedure: The animal was injected intravenously via the marginal ear vein with the test extract at 10 mL/kg of body weight. For all animals, temperatures were recorded at 30 minute intervals between 1 and 3 hours after injection. If no single animal showed a rise of 0.5°C or more above its baseline temperature, then the extract was judged nonpyrogenic. If the total maximum temperature rise of all three animals exceeded 3.3°C the extract was judged pyrogenic.

Reviewer comments

The performed test procedure is consistent with the USP <151>. I have no concern.

Result: No single animal showed a temperature rise of 0.5°C or more above its baseline temperature. The total rise of the rabbits' temperature during 3 hours was 0.2°C. Individual temperatures are presented in Appendix 1.

Animal Number	Sex	Weight (kg)	Dose Volume (mL)	Temperature (°C)							Maximum Rise
				Before Injection		Hours after Injection					
				Control 1	Baseline	1.0	1.5	2.0	2.5	3.0	
19985*	Male	3.7	37	39.0	38.9	38.7	38.7	38.8	38.7	38.8	0.0
19986*	Male	3.2	32	39.1	39.1	39.0	39.0	38.9	39.0	39.0	0.0
20430*	Male	2.9	29	39.1	39.1	39.3	39.3	39.3	39.3	39.1	0.2
TOTAL RISE:											0.2

*Previous use history traceable in laboratory records.

Conclusion: The total rise of rabbit temperatures during the 3 hour observation period was 0.2°C and was within acceptable USP limits. The test article extract was judged as nonpyrogenic.

Reviewer comments

- *The sponsor concluded that the premature death of the animal in the rabbit pyrogenicity study on “Collagen Sponge with Drug Coating” was due to bupivacaine overdose through intravenous administration. The sponsor repeated the rabbit pyrogenicity study on “Xaracoll Collagen Sponge Only” using the same method and concluded that the collagen sponge only is non-pyrogenic. The consultant has no concern on the test methods and test results for these two studies.*
- *However, to fully mitigate the risk of the presence of pyrogens in the Xaracoll final product, sponsor should also provide toxicological information of raw materials/chemicals used in the manufacture process, and extractable/leachables in the final product, and evaluate their pyrogenicity, to capture the full and complete manufacturing process of the finished product. As the sponsor provided extractable/leachable analysis and toxicology risk assessment, I defer to CDER non-clinical review group to review.*

Acute systemic toxicity in mice (report number: T0625_500 and T0625_500/S)

Sponsor submitted two Acute Systemic Toxicity studies in mice. The test articles are identified as “Xaracoll Collagen Sponge Only” (Test article identification: 15020502) for report T0625_500 and as “Collagen Sponge with Drug Coating” (Test article identification: 15041002) for report T0625_500/S, respectively.

Acute systemic toxicity in mice (report number: T0625_500)

Study title: ISO Acute Systemic Toxicity Study in Mice

Testing facility: (b) (4)

Purpose: to evaluate the acute systemic toxicity of a test article extract following injection in mice.

Test guidelines: ISO 10993-11, 21 CFR 58

Test article:

Table 1: Test Article

Name:	Xaracoll Collagen Sponge Only
Identification:	15020502
Stability Testing:	In progress (per sponsor)
Expiration Date:	Stable for duration of intended testing (per sponsor)
Strength, Purity and Composition:	Strength: not applicable because no active ingredients are used to formulate a concentration; Purity: not applicable because the test article does not contain an active ingredient; Composition: Type 1 bovine collagen
Physical Description of the Test Article:	White sponge material containing type 1 bovine collagen
Storage Conditions:	Room Temperature

Control article:**Table 2: Control Articles**

Name:	0.9% sodium chloride USP solution (SC) sesame oil, NF (SO)
Stability Testing:	SC and SO: Marketed product, stability characterized by its labeling
Strength, Purity, Composition or Other Characteristics:	SC: Purity: Meets requirements of USP Sodium Chloride for Injection and is certified as USP Grade; Composition: 0.9% NaCl ± (b) (4) balance is water; sodium chloride CAS No.: 7647-14-5/water CAS No.: 7732-18-5 SO: Purity: Meets the requirements of National Formulary. Composition: CAS No.: 8008-74-0

Animal: 20 male mice

Test and Control Article Preparation: The test article and the control blank (extraction vehicle without the test article) were subjected to the extraction conditions as described below. The extracts were continuously agitated during extraction.

Table 3: Extraction

Vehicle	Extraction Ratio	Article Amount	Volume of Vehicle	Extraction Condition
SC	60 cm ² :27 mL	49.5 cm ²	22 mL	37°C for 72 hours
SO	60 cm ² :28 mL	49.5 cm ²	23 mL	37°C for 72 hours

The following table contains a description of the test and control article extract conditions.

Table 4: Condition of Extracts

Vehicle	Time Observed	Extract	Condition of Extracts		
			Color	Clarity	Particulates
SC	Before Extraction	Test	Colorless	Clear	None
		Control	Colorless	Clear	None
	After Extraction	Test	Colorless	Clear	None
		Control	Colorless	Clear	None
	Prior to Use	Test	Colorless	Clear	None
		Control	Colorless	Clear	None
SO	Before Extraction	Test	Colorless	Clear	None
		Control	Colorless	Clear	None
	After Extraction	Test	Colorless	Clear	None
		Control	Colorless	Clear	None
	Prior to Use	Test	Colorless	Clear	None
		Control	Colorless	Clear	None

The test article remained visually unchanged following the extraction process. The extracts were maintained at ambient temperature for less than 4 hours before use. The extracts were not centrifuged, filtered, or otherwise altered prior to dosing.

Reviewer comments

The extraction vehicle and extraction condition are appropriate. The condition of the test extract appears normal both before and after extraction. I have no concern.

Test procedure: Prior to dosing, the animals were individually identified, weighed and arbitrarily assigned to a treatment group as shown below:

Table 5: Treatment Group Assignment

Extract	Treatment Group	Number of Animals	Sex	Dose	Route of Administration
SC	Test	5	Male	50 mL/kg	Intravenous
	Control	5	Male	50 mL/kg	Intravenous
SO	Test	5	Male	50 mL/kg	Intraperitoneal
	Control	5	Male	50 mL/kg	Intraperitoneal

A single dose of each test article extract was injected into each animal in the test group. Each control blank was similarly injected into each animal in the control group. Dosing occurred on day 0. Animals were observed for any adverse clinical reactions immediately after injection, and for signs of systemic reactions at 4, 24, 48 and 72 hours after injection. The animals were weighed daily for three days after dosing. If during the observation period, none of the animals treated with the individual test extract exhibited a significantly greater reaction than the control animals, the test article met the requirements of the standard. If two or more animals died, or if abnormal behavior such as convulsions or prostration occurred in two or more animals, or if body weight loss greater than 2 grams occurred in three or more animals, the test article did not meet the test requirements.

Reviewer comments

The performed test procedure is consistent with ISO 10993-11. I have no concern.

Results and discussion: There was no mortality during the study. All animals were clinically normal throughout the study and no weight loss for each animal through the study. There was no evidence of systemic toxicity from the extracts injected into mice. Each test article extract met the requirements of the study.

Reviewer comments

I have no concern on the testing methods and results. The test article, "Xaracoll Collagen Sponge Only", can be considered to be non-toxic in this acute systematic toxicity study.

Acute systemic toxicity in mice (report number: T0625_500/S)

Study title: ISO Acute Systemic Toxicity Study in Mice

Testing facility

Purpose: to evaluate the acute systemic toxicity of a test article extract following injection in mice.

Test guidelines: ISO 10993-11, 21 CFR 58

Test article:**Table 1: Test Article**

Name:	Collagen Sponge with Drug Coating
Identification:	15041002
Stability Testing:	In progress (per sponsor)
Expiration Date:	Stable for duration of intended testing (per sponsor)
Strength, Purity and Composition:	Strength: 100mg/sponge; Purity: See Appendix 4; Composition: Collagen sponge, bupivacaine coating
Physical Description of the Test Article:	Collagen sponges coated with bupivacaine
Storage Conditions:	Room Temperature

The control article, Test and Control Article Preparation, and the test procedure are same as those in report T0625_500.

The test article and the control blank (extraction vehicle without the test article) were subjected to the extraction conditions as described below.

Table 3: Extraction

Vehicle	Extraction Ratio	Article Amount	Volume of Vehicle	Extraction Condition
SC	60 cm ² :27 mL	56.8 cm ²	26 mL	37°C for 72 hours
SO	60 cm ² :28 mL	56.8 cm ²	27 mL	37°C for 72 hours

The following table contains a description of the test and control article extract conditions.

Table 4: Condition of Extracts

Vehicle	Time Observed	Extract	Condition of Extracts		
			Color	Clarity	Particulates
SC	Before Extraction	Test	Colorless	Clear	None
		Control	Colorless	Clear	None
	After Extraction	Test	Colorless	Clear	Many, fine, white*
		Control	Colorless	Clear	None
	Prior to Use	Test	Colorless	Clear	Many, fine, white
		Control	Colorless	Clear	None
SO	Before Extraction	Test	Colorless	Clear	None
		Control	Colorless	Clear	None
	After Extraction	Test	Colorless	Clear	None
		Control	Colorless	Clear	None
	Prior to Use	Test	Colorless	Clear	None
		Control	Colorless	Clear	None

The test article remained visually unchanged following the extraction process. The extracts were maintained at ambient temperature for less than 4 hours before use.

*The particulates were allowed to settle and an aliquot for testing was drawn off the top. Otherwise, the extracts were not centrifuged, filtered, or otherwise altered prior to dosing.

Reviewer comments

There are particulates in the saline test extract. The testing lab did not manipulate the test extract prior to dosing to the animal, which is appropriate.

Results:

1. All the SC test mice were found dead approximately five hours following the initial IP injection of the test article extract. A general necropsy was performed on all the animals found dead. Tissues were histologically processed for microscopic evaluation by a pathologist to try to determine the cause of death. After pathological evaluation the cause of death could not be determined.
2. All other animals were clinically normal throughout the study. All SO mice gained weight over the course of the study.

Appendix 1 - Observations - SC Extract

Table 1: Mortality Data

Extract	Treatment Group	Number Dead/Number Tested
SC	Test Extract	5/5
	Control Blank	0/5

Table 2: Clinical Observations

Extract	Treatment Group	Animal Number	Observation				
			Immediate	4 Hours	24 Hours	48 Hours	72 Hours
SC	Test Extract	11	Normal	Found Dead	*	*	*
		12	Normal	Found Dead	*	*	*
		13	Normal	Found Dead	*	*	*
		14	Normal	Found Dead	*	*	*
		15	Normal	Found Dead	*	*	*
	Control Blank	1	Normal	Normal	Normal	Normal	Normal
		2	Normal	Normal	Normal	Normal	Normal
		3	Normal	Normal	Normal	Normal	Normal
		4	Normal	Normal	Normal	Normal	Normal
		5	Normal	Normal	Normal	Normal	Normal

Table 3: Body Weight Data

Extract	Treatment Group	Animal Number	Weight (g)			
			Day 0	Day 1	Day 2	Day 3
SC	Test Extract	11	19	*	*	*
		12	21	*	*	*
		13	21	*	*	*
		14	21	*	*	*
		15	21	*	*	*
	Control Blank	1	21	22	23	24
		2	21	21	23	24
		3	19	20	21	22
		4	19	20	21	21
		5	19	21	21	22

*Not Applicable; found dead at approximately 5 hours after the first dose.

Appendix 2 - Observations - SO Extract

Table 1: Mortality Data

Extract	Treatment Group	Number Dead/Number Tested
SO	Test Extract	0/5
	Control Blank	0/5

Table 2: Clinical Observations

Extract	Treatment Group	Animal Number	Observation				
			Immediate	4 Hours	24 Hours	48 Hours	72 Hours
SO	Test Extract	16	Normal	Normal	Normal	Normal	Normal
		17	Normal	Normal	Normal	Normal	Normal
		18	Normal	Normal	Normal	Normal	Normal
		19	Normal	Normal	Normal	Normal	Normal
		20	Normal	Normal	Normal	Normal	Normal
	Control Blank	6	Normal	Normal	Normal	Normal	Normal
		7	Normal	Normal	Normal	Normal	Normal
		8	Normal	Normal	Normal	Normal	Normal
		9	Normal	Normal	Normal	Normal	Normal
		10	Normal	Normal	Normal	Normal	Normal

Table 3: Body Weight Data

Extract	Treatment Group	Animal Number	Weight (g)			
			Day 0	Day 1	Day 2	Day 3
SO	Test Extract	16	21	22	23	24
		17	20	22	23	25
		18	19	20	21	22
		19	20	22	24	25
		20	19	21	22	24
	Control Blank	6	20	21	22	23
		7	21	23	24	24
		8	20	21	22	23
		9	19	21	22	23
		10	19	20	21	23

Conclusion:

1. There was mortality or evidence of systemic toxicity from the SC extract injected into mice. The test article extract for SC did not meet the requirements of the study.
2. There was no mortality or evidence of systemic toxicity from the SO extract injected into mice. The test article extract for SO did meet the requirements of the study.

Discussion on the animal death of SC test mice: It is strongly believed that the cause of death was due to a bupivacaine overdose in the animals. This specific test article contained the drug bupivacaine at 100 mg per test article. One test article was approximately 56.8 cm². The test article was to be prepared at a ratio of 60 cm²: 27 mL based on absorbance capacity testing. One test article was used for the SC extraction and yielded 26 mL. This would result in a volume of approximately 3.8 mg of bupivacaine

per 1 mL of the extraction vehicle. If the average mouse weighs 0.02 kg and is dosed at a volume of 50 mL/kg then each mouse would receive around 1.9 mL per dose with a total volume of 3.8 mL. The LD50 value of bupivacaine IP in a mouse is 58.7 mg/kg which equates to 1.174 mg for a 0.02 kg mouse. In the initial dose the animals received a dose greater than the LD50 value likely resulting in death approximately five hours later.

Reviewer comments

- *I have no concern on the testing methods.*
- *The sesame oil extract of test article, "Collagen Sponge with Drug Coating", can be considered to be non-toxic in this acute systematic toxicity study.*
- *The saline extract of test article, "Collagen Sponge with Drug Coating", demonstrated systemic toxicity in this acute systematic toxicity study. The sponsor provided justification for animal death due to saline extracts of IV injection, which is "a bupivacaine overdose in the animals". This justification is same as the animal death in the rabbit pyrogenicity study on "Collagen Sponge with Drug Coating". However, the calculation of bupivacaine dosage is not correct (see the highlighted texts above). Therefore, the consultant calculated the bupivacaine dosage administered into the mice in this study:*
 - *Saline extract: 100 mg bupivacaine/matrix / 26 mL saline = 3.8 mg bupivacaine/mL saline*
 - *Each animal received bupivacaine: 50 mL/kg × 3.8 mg bupivacaine/mL saline = 190 mg bupivacaine/kg*
 - *The sponsor states that the LD50 value of bupivacaine IP in a mouse is 58.7 mg/kg; it appears that the bupivacaine in the saline extract injected intravenously into the mice in this study is much higher than that of the LD 50 value of bupivacaine IP injection, which may support sponsor's justification on the animal death is due to "a bupivacaine overdose". The consultant defers to the CDER reviewer to comment whether sponsor's LD 50 value of bupivacaine is correct and if sponsor's justification is acceptable.*
- *Additionally, to fully mitigate the risk of the presence of toxins in the Xaracoll final product, sponsor should also provide toxicological information of raw materials/chemicals used in the bupivacaine manufacture process, and extractable/leachables in the final product, and evaluate their toxins, to capture the full and complete manufacturing process of the finished product. As the sponsor provided extractable/leachable analysis and toxicology risk assessment, I defer to CDER non-clinical review group to review.*

Genotoxicity – in vitro testing (reports number: V0023_311 and V0573_200)

Sponsor submitted four *in vitro* genotoxicity testing. The consultant reviewed two testing, Bacterial reverse mutation assay (report number: report V0023_311) and Mouse Lymphoma Assay (report number: V0573_200) with the test article identified as "Collagen Sponge with Drug Coating" (Test article identification: 15041002).

Reviewer comments

- *This panel of genotoxicity testing is appropriate for an implant device according to CDRH's 2016 Biocompatibility Guidance.*
- *The consultant defers to CDER non-clinical review group to review the other two provided genotoxicity testing on bupivacaine component of the final product.*

Bacterial reverse mutation assay (report number: report V0023_311)

Study title: Bacterial Reverse Mutation Study with a Dose Range Finding Study

Testing facility: (b) (4)

Purpose: to evaluate whether a test article extract or dilution would cause mutagenic changes in *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* tester strain WPluvrA in the presence and absence of mammalian metabolic activation.

Test guidelines: ISO 10993-3, OECD 471, ISO 13485, 21 CFR 58

Test article:

Table 1: Test Article

Name:	Collagen Sponge with Drug Coating
Identification:	15041002
Stability Testing:	In progress (per sponsor)
Expiration Date:	Stable for duration of intended testing (per sponsor)
Strength, Purity and Composition:	Active Ingredient: Bupivacaine; Strength: 100mg/sponge; Purity: See Appendix 5; Composition: Collagen sponge, bupivacaine coating
Physical Description of the Test Article:	Collagen sponges coated with bupivacaine
Storage Conditions:	Refrigerated (2-8°C)

Negative control article:

Table 2: Negative Control Articles/Vehicles

Name:	Dimethyl sulfoxide (DMSO) Sodium Chloride for Irrigation, USP (Saline)
Stability Testing:	Marketed product, stability characterized by its labeling
Strength, Purity, Composition or Other Characteristics:	DMSO: Purity: 100.0%; Composition: CAS No. 67-68-5 Saline: Purity: Meets requirements of USP Sodium Chloride for Irrigation and is certified as USP Grade; Composition: 0.9% NaCl ± (b) (4), balance is water; sodium chloride CAS No.: 7647-14-5/water CAS No.: 7732-18-5

Reviewer comments

Saline is a polar extraction vehicle and DMSO can dissolve both polar and non-polar compounds. These two extraction vehicles can dissolve the collagen component of Xaracoll therefore they are appropriate extraction vehicles for the collagen. However, the consultant defers to CDER reviewer to determine whether they are appropriate for the Bupivacaine component of Xaracoll.

Positive control article:

Table 3: Positive Control Article

Name:	Sodium azide, methyl methanesulfonate (MMS), 2-aminoanthracene, benzo[a]pyrene, 2-nitrofluorene, and ICR-191 were included as positive controls to verify assay performance.
Stability Testing:	Stable for duration of intended testing
Strength, Purity, Composition or Other Characteristics:	Sodium azide: Purity: ≥99.5%; Composition: CAS No. 26628-22-8 MMS: Purity: ≥99.9%; Composition: CAS No. 66-27-3 2-aminoanthracene: Purity: ≥96%; Composition: CAS No. 613-13-8 Benzo[a]pyrene: Purity: ≥96%; Composition: CAS No. 50-32-8 2-Nitrofluorene: Purity: ≥97.5%; Composition: CAS No. 607-57-8 ICR-191: Purity: Not less than 90%; Identity: Proton NMR spectrum is consistent with structure of CAS No. 17070-45-0; Composition: CAS No. 17070-45-0

Bacterial system:

Table 4: Test System Description

Tester Strain	<i>his/trp</i> Mutation	Additional Mutations		Plasmid
		Repair	LPS	
TA98	<i>hisD3052</i> , frameshift	<i>uvrB</i>	<i>rfa</i>	pKM101
TA100	<i>hisG46</i> , missense	<i>uvrB</i>	<i>rfa</i>	pKM101
TA1535	<i>hisG46</i> , missense	<i>uvrB</i>	<i>rfa</i>	-
TA1537	<i>hisC3076</i> , frameshift	<i>uvrB</i>	<i>rfa</i>	-
WP2 <i>uvrA</i>	<i>trpE65</i> , missense	<i>uvrA</i>	-	-

rfa = causes partial loss of the lipopolysaccharide (LPS) wall which increases permeability of the cell to large molecules (i.e., crystal violet inhibition)

uvrB or *uvrA* = deficient DNA excision - repair system (i.e., ultraviolet sensitivity)

frameshift = base-pair addition/deletion

missense = base-pair substitution

pKM101 = plasmid confers ampicillin resistance (R-factor) and enhances sensitivity to mutagens

Reviewer comments

The five strains of bacteria used in this study are in compliance with OECD 471.

Test Article and Negative Control Article Preparation:

The test article and the control (extraction vehicle without the test article) were subjected to the extraction conditions as described below. The extracts were continuously agitated during extraction.

Table 6: Extraction for Preliminary Dose Range Finding Study

Vehicle	Extraction Ratio	Article Amount	Volume of Vehicle	Extraction Condition
DMSO (DRF)	60 cm ² :22 mL	56.8 cm ²	21 mL	37°C for 72 hours
DMSO (definitive)	60 cm ² :22 mL	56.8 cm ²	21 mL	37°C for 72 hours
Saline (DRF)	60 cm ² :23 mL	56.8 cm ²	22 mL	37°C for 72 hours
Saline (definitive)	60 cm ² :23 mL	56.8 cm ²	22 mL	37°C for 72 hours

The following table contains a description of the test and control article extract conditions:

Table 7: Condition of Extracts

Vehicle	Time Observed	Extract	Condition of Extracts		
			Color	Clarity	Particulates
DMSO (All)	Before Extraction	Test	Colorless	Clear	None
		Negative Control	Colorless	Clear	None
	After Extraction	Test	Colorless	Clear	None
		Negative Control	Colorless	Clear	None
	Prior to Use	Test	Colorless	Clear	None
		Negative Control	Colorless	Clear	None
Saline (DRF)	Before Extraction	Test	Colorless	Clear	None
		Negative Control	Colorless	Clear	None
	After Extraction	Test	Colorless	Clear	Few fiber-like, white
		Negative Control	Colorless	Clear	None
	Prior to Use	Test	Colorless	Clear	Few fiber-like, white
		Negative Control	Colorless	Clear	None
Saline (definitive)	Before Extraction	Test	Colorless	Clear	None
		Negative Control	Colorless	Clear	None
	After Extraction	Test	Colorless	Clear	None
		Negative Control	Colorless	Clear	None
	Prior to Use	Test	Colorless	Clear	None
		Negative Control	Colorless	Clear	None

The extracts were not centrifuged or filtered prior to dosing. Following extraction, the 100% DRF test article extracts were diluted with DMSO and saline to achieve 50%, 25%, and 12.5% dilutions. The condition of all dilutions was colorless and clear, with no particulates.

Reviewer comments

Note that in intracutaneous study (report number: TI251_800), same extraction vehicle (saline) and conditions were used, except for a higher volume of the saline, and the extracts were clear without particulates. The "few fiber-like, white" particulates in saline extract in current study are very likely to be precipitation of bupivacaine HCl due to lower volume of the saline vehicle. Please also see reviewer's comments on the particulates in the RPMI medium extracts in the Mouse Lymphoma Assay below. Because the testing lab did not manipulate the test extracts prior to dosing, the consultant does not have concern on the extraction method of the collagen component of Xaracoll.

Test procedure:

A preliminary, dose range finding study (DRF) was conducted to determine the dilution of the test article extracts to be used for the definitive mutagenicity assay. The following dilutions of the DMSO and saline test article extracts were tested in single plates in the absence and presence of metabolic activation: 100% (undiluted), 50%, 25%, and 12.5%. Parallel testing was conducted with negative controls (extraction vehicle alone). The 100% (undiluted) test article extract showed an acceptable level of toxicity and was used to evaluate the test article for mutagenicity.

Tubes containing molten top agar were inoculated with culture from one of the five tester strains, along with the DMSO or saline extract. An aliquot of sterile water for injection or rat liver S9 homogenate, providing metabolic activation, was added. The mixture was poured across triplicate plates. Parallel testing was conducted with negative controls (extraction vehicle alone) and positive controls. The mean number of revertants for the test extract plates was compared to the mean number of revertants of the negative control plates for each of the five tester strains.

For the DMSO and saline test extracts/dilutions to be evaluated as a test failure or "potential mutagen" there must have been a 2-fold or greater increase in the number of mean revertants over the means obtained from the negative control for strains TA98, TA100 and WPluvrA and/or a 3-fold or greater increase in the number of mean revertants over the means obtained from the negative control for strains TA1535 and TA1537. Calculation of fold increase is the mean number of revertants of the test divided by the mean number of revertants for the respective negative control. Each positive control mean must have exhibited at least a 3-fold increase over the negative control mean, irrespective of vehicle, for all five tester strains. The negative control results of each tester strain should exhibit a characteristic number of spontaneous revertants based on historical data collected at (b) (4).

Results:

In no case was there a 2-fold or greater increase in the mean number of revertants for tester strains TA98, TA100 and WP2uvrA or a 3-fold or greater increase in the mean number of revertants for tester strains TA1535 and TA1537 in the presence of DMSO and saline test article extracts (Table 11). The negative control results for each tester strain exhibited a characteristic number of spontaneous revertants based on historical data collected at (b) (4). Each positive control mean exhibited at least a 3-fold increase over the respective negative control mean for each of the five tester strains.

Table 11: Test Article to Negative Control Comparison

Tester Strain	Fold Over Negative Control - DMSO Test Article Extract*	Fold Over Negative Control - Saline Test Article Extract*
TA98 without S9	0.7	1.1
TA98 with S9	0.5	0.7
TA100 without S9	1.1	1.0
TA100 with S9	0.9	0.9
TA1535 without S9	1.3	0.8
TA1535 with S9	0.9	0.7
TA1537 without S9	0.6	0.4 ¹
TA1537 with S9	1.1	1.1
WP2uvrA without S9	1.0	0.9
WP2uvrA with S9	0.9	1.1

* Value based on mean number of test extract revertants divided by the mean number of negative control revertants.

Values ≤ 1.0 represent no increase.

Conclusion: The DMSO and saline test article extracts were considered to be nonmutagenic to *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537, and to *Escherichia coli* tester strain WP2uvrA.

Reviewer comments

I have no concern on the testing method and results. The AMES testing demonstrated that the collagen component of Xaracoll is non-mutagenic. I defer to the CDER reviewer to determine whether this testing is adequate to support that the Bupivacaine component of Xaracoll is non-mutagenic.

Mouse Lymphoma Assay (report number: V0573_200)

Study title: Genotoxicity: Dose Range Finding Study with a Definitive Mouse Lymphoma Assay

Testing facility: (b) (4)

Purpose: to satisfy, in part, the requirements of the International Organization for Standardization 10993-3, Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity by evaluating whether extracts produced from the test article induced gene mutations and chromosomal damage in mammalian cells.

Test guidelines: ISO 10993-3, OECD 490, ISO 13485, 21 CFR 58

Test article:**Table 1: Test Article**

Name:	Collagen Sponge with Drug Coating
Identification:	15041002
Stability Testing:	In progress (per sponsor)
Expiration Date:	Stable for duration of intended testing (per sponsor)
Strength, Purity and Composition:	Active Ingredient: Bupivacaine; Strength: 100mg/sponge; Purity: See Appendix 7; Composition: Collagen sponge, bupivacaine coating
Physical Description of the Test Article:	Collagen sponges coated with bupivacaine
Storage Conditions:	Room Temperature

Negative control articles and extraction vehicles:**Table 2: Negative Controls**

Name:	Dimethyl sulfoxide (DMSO) RPMI ₀ Medium
Stability Testing:	DMSO: Marketed product; stability characterized by its labeling. RPMI ₀ : Stable for duration of testing
Strength, Purity, Composition or Other Characteristics:	DMSO: Purity: 100%; Composition: CAS No.: 67-68-5 RPMI ₀ Medium: Composition: 98% Gibco RPMI containing GlutaMAX™ and 25 mM HEPES, 1% antibiotics (penicillin and streptomycin), 200 mg/L sodium pyruvate, 1% Pluronic F68

Reviewer comments

RPMI₀ medium (without serum) is a polar extraction vehicle. Both RPMI₀ medium and DMSO can dissolve the collagen component of Xaracoll therefore they are appropriate extraction vehicles for the collagen. However, the consultant defers to CDER reviewer to determine whether they are appropriate for the Bupivacaine component of Xaracoll.

Positive control article:**Table 3: Positive Controls**

Name:	Methyl methanesulfonate (MMS) and 3-methylcholanthrene (3-MCA) were included as positive controls to verify assay performance.
Stability Testing:	Marketed products; stability characterized by its labeling.
Strength, Purity, Composition or Other Characteristics:	MMS: Purity: 99.9%; Composition: CAS No.: 66-27-3 3-MCA: Purity: 98%; Composition: CAS No.: 56-49-5

Test System: The mouse lymphoma L5178Y/TK⁺ cell line was used for this assay.

Test Article and Negative Control Article Preparation:

The test article was extracted in serum-free cell culture medium (RPMI₀) and dimethyl sulfoxide (DMSO) with following condition (Table 6).

Table 6: Extraction

Vehicle	Extraction Ratio	Amount	Volume of Vehicle	Extraction Condition*
RPMI ₀	60 cm ² :23 mL	511.5 cm ³	196 mL	37°C for 72 hours
RPMI ₀ (DRF)	60 cm ² :23 mL	227.3 cm ³	87 mL	37°C for 72 hours
DMSO	60 cm ² :22 mL	56.8 cm ³	21 mL	37°C for 72 hours

*Justification: The test article was extracted at 37°C since the test article would have degraded at higher temperatures.

The following table contains a description of the test and control article extract conditions.

Table 7: Condition of Extracts

Vehicle	Time Observed	Extract	Condition of Extracts		
			Color	Clarity	Particulates
RPMI ₀	Before Extraction	Test	Pink	Clear	None
		Negative Control	Pink	Clear	None
	After Extraction	Test	Pink	Clear	Many fine white*
		Negative Control	Pink	Clear	None
RPMI ₀ (DRF)	Before Extraction	Test	Pink	Clear	Many fiber-like white
		Negative Control	Pink	Clear	None
	After Extraction	Test	Pink	Clear	Many fine white*
		Negative Control	Pink	Clear	None
DMSO	Before Extraction	Test	Colorless	Clear	None
		Negative Control	Colorless	Clear	None
	After Extraction	Test	Colorless	Clear	None
		Negative Control	Colorless	Clear	None

The test article swelled during the RPMI₀ extraction process. The test article remained visually unchanged following the DMSO extraction process. The extracts were tested immediately following extraction.

*The particulates (see Appendix 8) were allowed to settle and an aliquot for testing was drawn off the top. Otherwise, the extracts were not centrifuged, filtered, or otherwise altered prior to dosing.

All dilutions of the RPMI₀ and DMSO test article extracts were pink and clear with no particulates.

In Appendix 8 (particulate analysis report) of current study, the test article was analyzed by infrared spectroscopy to identify the species present as required by ISO I0993-18, Biological evaluation of medical devices – Part 18: Chemical characterization of materials. The infrared spectrum of the particulates (from the test extract of (b) (4) Lab Number 17T_24564_06) most closely matches that of bupivacaine.

Reviewer comments

- *The serum-free cell culture medium (RPMI) extraction of Xaracoll yielded “many fine white” or “many fiber-like, white” particulates, which are very similar to the saline extract in AMES testing. The report included a particulate analysis report on infrared spectrum of the particulates from the test extract of (b) (4) Lab Number “17T_24564_06” to support that the particulates found in current study are bupivacaine. The consultant defers to the CDER reviewer to determine if sponsor’s justification is acceptable and whether the bupivacaine component is tested in current study.*
- *However, because the testing lab did not manipulate the test extracts prior to dosing, the consultant does not have concern on the extraction method of the collagen component of Xaracoll.*

Test procedure:

The RPMI extract and dilutions of 100% (undiluted), 50%, 25% and 12.5% prepared with RPMI, were supplemented to a 3% serum concentration prior to the 4 hour treatments and supplemented to a 10% serum concentration prior to the 24 hour treatment. The DMSO extract was diluted to a final concentration of 1.0%, 0.5%, 0.25% and 0.125% with RPMI3 for the 4 hour treatments and with RPMI10 for the 24 hour treatment. Due to toxicity found in the 12.5% RPMI extract 24 hour treatment in the absence of metabolic activation, the following additional dilutions of the RPMI test extract were prepared using RPMI to determine a suitable concentration for the definitive study through a dose range finding assay: 6.25%, 3.125%, 1.56%, and 0.78% supplemented to a 10% serum concentration prior to the 24 hour treatment. Per the results of the dose range finding study, the 50% test dilution was selected for testing with the RPMI 4 hour assay in the absence of metabolic activation, the 25% test dilution was selected for testing with the RPMI 4 hour assay in the presence of metabolic activation and the 6.25% dilution was chosen for the RPMI 24 hour assay in the absence of metabolic activation. Per the results of the dose range finding study, the 1.0% test dilution was selected for testing with DMSO. This study was conducted by exposing the cells to the test article extracts and appropriate negative (extract vehicle alone) and positive controls. The treatment was performed for 4 hours in the presence and absence of metabolic activation and 24 hours in the absence of metabolic activation.

Relative Total Growth (RTG%) is used as a measure of cytotoxicity of the test article extract and positive control. Mutant frequencies of the test article extract with a RTG of < 10% were not acceptable for evaluation because the results obtained at such highly toxic levels are not biologically relevant. Since toxicity is expected with the known positive controls, a RTG > 10% was targeted. The test article was considered positive (for mutagenicity) if a 2-fold or greater increase in mutant frequency over the negative control was observed. The test article was considered negative (nonmutagenic) if a less than 2-fold increase is observed. The test article was considered equivocal if there was no valid evidence for either a mutagenic or nonmutagenic response.

Results:

The results for the test article extracts are presented below. The positive and negative controls performed as anticipated.

Table 10: Mean Mutant Frequency for Test Article Extract and Controls

Treatment Group	Testing Phase	Mean Mutant Frequency*
Test	4 hour treatment in the absence of metabolic activation – 50%	106
	4 hour treatment in the presence of metabolic activation – 25%	116
	24 hour treatment in the absence of metabolic activation – 6.25%	57
Negative Control	4 hour treatment in the absence of metabolic activation	55
	4 hour treatment in the presence of metabolic activation	67
	24 hour treatment in the absence of metabolic activation	57
Positive Control	4 hour treatment in the absence of metabolic activation (10 µg/mL MMS)	487
	4 hour treatment in the absence of metabolic activation (20 µg/mL MMS)	906
	4 hour treatment in the presence of metabolic activation (2.0 µg/mL 3-MCA)	703
	4 hour treatment in the presence of metabolic activation (4.0 µg/mL 3-MCA)	659
	24 hour treatment in the absence of metabolic activation (9.0 µg/mL MMS)	1,098
	24 hour treatment in the absence of metabolic activation (12 µg/mL MMS)	1,394

*Mutant frequencies for the positive controls are not mean values.

In no instance for the test article extract was a 2-fold or greater increase in the mean background mutant frequency over the respective negative control observed.

Table 13: Mean Mutant Frequency for Test Article Extract and Controls

Treatment Group	Testing Phase	Mean Mutant Frequency*
Test	4 hour treatment in the absence of metabolic activation – 1.0%	71
	4 hour treatment in the presence of metabolic activation – 1.0%	81
	24 hour treatment in the absence of metabolic activation – 1.0%	46
Negative Control	4 hour treatment in the absence of metabolic activation	62
	4 hour treatment in the presence of metabolic activation	66
	24 hour treatment in the absence of metabolic activation	57
Positive Control	4 hour treatment in the absence of metabolic activation (10 µg/mL MMS)	502
	4 hour treatment in the absence of metabolic activation (20 µg/mL MMS)	807
	4 hour treatment in the presence of metabolic activation (2.0 µg/mL 3-MCA)	778
	4 hour treatment in the presence of metabolic activation (4.0 µg/mL 3-MCA)	813
	24 hour treatment in the absence of metabolic activation (9.0 µg/mL MMS)	1,079
	24 hour treatment in the absence of metabolic activation (12 µg/mL MMS)	1,381

*Mutant frequencies for the positive controls are not mean values.

In no instance for the test article extract was a 2-fold or greater increase in the mean background mutant frequency over the respective negative control observed.

Conclusion: The RPMI and DMSO test article extracts did not cause a 2-fold or greater increase in the mean mutation frequency in the L5178 Y/TK+/" cell line either in the presence or absence of metabolic activation. The test article was not mutagenic.

Reviewer comments

I have no concern on the testing method and results. The Mouse Lymphoma Assay demonstrated that the collagen component of Xaracoll is non-mutagenic. I defer to the CDER reviewer to determine whether this testing is adequate to support that the Bupivacaine component of Xaracoll is non-mutagenic.

Summary and conclusion for the biocompatibility review of collagen component of Xaracoll

The sponsor has conducted an appropriate panel of biocompatibility testing and evaluation (i.e., risk assessment) as recommended in ISO10993-1 for a permanently implanted tissue-contacting device.

The consultant reviewed the following biocompatibility test reports in this NDA submission:

1. Report GLP-2018-0182: cytotoxicity on Xaracoll combination product, collagen matrix and bupivacaine.
2. Report TI251_800: intracutaneous reactivity on Xaracoll combination product.
3. Report TI261_300: sensitization study on Xaracoll combination product.
4. Report T0625_500/S and T0625_500: acute systemic toxicity on Xaracoll combination product and collagen matrix.
5. Report TU010_807: rabbit pyrogenicity on Xaracoll combination product and collagen matrix.
6. Report V0023_311: genotoxicity (AMES) on Xaracoll combination product.
7. Report V0573_200: genotoxicity (mouse lymphoma assay) on Xaracoll combination product.

The consultant's review founded that all of the biocompatibility testing above was conducted in compliance with 21 CFR 58 GLP regulations, and conformed to ISO 10993 standard, USP or OECD test methods. Review of these test reports indicates the controls performed as expected and the acceptance criteria were met in each test other than the exceptions below:

1. Animal death was observed in acute systemic toxicity and rabbit pyrogenicity on Xaracoll combination product and sponsor justified that the death is due to "overdose of bupivacaine" in these studies which is higher than LD 50 value of bupivacaine. The consultant defers to the CDER reviewer to comment whether sponsor's justification is acceptable.
2. Xaracoll combination product and bupivacaine were found to be cytotoxic. The consultant defers to CDER reviewer to comment on the cytotoxic effect of the bupivacaine component of XARACOLL combination product.
3. Particulates were found in test extracts of polar solvent in some testing reports above. The sponsor justified that the particulates are bupivacaine precipitated during extraction. The consultant defers to the CDER reviewer to determine if sponsor's justification is acceptable and whether the bupivacaine component is tested sufficiently in these studies.

In conclusion, the consultant believes that the above 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. To fully demonstrate that the

collagen component is biocompatible and is safe for clinical use, the consultant defers to CDER non-clinical review group to evaluate the local tissue response (implantation study) and longer term systemic toxicity (subacute/Subchronic toxicity), the toxicological information of raw materials/chemicals used in the Xaracoll manufacture process, and extractable/leachables in the final product to capture the full and complete manufacturing process of the finished product.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Lixin Liu -S 2018.08.03 15:41:25 -04'00'
Branch Chief Sign-Off (optional)	Cynthia Chang -S 2018.08.09 11:39:32 -04'00'
Division Sign-Off (optional)	David Krause -S 2018.08.10 14:28:23 -04'00'

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/s/

ALLISON MEYER
02/28/2020 09:53:36 AM

Clinical Inspection Summary

Date	October 30, 2018
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Rigoberto Roca, M.D., Deputy Director Renee Petit-Scott, M.D., Clinical Reviewer Allison Meyer, Regulatory Project Manager
NDA#	209511
Applicant	Innocoll Pharmaceuticals
Drug	Xaracoll® (bupivacaine hydrochloride collagen matrix implants)
NME	No
Review Priority	Standard
Proposed Indication	For single-dose placement into the surgical site to produce postsurgical analgesia following (b) (4)
Consultation Request Date	June 6, 2018
Summary Goal Date	November 2, 2018
Action Goal Date	November 30, 2018
PDUFA Date	November 30, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Saba, Suarez, and Deck were inspected in support of this NDA. Based on the results of these inspections, the studies (Protocols INN-CB-014 and INN-CB-016) appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final compliance classification of the inspections of Drs. Saba, Suarez, and Deck was No Action Indicated (NAI).

II. BACKGROUND

The Applicant submitted this NDA to support the use of Xaracoll® for single-dose placement into the surgical site to produce postsurgical analgesia following (b) (4)

Clinical inspections were requested for the following protocols in support of this application:

- Protocol INN-CB-014, “A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of the Xaracoll Bupivacaine Implant (300mg Bupivacaine Hydrochloride) After Open Laparotomy Hernioplasty”
 - This study randomized 305 subjects at 20 study sites in the U.S.
- Protocol INN-CB-016, “A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of the Xaracoll® Bupivacaine Implant (300mg Bupivacaine Hydrochloride) After Open Laparotomy Hernioplasty”

- o This study randomized 319 subjects at 19 study sites in the U.S.

(b) (4)

The primary efficacy endpoint was the time-weighted sum of pain intensity from 0 to 24 hours (SPI24).

Rationale for Site Selection

Dr. Saba's and Dr. Deck's sites were selected for inspection because of high enrollment and significant treatment effect. Dr. Suarez's site was selected because of high enrollment.

III.RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
Site #417 Dr. Fadi Saba Professional Health Care of Pinellas, Inc. 1839 Central Avenue St. Petersburg, FL 33713	INN-CB-014 Subjects: 50	10-20 Sep 2018	NAI
Site #420 Dr. Jose Suarez Medical Research Center 922 SW 82nd Avenue Miami, FL 33144	INN-CB-014 Subjects: 39	13-17 Aug 2018	NAI
Site #603 Dr. Kenneth Deck Alliance Research Centers 24012 Calle de la Plata, Ste. 203 Laguna Hills, CA 92653	INN-CB-016 Subjects: 45	1-5 Oct 2018	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

1. Dr. Fadi Saba

At this site for Protocol INN-CB-014, 62 subjects were screened, 50 subjects were enrolled in the study, and 47 subjects completed the study. Informed consent for all 62 screened subjects was obtained appropriately prior to any study-related activities. The records of all 62 randomized subjects were compared to the data listings.

Other records reviewed included IRB, monitoring, and sponsor correspondence; financial disclosure; source records including, but not limited to, laboratory results, physical examination results, opioid and acetaminophen use, and EKGs; inclusion/exclusion criteria; protocol deviations; concomitant medications; and test article accountability and storage.

The primary efficacy endpoint was verifiable, and there was no evidence of under-reporting of adverse events.

2. Dr. Jose Suarez

At this site for Protocol INN-CB-014, 52 subjects were screened, and 39 subjects were randomized into and completed the study. Informed consent for all 52 screened subjects was obtained appropriately prior to any study-related activities. The records of the 39 randomized subjects were compared to the data listings.

Other records reviewed included financial disclosures, training records, delegation of authority, laboratory certifications, IRB, monitoring/sponsor correspondence, medical histories, patient assessments, adverse events, concomitant medications, and test article accountability and storage. There was no evidence of under-reporting of adverse events.

For the primary efficacy endpoint, the data line listings provided by the sponsor were compared with the source for the e-diaries. For some subjects, there were entries in the data listings that were not reflected in the e-diaries; for other subjects, there were entries in the e-diaries not reflected in the data listings (see Table 1 below).

Table 1: Discrepancies between sponsor data line listings and e-diaries

Subject #	E-diary data points not included in the data listing (hrs)	Data listing data points not included in the e-diary (hrs)
(b) (6)	3,5,8	72
		1, 2, 3, 72
		3, 8
		72
	24, 48	
	24, 48, 72	
		1
		5, 8, 72
		24
		72
		1
		3
		1
		2
	72	
		1, 8
		72

Reviewer Comments: For those subjects with data listing entries not reflected in the e-diaries, the discrepancies appear to be the result of data imputation or interpolation as described in the footnotes for Data Listing 16.2.6.1 of the CSR, which note the various types of imputation, including “last-observation-carried-forward”(LOCF), “linear interpolation” (INTERP), “worst-observed case” (WO), “last-observed pre-rescue value carried forward” (LOPR), and “worst-observed case carried forward”. For example, Subject (b) (6) (Xaracoll) had pain intensities of “4.0” at Hours 1, 2, and 3, and of “3.0” at Hour 72 in the line listings; however, these pain intensities were not from the e-diary but rather they were the imputed Pain Intensity values resulting from following the data handling rules in the SAP. We refer to the review division as to whether these data imputation and interpolation methods are acceptable.

On the other hand, for those subjects with e-diary entries not reflected in the data line listings, the subjects are noted as not being in the Per-Protocol population (Data Listing 16.2.3) for either lacking the appropriate number of assessments or for taking prohibited medications. Since these subjects are not in the Per-Protocol analysis, these discrepancies between their e-diary entries and the data line listings would not impact the efficacy results for this study.

3. Dr. Kenneth Deck

At this site for Protocol INN-CB-016, 52 subjects were screened, 45 subjects were randomized to treatment, 43 subjects received the investigational product (IP), and 43 subjects completed the study. The records of 32 subjects were reviewed for verification of the primary efficacy endpoint and adverse events.

The primary efficacy endpoint was verifiable. There was one observation in which Subject (b) (6) had a pain score of “7” pre-rescue with hydromorphone at 16:18 hrs per source documents, but this was not reported in the eCRF. In the eCRF, the pain score was “7” prior to this report (15:46 hrs) and “6” after this report (16:32 hrs).

There was also one observation of the under-reporting of adverse events. Subject (b) (6) experienced opioid-induced constipation and one episode of vomiting. Both adverse events were classified as mild and resolved.

The records of 27 subjects were reviewed in their entirety with respect to the compliance program. There was one observation regarding concomitant medications in which Subject (b) (6) received lidocaine intravenously prior to propofol induction. The use of lidocaine was reported in the source documents but not in the eCRF.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
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Kassa Ayalew, M.D., M.P.H
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Central Doc. Rm.\NDA 209511

DAAAP\Division Director\Sharon Hertz

DAAAP\Team Leader\Rigo Roca

DAAAP\Medical Officer\Renee Petit-Scott

DAAAP\Project Manager\Allison Meyer

OS\DCCE\Division Director\Ni Khin

OS\DCCE\GCPAB\Branch Chief\Kassa Ayalew

OS\DCCE\GCPAB\Team Leader\Phillip Kronstein

OS\DCCE\GCPAB\Reviewer\Roy Blay

OS\DCCE\Program Analysts\Yolanda Patague

OS\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
11/01/2018

PHILLIP D KRONSTEIN
11/01/2018

KASSA AYALEW
11/01/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 15, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 209511
Product Name and Strength:	Xaracoll (bupivacaine HCl collagen-matrix implant), 100 mg
Applicant/Sponsor Name:	Innocoll Pharmaceuticals
FDA Received Date:	10/4/2018
OSE RCM #:	2018-2968-1
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

DAAAP requested that we review the revised blister container label, pouch labeling and carton labeling for Xaracoll (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised blister container label, pouch labeling and carton labeling for Xaracoll are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Johnson, C. Label and Labeling Review for Xaracoll NDA 209511. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 31. RCM No.: 2018-2968.

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/s/

CAMERON D JOHNSON
10/15/2018

OTTO L TOWNSEND
10/15/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	August 31, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia and Addiction Products (DAAAP)
Application Type and Number:	NDA 209511
Product Type:	Combination Product
Drug Constituent Name and Strength:	Xaracoll (bupivacaine HCl collagen-matrix implant), 100 mg
Device Constituent:	Collagen-matrix implant
Rx or OTC:	Rx
Applicant/Sponsor Name:	Innocoll Pharmaceuticals
FDA Received Date:	May 2, 2018 and July 2, 2018
OSE RCM #:	2018-1365 and 2018-2968
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW

As part of the approval process for Xaracoll (bupivacaine collagen matrix implants), DAAAP requested that we review the proposed blister container label, pouch labeling, carton labeling and prescribing information (PI) for vulnerabilities to medication errors.

1.1 PRODUCT BACKGROUND

Xaracoll has the proposed indication for placement into the surgical site to produce postsurgical analgesia following (b) (4). A single collagen-matrix implant contains 100 mg of bupivacaine that can be cut and placed at multiple tissue layers within the surgical site.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of the material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Information Request	E
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

2.1 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

While reviewing the proposed labels and labeling submitted by Innocoll on February 2, 2018, we noted that the placement instructions stated that the implant could be cut, and the instructions did not clearly convey how and in what circumstances the implant needs to be cut. An Information Request was sent to Innocoll requesting that they submit more comprehensive instructions as well as a use related risk analysis (see Appendix E).

Our review of the proposed blister container label, pouch labeling, carton labeling, Prescribing Information, and response to our IR, identified deficiencies that should be addressed to ensure safe and effective use of the product.

3 CONCLUSIONS AND RECOMMENDATIONS

We recommend several changes be implemented to the proposed blister container label, pouch labeling, carton labeling and prescribing information (PI) for Xaracoll (bupivacaine collagen matrix implants) to ensure safe and effective use. See sections 4.1 and 4.2 below.

3.1 COMMENTS AND RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. In the Dosage Forms and Strengths section of the Highlights and Full Prescribing Information, the strength is listed as (b) (4). Since this section should only contain the strength of the product (100 mg) (b) (4), this section should be revised to accurately convey the strength as “100 mg per implant”.
2. We note the use of passive statements in the Placement Instructions subsection. For example, (b) (4). All passive statements should be changed to include command language (e.g., (b) (4)).
3. In the How Supplied section Xaracoll is described as (b) (4). This may cause confusion if the user overlooks (b) (4) and misinterprets that (b) (4). Revise this statement by removing (b) (4). For example, “XARACOLL (bupivacaine HCl collagen-matrix implants) is supplied as three sterile surgical implants (approximately 5 cm x 5 cm x 0.5 cm), each containing 100 mg of bupivacaine HCl (equivalent to 88.8 bupivacaine) in individually sealed blisters.” For consistency also revise the statement (b) (4) to read (b) (4).

3.2 COMMENTS AND RECOMMENDATIONS FOR INNOCOLL INC.

We recommend the following changes be implemented to address the risk of medication errors:

A. Blister container label

1. The established name has not been included on the container label which is required per 21 CFR 201.10(i). Include the established name on the label to comply with 21 CFR 201.10(i). Furthermore, ensure that the established name is at least half the size of the proprietary name to comply with 21 CFR 201.10(g)(2).
2. The name of the manufacturer, packer, or distributor of the product has not been included on the container label and this is required per 21 CFR 201.10(i). Include the manufacturer, packer, or distributor on the label.

B. Pouch labeling and Carton labeling

1. The strength is expressed (b) (4) as opposed to the strength per implant (100 mg). The product strength should be

expressed as the milligram strength contained in a single implant to reduce the potential of the user misinterpreting the strength (b) (4) mg. Revise the strength to read “100 mg per implant”.

2. There is no linear barcode on the pouch or carton labeling. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. We request you add the products linear barcode to each individual pouch and carton labeling to comply with 21 CFR 201.25(c)(2).

C. Blister container label and Carton labeling

1. As currently presented, the format of the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either:
 - a. DDMMYYYY (e.g., 31JAN2013)
 - b. MMMYYYY (e.g., JAN2013)
 - c. YYYY-MMM-DD (e.g., 2013-JAN-31)
 - d. YYYY-MM-DD (e.g., 2013-01-31)

D. Carton Labeling

1. The content statement, (b) (4) dose not adequately describe the contents of the carton. Change the content statement so that it informs users that the internal pouch includes 3 implants that are 100 mg each. For example, “Contents: 1 Pouch containing 3 x 100 mg Sterile Implants”

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xaracoll received on March 30, 2018 from Innocoll, Inc.

Table 2. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	anesthetic
Active Ingredient (Drug or Biologic)	bupivacaine
Indication	Placement into the surgical site to produce postsurgical analgesia following (b) (4)
Route of Administration	Surgical implantation
Dosage Form	Collagen-matrix implant
Strength	100 mg
Dose and Frequency	300 mg (3 x 100 mg implants) placed into the surgical site once
How Supplied	3 sterile surgical implants (5 cm x 5 cm x 0.5 cm), each containing 100 mg bupivacaine in individually sealed blisters; a tray of three blisters in a sterile pouch is provided in one carton
Storage	Room temperature
Device Constituent	Collagen-matrix implant
Intended Users	Healthcare professionals
Intended Use Environment	Operating room

APPENDIX B. N/A

APPENDIX C. N/A

APPENDIX D. N/A

APPENDIX E. INFORMATION REQUEST

We sent an information request to the Applicant on March 19, 2018. Our information request and the Applicant's response can be accessed in EDR via:

<\\cdsesub1\evsprod\nda209511\0013\m1\us\1-11-4-multi-mod-info-amend-rfi-response.pdf>

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Xaracoll labels and labeling submitted by Innocoll, Inc.

- Blister container label received on 7/2/2018
- Pouch labeling received on 7/2/2018
- Carton labeling received on 7/2/2018
- Prescribing Information (Image not shown) received on 5/2/2018

F.2 Labels and Labeling



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

CAMERON D JOHNSON
08/31/2018

OTTO L TOWNSEND
08/31/2018

Intercenter consult request from CDER – ICCR2017-01101
Biocompatibility review
Application: NDA 209511
CDRH consult number: CON1713242

To: Ogochukwu Ogoegbunam, PharmD.
Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP

From: Lixin Liu, Ph.D., Biologist
CDRH/ODE/DSD/PRSB2

Date: June 22, 2017

Product: Xaracoll (bupivacaine collagen matrix implant)

Sponsor: Innocoll Pharmaceuticals

Consult: Follow-up question after type A meeting regarding the biocompatibility of collagen matrix component of Xaracoll

Introduction

The sponsor, Innocoll Pharmaceuticals, submitted an NDA for their drug/device combination product, Xaracoll (bupivacaine collagen matrix implant) (NDA 209511) for review by CDER/FDA. I conducted an intercenter consultative filing review of the biocompatibility testing of the collagen matrix, the device component of Xaracoll, provided in the NDA. As the sponsor did not provide any biocompatibility information of the collagen matrix of XARACOLL, I recommended Non-Filing of this NDA, and recommended the sponsor to provide the biocompatibility information of the collagen component of XARACOLL. The Refuse to File letter was issued on December 23, 2016. A Type A meeting was held on February 23, 2017 to clarify issues identified in the 23December2016 RTF letter, and to discuss sponsor's approaches for resubmission to address the agency's concerns. After the Type A meeting, the sponsor initiated a rabbit pyrogenicity study on XARACOLL resulting in premature death of the test animal. The sponsor sent an e-mail to the agency on May 31, 2017, stated that "the premature death of the animal was considered most likely due to bupivacaine overdose" and proposed not to conduct the rabbit pyrogenicity study. The project manager, Dr. Ogochukwu Ogoegbunam, has requested an intercenter consultative review of sponsor's request to waive the requirement of the rabbit pyrogenicity study. As I do not have access to DARRAS, the CDER submission database, my review and comments are limited to the information provided by Dr. Ogoegbunam and the NDA 209511 submission provided by CDER during the review of the NDA submission.

Recommendation

I recommend that the sponsor repeat the rabbit pyrogenicity testing on the collagen matrix component without bupivacaine. The collagen matrix test article should undergo the same manufacturing process as the XARACOLL final product. In addition, the sponsor should provide toxicological information of raw materials/chemicals used in the bupivacaine manufacturing process to capture the full and complete manufacturing process of the finished product. I have prepared the feedback to the sponsor at the end of this consult memo.

Product Summary

XARACOLL® (bupivacaine collagen implant) is a surgical implant composed of a (b) (4) purified resorbable Type I bovine collagen matrix. Each implant (5 × 5 × 0.5 cm) contains 100.0 mg of uniformly distributed bupivacaine HCl (equivalent to 88.8 mg bupivacaine as the free base) and is designed to provide controlled drug release via dissolution and diffusion from the porous matrix. (b) (4)

(b) (4) The composition of the drug product is provided in Table 1.

Table 1 Composition of XARACOLL

Component	Quality standard	Quantity per matrix	Function
Bovine type I collagen, purified	Ph.Eur. monograph 5.2.8	75 mg	Drug delivery system
Bupivacaine HCl	USP	100 mg	Drug substance

XARACOLL product manufacturing process

XARACOLL is prepared by (b) (4)

(b) (4) The 3 implants in an (b) (4) sterile pouch are then labeled and packed into an (b) (4) carton for commercial distribution.

Reviewer comments

The provided manufacturing information is limited. It is not clear to the consultant (b) (4)

Intended use/indication for use

Use of XARACOLL is intended to produce local anesthetic concentrations at the surgical site and can be implanted at different layers within the surgical cavity. This local anesthetic administration also reduces systemic bupivacaine absorption so that the drug's most serious potential systemic toxicities, namely central nervous system and cardiovascular system toxicity, are minimized.

Summary of biocompatibility review in NDA 209511 and type A meeting

- The sponsor stated that XARACOLL is a surgical implant which is intended to produce local anesthetic concentrations at the surgical site. The product can be implanted at different layers within the surgical cavity. The sponsor did not identify the biocompatibility contact classification (the nature and duration of contact) of the collagen matrix component of XARACOLL.
- Given the properties and intended use of the product, the aforementioned considerations and data needs are applicable regardless of whether the implant is considered a permanent implant or a prolonged implant: cytotoxicity, sensitization, irritation, acute systemic toxicity, subacute/subchronic toxicity, implantation, material-mediated pyrogenicity, genotoxicity, chronic toxicity and carcinogenicity. The biocompatibility testing should be conducted on the final, sterilized product containing both the bupivacaine and collagen matrix.
- The sponsor proposed a chemical characterization of the product to address the chronic toxicity and carcinogenicity concerns. This may be an acceptable alternative approach. Provide toxicological information of raw materials/chemicals used in the manufacture process as well as the residues/leachables in the final product (e.g., Certificates of analysis (CoA), Material safety data sheets (MSDS)). Conduct a toxicology risk assessment as specified in ISO 10993-17, e.g., LD50's, NOAEL, LOAEL, etc., with a worst case comparison of a patient's exposure (i.e., consider the maximum product size and multiple product application) to known toxicity values. The acceptability of these data will be determined during the review of the resubmission.

Sponsor's justification on animal premature death in the rabbit pyrogenicity study

The sponsor stated in 31May2017 e-mail that they initiated a rabbit pyrogenicity study as directed in the RTF minutes at the contract lab, (b) (4) and after dosing the first rabbit, who died, an investigation uncovered that the study cannot be conducted per ISO guidelines:

"The studies are driven by the extract requirements outlined in the ISO regulations to ensure the studies capture all particulates in the biomaterial. With respect to the ISO studies we are undertaking, the extract ratios for polar and non-polar extracts are based on the surface area and required dosing volume for each species. Where sponge material is present (as in XARACOLL), an initial absorbance capacity test is conducted to evaluate how much of the extraction volume is absorbed by the sponge material and then it is adjusted to provide the required extract ratio and dosing volume. For the Xaracoll studies, the ratio set forth in the guidances requires 60cm² of extract material: 27 mL saline or sesame oil. In the case of the pyrogenicity study, 8 sponges were used (8 x100 mg) bupivacaine to provide a total dosing volume of 205 mL. This calculated to 3.9 mg/mL bupivacaine x 2.5 kg rabbit. The dosing volume requirement was 10mL/kg, resulting in 97.5 mg bupivacaine injected IV. We know based on the NOAEL for implantation in rats that the MTD for bupivacaine is 8 mg. The LD50 values in rabbits reported in the literature are 1.62 and 3.4 mg/kg for IV bupivacaine. If we use the highest LD50 value as 3.4 mg/kg, for a 2.5kg

rabbit this results in 8.5mg bupivacaine. The rabbit in the pyrogenicity study was overdosed by 12x the LD50 value, thus leading to toxicity and death.

Based on this information and moving forward, the pyrogenicity study will not be possible under the ISO guidelines based on bupivacaine toxicity in rabbits, the requirement for IV dosing and the dose level per sponge. To meet the extraction ratio for IV injection in rabbits, we would exceed the LD50 for bupivacaine in rabbits. If we were to dilute the extract to lower the dose, the study would not be in compliance with ISO. The Director of Toxicology, (b) (4) at (b) (4), concluded that the study is not feasible under the ISO guidelines and extract dilution is not an option because it would also lead to dilution of the biomaterial particulates and would this invalidate the study. (b) (4) serves on the ISO committee and works closely with FDA. His recommendation is to write a risk assessment stating what has been stated here to justify not conducting the study. Since FDA asked for this as a material mediated study, omission of testing based on bupivacaine toxicity by IV administration is justified.”

The sponsor then provided the following documents in their 1June2017 e-mail:

1. a GLP report received today from (b) (4) for the study;
2. the signed study protocol;
3. a data sheet from (b) (4) showing the toxicology data and LD50 information for bupivacaine;
4. GLP study report for the intracutaneous study report obtained from (b) (4) today.

USP rabbit pyrogenicity study, Material mediated

Purpose: to determine whether an extract of the test article induced a pyrogenic response following intravenous injection in rabbits.

Test guidelines: USP, General Chapter <151>, Pyrogen Test

Test article: Collagen Sponge with Drug Coating

Test article identification: 15041002

Animal: rabbit, New Zealand White

Test article preparation:

Table 3: Extraction

Vehicle	Extraction Ratio	Article Amount	Volume of Vehicle	Extraction Condition
SNPS	60 cm ² :27 mL	454.7 cm ²	205 mL	37°C for 72 hours

Table 4: Condition of Extract

Vehicle	Time Observed	Extract	Condition of Extract		
			Color	Clarity	Particulates
SNPS	Before Extraction	Test	Colorless	Clear	None
	After Extraction	Test	Colorless	Clear	None
	Prior to Use	Test	Colorless	Clear	None

Reviewer comments

The extraction vehicle and extraction condition are appropriate. The condition of the test extract appears normal both before and after extraction. I have no concern.

Test procedure: The animal was injected intravenously via the marginal ear vein with the test extract at 10 mL/kg of body weight.

Reviewer comments

The performed test procedure is consistent with the USP <151>. I have no concern.

Result: Animal 18033 died immediately after injecting only 21 mL of the 36 mL that was to be injected. This animal was subjected to a gross necropsy. All tissues appeared macroscopically normal at necropsy.

Conclusion: Due to the death and early termination of the two animals, no additional animals were dosed and the study was terminated. No conclusions were drawn from this study.

Discussion: The test article did contain Bupivacaine at 100 mg per test article. 8 test articles were included in the preparation. The volume yielded after extraction was 205 mL. This means that the drug volume was 3.9 mg/mL. The animal was to be injected with 36 mL which would have been a total of 97.5 mg of the drug. The LD50 value of Bupivacaine in a rabbit IV is 3.4 mg/mL. For this particular rabbit the LD50 value would have been 12.24 mg of the drug. The animal was dosed with 8x the amount of the LD50 value at 97.5 mg. Therefore, the death of the animal was more than likely from an overdose of the drug.

Reviewer comments

The sponsor concluded that the premature death of the animal was due to bupivacaine overdose through intravenous administration. Please see reviewer comments on other evidences provided by the sponsor below.

Dose of bupivacaine administered in rabbit pyrogenicity study as compared to the LD50 value

The sponsor calculated the dosage of bupivacaine injected intravenously in the dead animal, which is 81.9 mg total dose of bupivacaine, based on the assumption that all bupivacaine would be dissolved

in the extraction solution. The sponsor also provided a data sheet from (b) (4) showing the toxicology data and LD50 information for bupivacaine. They justified that, based on data derived from literature (b) (4) reference source) the LD50 (median lethal dose) values for IV injectable bupivacaine in rabbits is 3.4 mg/kg; the animal received a dose of bupivacaine significantly in excess (x8-fold) of the LD50 for bupivacaine in rabbits. No literature-derived NOAEL data were available for bupivacaine IV administration in rabbits.

Reviewer comments

The consultant contacted CDER/Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) to comment if sponsor's justification is acceptable. Dr. Daniel Mellon, Pharmacology Toxicology Supervisor from DAAAP commented that, "It is certainly true that IV bupivacaine doses around the LD50 value are likely to result in death of approximately 50% of the animals dosed. According to ChemID database search:

rat	LD50	intravenous	5600ug/kg (5.6mg/kg)	Acta Pharmacologica et Toxicologica. Vol. 31, Pg. 273, 1972.
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LD50 values are not always exact as to get an accurate LD50 you need to test a very large number of animals, so variation in values reported in the literature is not surprising".

Dr. Mellon provided a LD50 value for IV administration of bupivacaine in rat, 5.6mg/kg, which is similar to the LD50 value in rabbit provided by the sponsor. Therefore, I believe that sponsor's justification is scientific reasonable.

ISO Intracutaneous study in rabbits

The sponsor provided an intracutaneous study report, to evaluate the potential of Collagen Sponge with Drug Coating to cause irritation following intracutaneous injection in rabbits per ISO 10993-10. The test article (Test article identification: 15041002) was extracted in 0.9% sodium chloride USP solution (SC) and sesame oil, NF (SO). A 0.2 mL dose of the appropriate test article extract was injected intracutaneously into five separate sites on the right side of the back of each of three animals. Similarly, the extract vehicle alone (control) was injected on the left side of the back of each animal. The injection sites were observed immediately after injection. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection. The test article extract met the requirements of the test since the difference between each test article extract overall mean score and corresponding control extract overall mean score was 0.0 and 0.2 for the SC and SO test article extracts, respectively.

The sponsor stated that, the premature death of animal in the rabbit pyrogenicity study "was not considered related to the presence of material particulates/degradants within the test article or related to the extract conditions, since the same extract conditions, using the same Xaracoll combination product were used for an ISO intracutaneous study in rabbits with no evidence of localized or systemic toxicity (study report pending)."

Reviewer comments

I reviewed the provided intracutaneous study report, and have no concern on the test methods and test results. I found that the test article is identical for the intracutaneous study and the rabbit pyrogenicity study; the extraction conditions for both studies are also same. The animal received an intracutaneous injection of 1 ml total volume of test extracts in the intracutaneous study, while the dead animal received an IV injection of 21mL in the rabbit pyrogenicity study.

I believe that sponsor's justification on the animal premature death in the rabbit pyrogenicity, which is due to bupivacaine overdose through intravenous injection, is scientific reasonable.

Sponsor's request to waive the requirement of the rabbit pyrogenicity study

The sponsor requested not to conduct the rabbit pyrogenicity study. They justified that, "Given requirements of the USP and ISO-10993 Part-11 protocol to provide the appropriate extract ratio and dosing volume and route of administration, any dilution of the test article extract to effectively lower the bupivacaine dose to below the LD50 values, would significantly dilute any test article particulates that would be derived from the combination product in its entirety, and thus would invalidate the USP and ISO requirements for testing. Therefore, it is considered unfeasible to conduct pyrogenicity testing for the Xaracoll combination product under the auspices of the USP and ISO guidance."

Reviewer comments

1. *The pyrogenicity testing is used to help protect patients from the risk of febrile reaction due to either gram-negative bacterial endotoxins or other sources of pyrogens (e.g., material-mediated pyrogens). Material-mediated pyrogens are chemicals that can leach from a medical product and are traditionally addressed as part of the biocompatibility assessment. The USP Chapter <151> Pyrogenicity Test (the rabbit pyrogen test) is recommended to mitigate the risk of the presence of pyrogens that can leach from the product. Therefore, I disagree that the sponsor may waive the requirement of the rabbit pyrogenicity study.*
2. *We generally recommend that the sponsor perform the biocompatibility studies on the product in its entirety. Evaluation of the final, finished version of the product would allow for assessment of material biocompatibility that captures the full and complete manufacturing process of the finished product. If testing of the final, finished version of the combination product results in any negative biocompatibility outcomes, then the sponsor will need to determine the reason for failure, including investigation of which of the product components contributed to the failed biocompatibility testing. Innocoll Inc. conducted the rabbit pyrogenicity study on the final, finished Xaracoll product and found that the animal died immediately after IV administration of the test article extracts. The sponsor provided justification on the premature death of the animal, which is due to bupivacaine overdose through intravenous injection. I believe that sponsor's justification is scientific reasonable.*
3. *To mitigate the risk of the presence of pyrogens in the Xaracoll final product, I recommend that the sponsor repeat the rabbit pyrogenicity testing on the collagen matrix without bupivacaine (the placebo sponge). The collagen matrix test article should undergo the same manufacturing process as the XARACOLL final product, including packaging and sterilization.*

(b) (4)

(b) (4) *In addition to the requested rabbit pyrogenicity testing, the sponsor should also provide toxicological information of raw materials/chemicals used in the bupivacaine manufacture process (e.g., Certificates of analysis (CoA), Material safety data sheets (MSDS)), to capture the full and complete manufacturing process of the finished product.*

FDA feedback to the sponsor

You conducted the rabbit pyrogenicity study on the Xaracoll final product and found that the animal died immediately after intravenous administration of the test article extracts. You provided justification that the premature death of the animal is due to bupivacaine overdose through intravenous injection. We believe this justification is scientific reasonable. However, we disagree that you may waive the requirement of the rabbit pyrogenicity study. Please note that the pyrogenicity testing is used to help protect patients from the risk of febrile reaction due to either gram-negative bacterial endotoxins or other sources of pyrogens (e.g., material-mediated pyrogens) in the product. The USP Chapter <151> Pyrogenicity Test (the rabbit pyrogen test) is recommended to mitigate the risk of the presence of pyrogens that can leach from the product.

To mitigate the risk of the presence of pyrogens in the Xaracoll final product, we request that you repeat the rabbit pyrogenicity testing on the collagen matrix component without bupivacaine (the placebo sponge). The collagen matrix test article should undergo the same manufacturing process as the XARACOLL final product, including packaging and sterilization. (b) (4)

(b) (4) In addition to the requested rabbit pyrogenicity testing, you should also provide toxicological information of raw materials/chemicals used in the bupivacaine manufacture process (e.g., Certificates of analysis (CoA), Material safety data sheets (MSDS)) and evaluate their pyrogenicity, to capture the full and complete manufacturing process of the finished product.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Lixin Liu -S 2017.06.22 10:55:02 -04'00'
Branch Chief Sign-Off (optional)	Cynthia Chang -S Cynthia Chang -S 2017.06.23 11:13:47 -04'00'
Division Sign-Off (optional)	David Krause -S 2017.06.23 12:54:55 -04'00'

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

/s/

OGOCHUKWU U OGOEGBUNAM
06/30/2017

Date: December 14, 2016

To: Steven Kinsley, CDER/OPQ/OPRO/DRBPMI/RBPMBI, WO75 Rm 4668
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Through: Robert Kang, Acting Branch Chief, CDRH/OC/DMQ/POND,
Robert.Kang@fda.hhs.gov

Robert Kang -S
2016.12.19 15:59:48 -05'00'

From: Bella Pelina, CDRH/OC/DMQ/POND, Arabella.Pelina@fda.hhs.gov

Applicant: Innocoll Pharmaceuticals
Monksland Business Park
Unit 9 Block D
Athlone, Co. Roscommon
Ireland W37K30

Application # NDA 209511

Consult # ICC1600813

Product Name: XARACOLL® (bupivacaine HCL collagen-matrix implants) 300mg

Pre-Approval Inspection: Yes

Documentation Review: Additional Information Required

Final Recommendation: **DELAY**

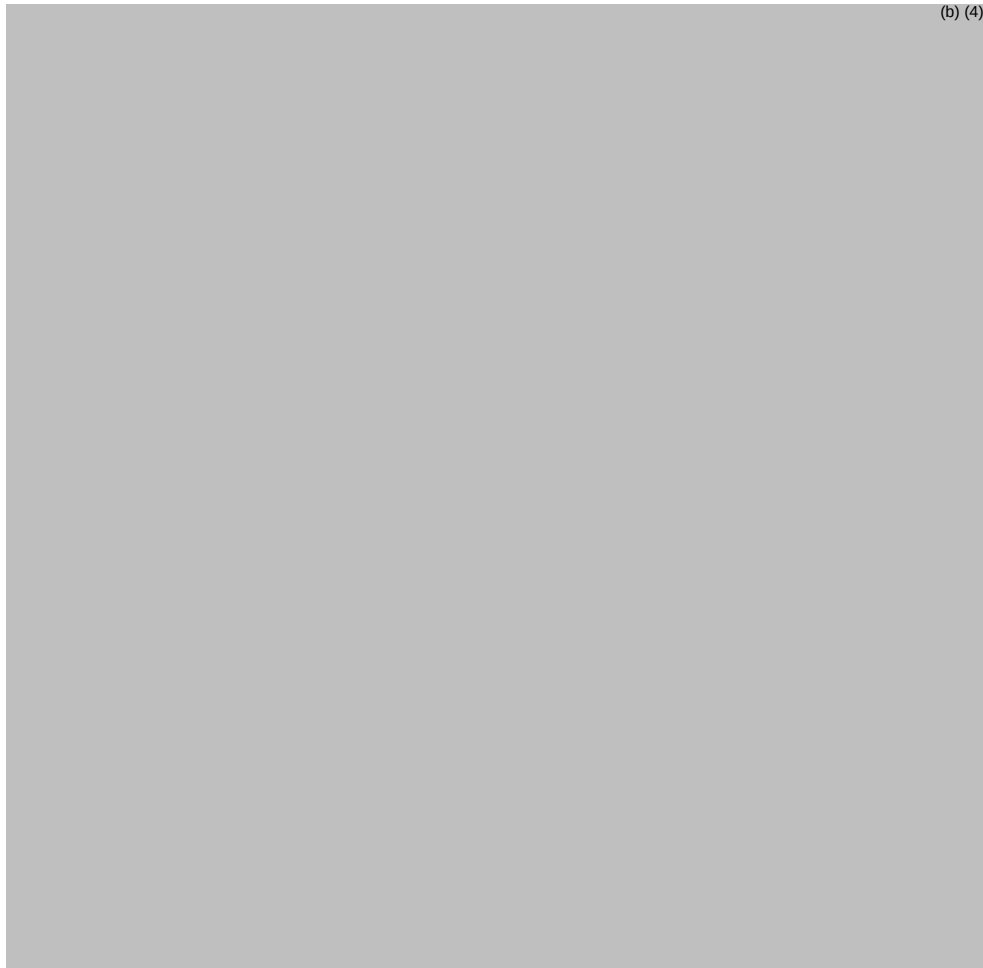
The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA 209511.

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 x 5 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 with a (b) (4) lid. The blister is considered primary packaging. This plastic frame containing the 3 individual blisters will be placed into a pouch (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 (b) (4) (b) (4) carton (170 x 25 x 287 mm).



REGULATORY HISTORY

The following facility was identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. Syntacoll GmbH
Donaustrasse 24, Auf dem Gries 75
Saal/Donau, Bavaria
Germany 93342
Evionnaz, Saint-Maurice, Switzerland 1902
FEI: 3005433617

Responsibility – API testing and release, drug product (DP) manufacturing, release testing, packaging, labeling, and stability testing

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that it has never been inspected.

Inspection Recommendation:

An inspection is required because:

- The firm is responsible for major activities related to the manufacturing and development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm has not been performed.

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

(b) (4)

Documentation Review Recommendation

This application was deficient overall. Additional information is required for an adequate documentation review.

Deficiencies to be conveyed to the applicant

The following deficiencies have been identified while conducting the documentation review of application NDA 209511 for XARACOLL® (bupivacaine HCL collagen-matrix implants) 300mg in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

RECOMMENDATION

The approvability of application NDA 209511 for XARACOLL® (bupivacaine HCL collagen-matrix implants) 300mg should be delayed for the following reasons:

- (1) Deficiencies were identified during the documentation review. Additional information from the firm is needed to complete the documentation review.
- (2) A pre-approval inspection is recommended for the following facility:

Syntacoll GmbH
Donaustrasse 24, Auf dem Gries 75
Saal/Donau, Bavaria
Germany 93342
Evionnaz, Saint-Maurice, Switzerland 1902
FEI: 3005433617

Arabella Pelina -S
2016.12.14 06:40:08 -05'00'

Bella Pelina

Prepared: APelina: 12/14/16
Reviewed: RKang 12/19/16

CTS: ICC1600813
NDA 209511

INSPECTIONAL GUIDANCE

Firm to be inspected:

Syntacoll GmbH
Donaustrasse 24, Auf dem Gries 75
Saal/Donau, Bavaria
Germany 93342
Evionnaz, Saint-Maurice, Switzerland 1902
FEI: 3005433617

CDRH recommends a limited inspection of the firm listed above focusing on (b) (4)
(b) (4)
(b) (4) for NDA
209511 - XARACOLL® (bupivacaine HCL collagen-matrix implants) 300mg.

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Bella Pelina
Consumer Safety Officer
Physical Medicine, Orthopedic, Neurology, and Dental Devices Branch
Division of Manufacturing and Quality
Office of Compliance, WO66 Rm 3453
Phone: 240-402-6010

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Robert Kang
Acting Branch Chief
Physical Medicine, Orthopedic, Neurology, and Dental Devices Branch
Division of Manufacturing and Quality
Office of Compliance, WO66 Rm 3438
Phone: 301-796-6614

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

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

/s/

AYANNA S AUGUSTUS
12/21/2016