CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209511Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 209511

MEETING MINUTES

Innocoll Pharmaceuticals
c/o The Weinberg Group
3803 West Chester Pike
Newtown Square, PA 19073

Attention: Laura Grablutz
Head of Regulatory Affairs

Dear Ms. Grablutz:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bupivacaine hydrochloride collagen-matrix implants, 100 mg per implant.

We also refer to the teleconference between representatives of your firm and the FDA on May 28, 2019. The purpose of the meeting was to discuss the complete response letter issued on November 30, 2018.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: Post-Action meeting
Meeting Date and Time: May 28, 2019, 12:00 p.m. (Eastern time)
Call-in Number: tbd
Application Number: 209511
Product Name: Xaracoll (bupivacaine collagen-matrix implant)
Indication: For placement into the surgical site in adults to produce postsurgical local analgesia following open inguinal hernia repair
Sponsor Name: Innocoll Inc.

FDA ATTENDEES

Sharon Hertz, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, MD	Deputy Director, DAAAP
Martha Van Clief, MD	Acting Team Leader, DAAAP
Renee Petit-Scott, MD	Clinical Reviewer, DAAAP
Julia Pinto, PhD	Branch Chief, Office of Pharmaceutical Quality (OPQ), DNDP II
Jay Chang, PhD	Pharmacology/Toxicology Team Leader, DAAAP
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Gary Bond, PhD	Pharmacology/Toxicology Reviewer, DAAAP
David Lee, PhD	Clinical Pharmacology Reviewer
Yun Xu, PhD	Team Leader, Clinical Pharmacology
Cameron Johnson, PharmD	Safety Evaluator, OSE
Innocoll	**Title**
Gwendolyn Niebler, DO	Chief Medical Officer
Richard Fante	Chief Executive Officer
Laura Grablutz	Head of Regulatory Affairs
Consultants	**Affiliation**
(b) (4)	

1.0 BACKGROUND

(i) The purpose of this meeting is to clarify/resolve issues identified by the Agency detailed in the complete response letter dated November 30, 2018.

(ii) As described by the Sponsor, "XARACOLL is a single-application drug-device combination product designed to deliver bupivacaine over an extended period of time" after open inguinal hernia repair. It is placed (b) (4) at the surgical site.

(iii) The Sponsor is relying on the Agency's previous findings of safety and effectiveness for Marcaine 0.25% (NDA 016964).

FDA sent Preliminary Comments on May 23, 2019.

2. DISCUSSION

Question 1

(a) Does the Agency agree that the clinical data in aggregate (ie, pharmacokinetic analyses that create a bridge from XARACOLL to Marcaine [the listed drug for XARACOLL NDA], nonclinical and clinical literature, and the XARACOLL risk assessment made on the basis of the extensive clinical safety database from the clinical development program) are adequate to address nonclinical deficiency 1 in the CRL and that additional nonclinical studies are not required?

While Innocoll strongly believes that the bridge between XARACOLL and Marcaine created through the data package submitted in this document supports the safety of the bupivacaine exposure with XARACOLL, in the event that the Agency believes that this bridge is not adequate in and of itself to address the deficiency, Innocoll would like to gain an understanding of the Agency's expectations for completion of the nonclinical requirement for the resubmission of the XARACOLL NDA. Questions in this regard are as follows:

(b) Given the results of previous rodent toxicology studies with XARACOLL and challenges related to achieving the desired bupivacaine exposure because of limitations on the number of XARACOLL implants that can be placed in a small animal species, would it be acceptable to the Agency to conduct only 1 toxicology study in a nonrodent species to address this deficiency?

(c) Does the Agency agree that the dog, representing a nonrodent species, would be an acceptable animal model?

(d) Does the Agency agree that achieving an AUC value in an animal species that is at least equal to the value seen in humans would be an acceptable approach in a toxicology study undertaken to address the deficiency?

(e) Can the Agency clarify whether the expectation is to conduct the additional toxicology work using XARACOLL or is using the drug substance bupivacaine HCl also an option.

FDA Response:

(a) In response to Nonclinical Deficiency 1 outlined in the Complete Response Letter, dated November 30, 2018, you have provided additional pharmacokinetic (PK) information to justify the systemic safety of bupivacaine exposure via your drug product formulation. Specifically, you have conducted additional PK analyses using nonparametric superposition methods to establish a scientific bridge between Xaracoll 300 mg and Marcaine 400 mg, the maximum recommended daily dose (Marcaine product label, 2018). It appears you evaluated different dosing regimens for Marcaine 400 mg using these methods, including a single infiltration. We have the following comments regarding your proposal:

- **You may use this pharmacokinetic modeling approach to create a bridge from Xaracoll to Marcaine; however, the acceptability of this approach will be determined during the NDA review cycle. You also need to provide rationale to justify why you choose this approach instead of conducting a PK study.**

- **The nonparametric superposition methods you propose appear reasonable to predict the systemic exposure of Marcaine; however, the acceptability of the resulting prediction(s) will be determined during the NDA review cycle.**

- **You propose several different dosing regimens for Marcaine 400 mg to predict its systemic exposure, including:**

  - **A single 400 mg dose**

  - **Three 133.3 mg doses administered every three hours**

  - **An initial 225 mg dose of bupivacaine HCl (with epinephrine) followed by two 87.5 mg doses administered every three hours**

  - **An initial 175 mg dose of bupivacaine HCl (without epinephrine) followed by two 112.5 mg doses administered every three hours**

You have not, however, provided adequate justification that these proposed dosing regimens are clinically relevant, and we have the following comments:

- **A single infiltration of Marcaine 400 mg is not routinely administered for the management of postsurgical pain. Intraoperatively, there is generally adherence to the recommended milligram per kilogram (mg/kg) dose of bupivacaine (i.e., 2.5 mg/kg), such that 400 mg would not be administered in most surgical situations.**

- **Repeat postsurgical local anesthetic wound infiltrations (e.g., every three hours), after the initial surgical procedure, are not routine clinical practice, unless there is a subsequent or repeat surgical procedure.**

- **Regional anesthetic techniques are widely used in the management of postsurgical pain and local anesthetic administration in this setting generally does not exceed the maximum recommended mg/kg dose. Because there is no need for infiltration of high doses of immediate-release local anesthetics into surgical wounds, your proposed dosing regimens are not clinically relevant.**

- **If you intend to rely on published literature, you need to provide adequate justification that the results from literature can be used to support your product, considering the potential difference in patient population, drug formulation, route of administration, dosing regimen, etc. To rely on PK data in the published literature, provide information on whether appropriate bioanalytical information such as precision, accuracy, stability, and incurred- sample-reanalysis is available for the bioanalytical methods used for quantifying the drug concentration in those articles. Also, refer to our 505(b)(2) comments regarding the 'right of reference' for literature articles. If you plan to use data from a product other than Marcaine (e.g., (b) (4) mentioned in your meeting package), that product also need to be included as a listed drug for your 505(b)(2) application.**

- **The safety database from your Phase 3 clinical development program and the additional PK analyses you have conducted may support the narrow labeling indication you propose; i.e., postsurgical local analgesia following open inguinal hernia repair. Refer to our response to Question 2.**

(b) In the event that the clinical data that you intend to submit to support the systemic safety of bupivacaine for the intended clinical use is determined to

be inadequate to address Deficiency 1 per the Complete Response Letter dated 11/30/2018, toxicology studies in two species that provide adequate coverage for the proposed human exposures via your drug product (AUC and C_{max}) will be required as outlined in the letter. Note that the drug product does not necessarily have to be tested in these nonclinical studies if there are challenges related to achieving adequate exposures due to the limited number of Xaracoll implants that can be placed in the animals. The focus of these studies is to qualify the systemic safety of bupivacaine for the intended clinical use; therefore, bupivacaine alone may be tested provided that the studies provide coverage for both AUC and C_{max} associated with the clinical use at the maximum recommended human dose (MRHD). Additionally, studies in two appropriately justified non-rodent species may be acceptable if adequate exposures cannot be achieved in rodent species.
We note that you have cited nonclinical literature in your briefing package to support your proposal to conduct a new toxicology study in only one species. Note that if a product is identified by proprietary name and the information in the literature article is required for approval, including for the labeling, then that product must be included in the list of products relied upon for approval and the required patent notification and certification procedures followed. In addition, published literature to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. A final determination of whether submitted literature may adequately support the safety of your product will be a matter of review.

(c) Yes, the dog appears to be an acceptable nonrodent animal model provided that adequate bupivacaine exposures (AUC and C_{max}) can be achieved to provide coverage for the intended clinical use. We note you have proposed to conduct an extended single-dose toxicology study with an acute sacrifice of 3 dogs/sex/group at about 72 hours post dose and a delayed sacrifice of 2 dogs/sex/group at approximately 2-weeks post dose. While an extended single-dose study may be acceptable to support a single-dose clinical study during drug development, repeat-dose toxicology studies of up to one month are recommended to support marketing of a product with a proposed duration of treatment of up to 2 weeks per the ICH guidance for industry: *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*, available at: https://www.fda.gov/media/71542/download. However, studies with duration of at least 14 days may be justified if they adequately characterize the toxicological potential of the drug. We also recommend that toxicology studies include at least 10 animals/sex/group/time point for rodents and 4-6 animals/sex/group/time point for nonrodents.

(d) No. A toxicology study should characterize the toxicological potential of a drug and define a NOAEL that provides reasonable exposure margins to

support the clinical use of the drug. We note that safety margins based on both AUC and C_{max} in humans at the MRHD should be characterized by nonclinical toxicity studies in two species.

(e) Using the drug substance bupivacaine HCl is an option to achieve adequate exposure levels when not possible with the drug product as noted in our response to Question 1b.

Discussion: The Division advised the Sponsor that it is important to understand the overall systemic exposure to bupivacaine after administration of Xaracoll. Based on the release profile of the product, the goal is to define the safety profile based on the AUC. Conducting toxicology studies in two non-rodent species is an option, if achieving adequate exposure levels in rodents poses significant challenges. The toxicology studies may be conducted with drug substance, bupivacaine, instead of the Xaracoll drug product. A study design with repeat dosing attaining a safety margin above a clinically relevant AUC and a controlled C_{max} may also be considered. However, the Division clarified that the goal of the studies should be to characterize the toxicological potential of bupivacaine and, therefore, doses must be selected to identify a NOAEL, characterize the toxicity profile (e.g., local and systemic target organ toxicity) or employ the maximum feasible dose, and provide adequate safety margins for the maximum recommended human dose based on pharmacokinetic/toxicokinetic (PK/TK – AUC, C_{max}) comparisons. The adequacy of the safety margins will be dependent on the types and severity of adverse effects observed, if any. Various dosing regimens with potential multiple drug substance exposures per week in order to obtain a target AUC in a repeat dose study may be justified. However, the Division noted that if an immediate-release bupivacaine product is used, consecutive day dosing with several doses per day would likely be needed. Also, the Division did note that toxicology studies of at least 14-days duration may be justified instead of a 28-day repeat-dose toxicology study if the toxicological potential of the bupivacaine is demonstrated is these studies. The Division offered to provide feedback on draft protocols for these toxicology studies but noted that the timeline for a response would be dependent on workload.

Question 2
Can the Agency please provide any preliminary comments on the revised proposed indication?

FDA Response:
The efficacy and safety results from your Phase 3 studies conducted in patients undergoing open unilateral inguinal hernia repair with mesh appear to support the revised proposed indication; however, the final determination of the acceptability of the proposed language will be made during the NDA review cycle.

Discussion: There was no further discussion on this question.

Questions 3

(a) Is the content of safety update report, as described, acceptable to the Agency?
(b) Does the Agency agree with not integrating the data from ongoing Study INN-CB-020 in pediatric patients with the previously submitted data in adults?
(c) Are the data displays (summary tables and listings) proposed for Study INN-CB-020 in the safety update report acceptable?
(d) If the Agency does not agree with the proposed content of the safety update report including data displays and no further data integration, can the Agency please provide specific recommendations?

FDA Response:

(a) It appears that you plan to include all the necessary requirements of the safety update report as described in 21 CFR 314.50(d)(5)(vi)(b). We remind you that the safety update report must include case report forms for any patients who died or withdrew from a study. Although summaries of the nonclinical studies and literature may be included in the safety update, actual study reports for new nonclinical studies must be included in Module 4 of the submission. Refer to our responses to Questions 3b, 3c, and 3d for additional information regarding the acceptability of your proposal to submit the pediatric safety information separate from the previously submitted adult data.

(b) You have indicated that because new clinical safety data are anticipated to come from a low number of treated pediatric patients in Study INN-CB-020 (i.e., approximately 15 patients), you propose to not integrate this data with the previously submitted adult data in the ISS dataset. This may be acceptable; however, we have the following comments:

- **If the number of anticipated treated pediatric patients is higher than you have indicated, or the study is completed, and the overall safety profile of your drug product may be impacted, it is likely that integration and tabulation of the new safety data with that from the original application will be required. Furthermore, analysis and comparison of the pediatric and adult safety data, including the incidence and severity of adverse events, will be required if a large number of pediatric patients have been treated.**

- **You have provided the following additional justification for your proposal to not integrate new pediatric safety data with that from the original application:**
  "…these patients are outside the planned requested age for the indication (ie, adults), Innocoll proposes that the pediatric data not be integrated with the adult data previously submitted in the NDA in the Integrated Summary of Safety dataset"
  We remind you that any new information to assess the overall safety of administering your drug product in the patient populations you have

studied and are currently studying, regardless of the proposed indicated patient population, must be submitted.

(c) Your proposed data displays, the summary tables and listings, appear acceptable, however, we have the following comments:

- **The safety data from Study INN-CB-020 must be submitted in the same format as in the original NDA submission, including adverse event information for the required demographic groups, severity, and relationship to study drug treatment.**
- **Adverse events of special interest, including those associated with local anesthetic systemic toxicity and impaired or delayed wound healing, must be included in your safety update report.**

(d) Your proposed content and format of the safety update report appears acceptable. Nonclinical data should be included in Module 4 with summaries in Module 2.4.
For additional information, refer to our responses to Questions 3a, 3b, and 3c.

Discussion: The Division stated that the approach for establishing the PK bridge outlined in the briefing package does not include bupivacaine dosing regimens that are clinically relevant. The Sponsor stated it is not clear how they can obtain the necessary bridging information if a single dose administration is limited to 2.5 mg/kg. The Division requested the Sponsor submit additional PK information regarding 2.5 mg/kg dosing compared to a single or divided 400 mg dose. Estimated bupivacaine exposure obtained from modeling/simulation using previously stated nonparametric superposition (NPS) method may be one option to predict and compare the systemic exposures after recommended mg/kg dosing and other 400 mg dosing scenarios. Additional information submitted by the Sponsor should include how the NPS predictions for mg/kg and 400 mg dosing compare to a single Xaracoll 300 mg dose. The Sponsor asked how success would be defined. The Division stated that the bioequivalence criterion of 90% confidence intervals for the C_{max} and AUC ratios is one of the guidances that the Sponsor can consider.

A post-meeting note will include an evaluation of the additional information submitted and any additional recommendations.

POST-MEETING NOTE:

The Sponsor submitted additional information to support using existing Xaracoll PK data with the predicted bupivacaine data using the NPS method to establish a bridge between Xaracoll and Marcaine. Specifically, individual bupivacaine AUC_{inf} and C_{max} values from patients treated with Xaracoll (300 mg single dose) and Marcaine (175 mg single dose) infiltration in Study INN-CB-022, the pivotal PK study, were plotted versus body weights ranging from 57 to 120.2 kg. The Sponsor stated that the results suggest there were no differences in PK

parameters by body weight. Since there were "no obvious changes in PK parameters by body weight, the Sponsor, therefore, argues that use of the NPS method is supported to establish a bridge between Xaracoll and Marcaine. Looking at the submitted distribution plots of observed bupivacaine AUC_{inf} and C_{max} against body weight, it is noted that there were no apparent differences in bupivacaine C_{max} between Xaracoll and Marcaine. Regarding observed AUC_{inf}, it appears that Marcaine generally showed higher AUC_{inf} than Xaracoll. It appears that it is reasonable to look at the relationship between bupivacaine exposure and body weight using the NPS method.

Furthermore, to establish a bridge using the NPS method between single dose Xaracoll 300 mg (observed values from Study INN-CB-022) and Marcaine 400 mg (predicted values for Marcaine 400 mg single-dose, the highest labeled dose), the Sponsor also submitted plots of bupivacaine AUC_{inf} and C_{max} versus calculated doses as mg/kg. The Sponsor states that there were no "obvious changes in PK parameters on a mg/kg basis, including doses of 2.5 mg/kg or higher." Looking at the submitted distribution plots of bupivacaine AUC_{inf} and C_{max} against calculated doses as mg/kg, it is noted that there were no apparent differences in observed bupivacaine AUC_{inf} from Xaracoll and predicted bupivacaine AUC_{inf} from Marcaine. However, it appears that observed bupivacaine C_{max} from Xaracoll was somewhat lower (up to approx. 50% lower) than predicted C_{max} from Marcaine.

AUC ratios were evaluated by total reference dose using interpolation of the bupivacaine HCl AUC from the NPS AUC prediction at 400 mg bupivacaine HCl and the assumption of PK parameter linearity. AUC ratio predications were determined across Marcaine's dose range, providing a ratio to the observed AUC for Xaracoll 300 mg (no change in dose). The geometric mean ratio (GMR) and 90% confidence intervals (CIs) for AUC from INN-CB-022 and GMR (90% CIs) for the NPS predicted bupivacaine HCl 400 mg with the 80-125% bioequivalence (BE) bounds are provided. Based on the predicted AUC values (Table 1) from Marcaine 400 mg single dose, the AUC ratio appears to be less than approximately 1 between observed AUC Xaracoll 300 mg single-dose and predicted bupivacaine AUC from Marcaine 400 mg single dose [Note: the observed AUC_{inf} from Xaracoll 300 mg single dose (Study INN-CB-022) was 20,368 ng.h/mL, whereas predicted bupivacaine AUC from Marcaine 400 mg single dose ranges from 22326 to 23940 ng.h/mL (Table 1)].

Based on the provided information, it appears that the PK results from Study INN-CB-022, after administration of Xaracoll 300 mg, demonstrated an AUC similar to that predicted after administration of a single Marcaine 400 mg dose using NPS estimation.

Question 4

In the NDA resubmission, Innocoll intends to update all Module 2 nonclinical summaries, and all clinical summaries with the exception of Module 2.7.3 (Summary of Clinical Efficacy), Module 2.7.4 (Summary of Clinical Safety), and Module 2.7.6 (Synopses of Individual Studies) because there are no new clinical data from completed clinical studies in the proposed population (adults) for the indication; any new safety data will be provided in the safety update report.
Does the Agency agree with this approach?

FDA Response:
Your proposal to not update the Summaries of Clinical Efficacy and Clinical Safety may be acceptable; however, we have the following comments:

- **If Study INN-CB-020 has enrolled and treated the planned 159 patients, the number indicated in your pediatric study status update received December 26, 2018, these summaries will need to be updated with the efficacy and safety information from the completed study.**

- **All safety data obtained from treated pediatric patients in Study INN-CB-020 must be included in the safety update report, as described in our responses to Questions 3a, 3b, 3c, and 3d.**

- **The Clinical Study Report(s) for all completed studies, including completed pediatric studies, must be included in the NDA resubmission.**

Discussion: There was no additional discussion for this question.

Question 5
Innocoll intends to submit a "clean" version of the revised proposed full prescribing information (FPI), along with revised structured product labeling (SPL) in the NDA resubmission.
Does the Agency agree with this plan?

FDA Response:
Your proposal to submit a "clean" version of the revised proposed full prescribing information along with the revised structured product labeling is acceptable.

Discussion: There was no additional discussion for this question.

Question 6
Innocoll has recently decided to supply the product in final packaging cartons of 4 and 10 units, with each unit packaged in an individual carton as previously indicated in the NDA. The 4- and 10-pack cartons are based on the single-unit carton for which the Agency provided comments.

Does the Agency agree that Innocoll can submit the artwork for the 4- and 10-pack cartons and add the associated NDC to the HOW SUPPLIED section of the FPI in the NDA resubmission?

FDA Response:
This approach seems reasonable; however, the acceptability of the proposed labeling will be determined during the NDA review cycle. We recommend that the package code portion (last 1 to 2 digits) of the National Drug Code (NDC) be unique for the pouch, 4-pack carton, and 10-pack carton to allow for easy identification and differentiation of the different layers and types of packaging.

Discussion: There was no additional discussion for this question.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

In addition, your iPSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08 4159.htm

[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09 3307.htm

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

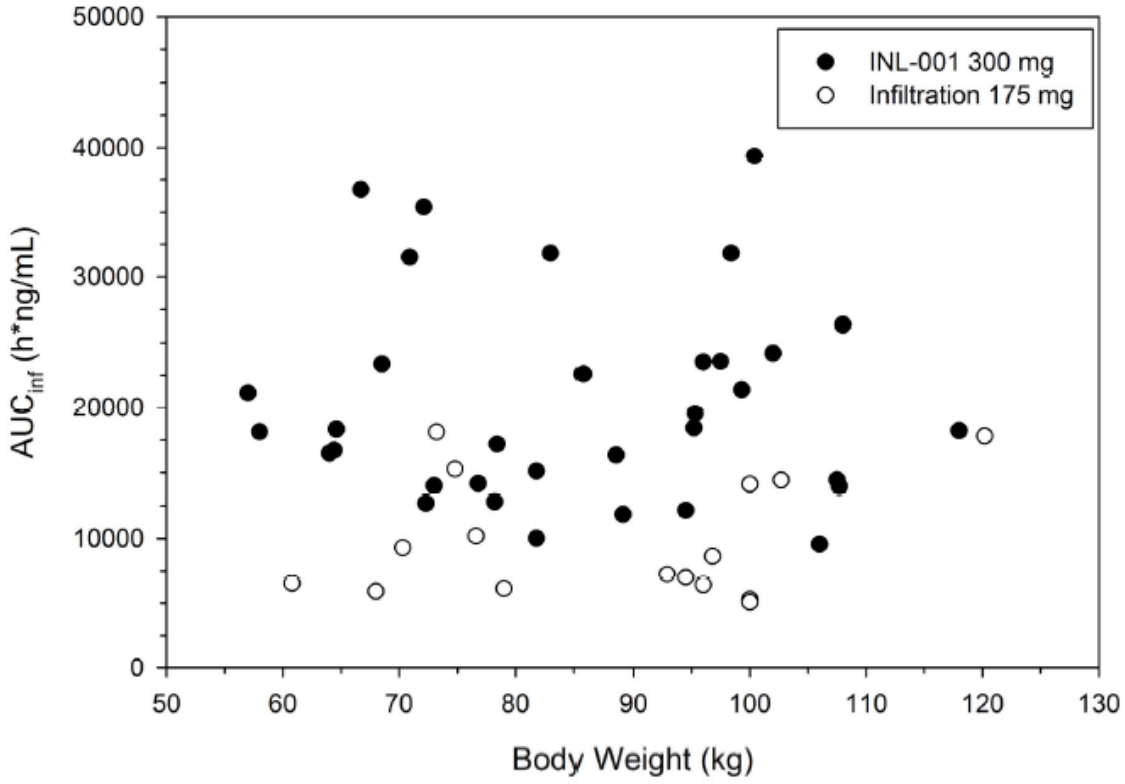
Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

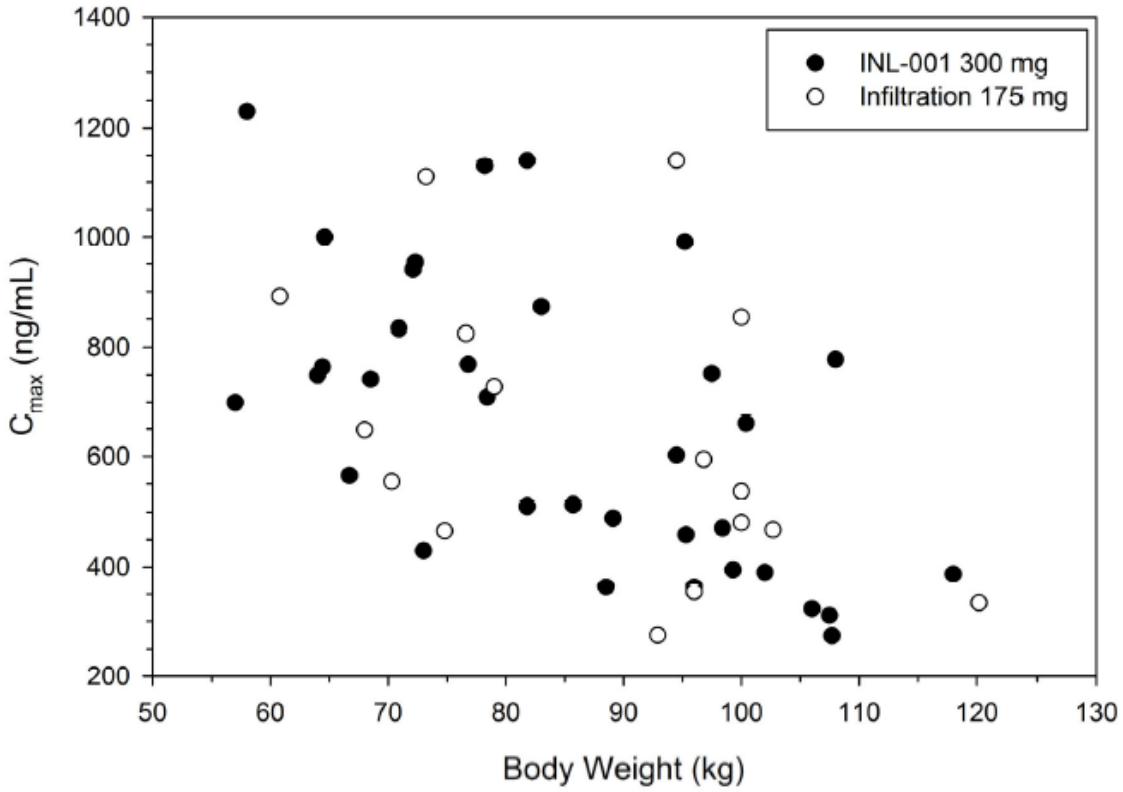
In follow-up to the discussion at the Type A Post-Action Meeting on May 28, 2019, Innocoll is providing information to supplement the data from its Meeting Package to support using XARACOLL (INL-001) clinical pharmacokinetic (PK) data with the nonparametric superposition (NPS) method to establish a bridge between XARACOLL and the listed drug, Marcaine.

Individual bupivacaine area under the curve (AUC) and maximum concentration (C_{max}) values from subjects in the pivotal PK Study (INN-CB-022), who received XARACOLL 300 mg or bupivacaine HCl 175 mg infiltration, were plotted versus body weights (BW) ranging from 57.0-120.2 kg (**Figure 1**). The same graphs are provided for Study INN-CB-013 in Appendix A with BW ranging from 58.5-151.0 kg (**Figure A1**). There were no obvious changes in PK parameters by BW, supporting use of the NPS method to establish a bridge between XARACOLL and Marcaine.

Figure 1. Distribution of bupivacaine AUC and C_{max} by subject body weight for XARACOLL (INL-001) 300 mg and bupivacaine HCl 175 mg
a) Bupivacaine AUC versus body weight



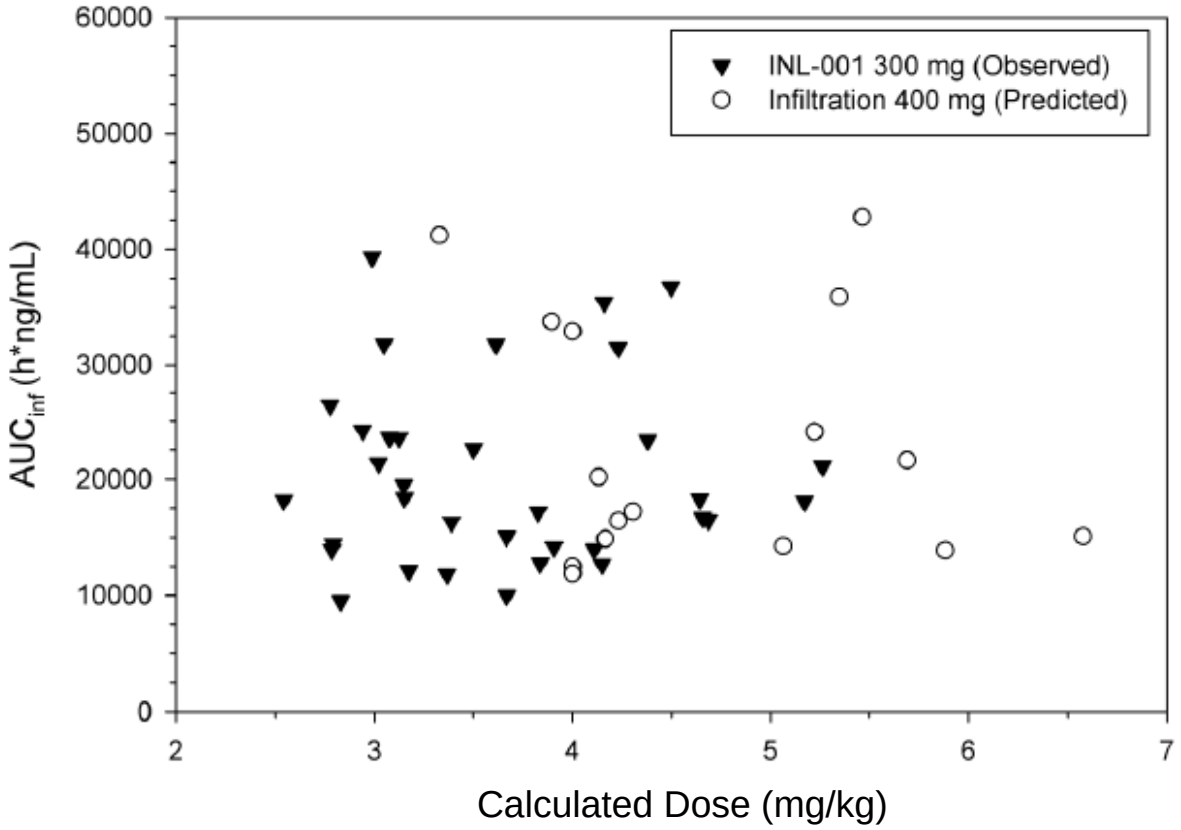
b) Bupivacaine C_{max} versus body weight



Individual bupivacaine AUC and C_{max} observed values for XARACOLL 300 mg and predicted values for Marcaine 400 mg (the highest labeled dose) from the NPS (previously submitted in the Meeting Package) were plotted versus dose converted to miligrams per kilogram (mg/kg) (INN-CB-022) (**Figure 2**). The same graphs are provided for INN-CB-013 in Appendix A (**Figure A2**). PK parameter data are also provided on a mg/kg range basis for INN-CB-022 (**Table 1**). There were no obvious changes in PK parameters on a mg/kg basis, including doses of 2.5 mg/kg or higher.

Figure 2. Observed XARACOLL (INL-001) 300 mg and predicted bupivacaine HCl 400 mg (single dose) AUC and C_{max} by calculated mg/kg dose (INN-CB-022)

a) Bupivacaine AUC versus mg/kg dose



b) Bupivacaine C_{max} versus mg/kg dose

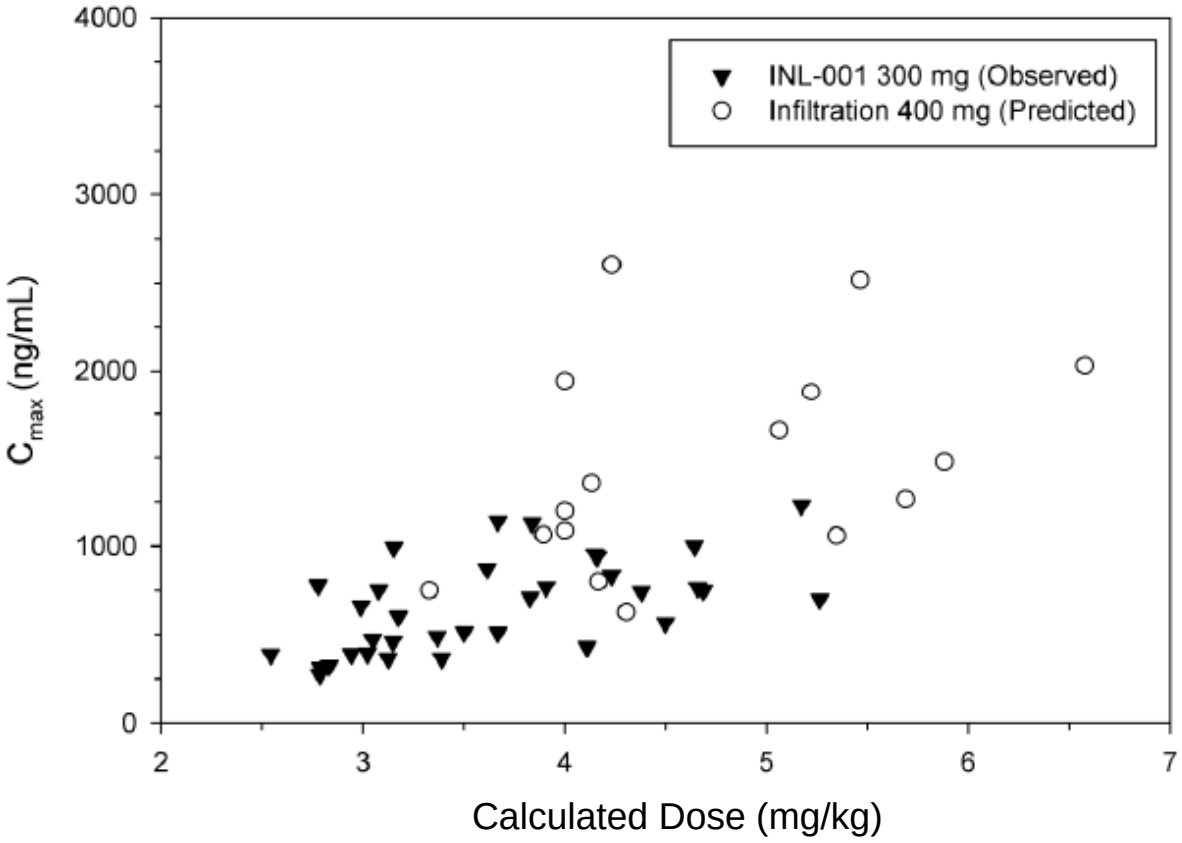
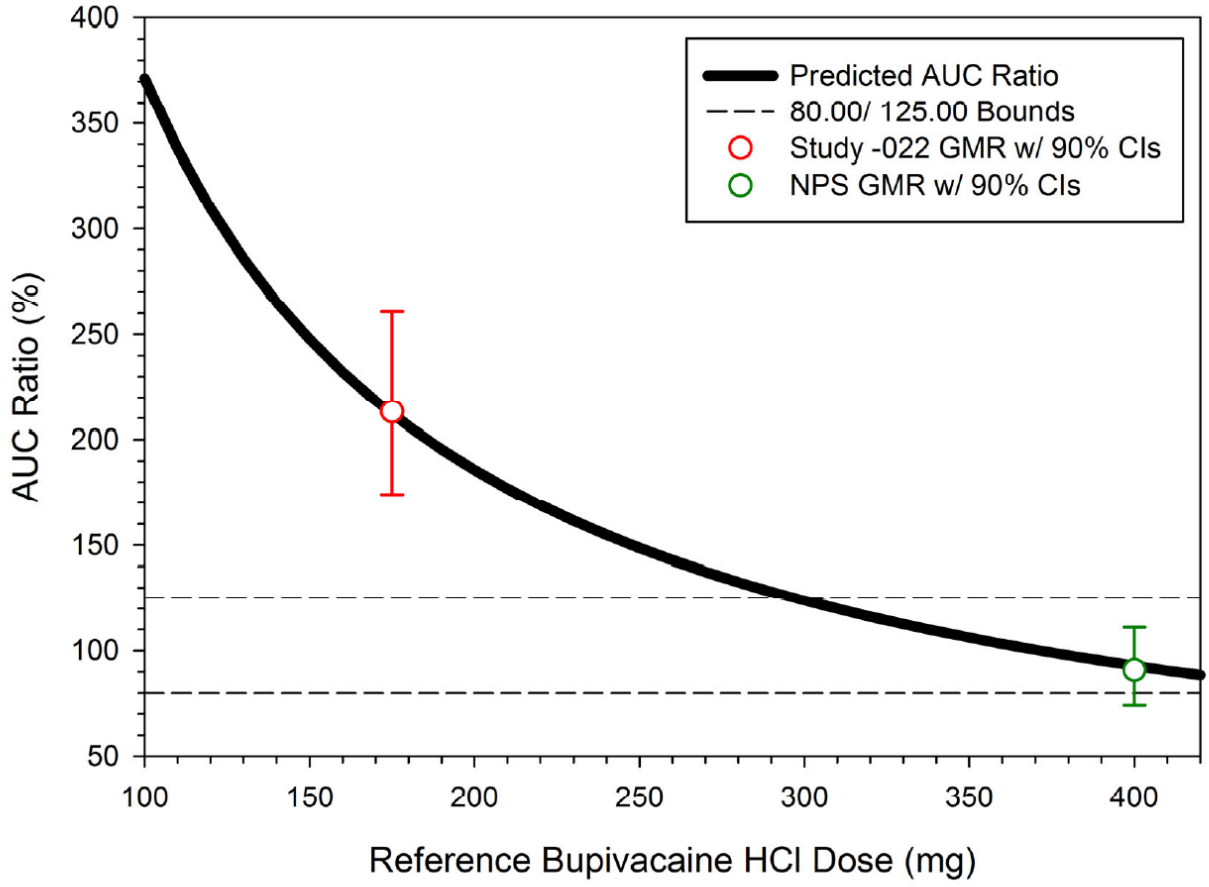


Table 1: Calculated mg/kg dose ranges - AUC and C_{max} for XARACOLL 300 mg (observed) and bupivacaine HCl 400 mg (predicted; single dose) (INN-CB-022)

	XARACOLL 300 mg				Bupivacaine HCl 400 mg	
Dose received based on body weight (mg/kg)	**≥2.5 to <3.3**	**≥3.3 to <4.5**	**≥4.5**		**≥3.3 to <4.5**	**≥4.5**
Weight Range (kg)	94.5-118.0	68.5-89.1	57.0-66.7		92.9-120.2	60.8-79.0
AUC						
n	14	14	6		9	7
Mean	21168	19194	21243		22326	23940
Standard Deviation	7963	8350	7775		10761	11373
CV%	37.6	43.5	36.6		48.2	47.5
Minimum	9547	10009	16466		11894	13881
Maximum	39335	35402	36745		41208	42760
Cmax						
n	14	14	6		9	7
Mean	511	742	835		1270	1698
Standard Deviation	213	253	240		635	494
CV%	41.7	34.1	28.7		50.0	29.1
Minimum	274	363	565		626	1058
Maximum	991	1140	1230		2603	2517

Lastly, AUC ratios were evaluated by total reference dose (**Figure 3**), with: a) interpolation of the bupivacaine HCl AUC from the NPS AUC prediction at 400 mg bupivacaine HCl and b) assumption of PK parameter linearity. AUC ratio predications were determined across Marcaine's dose range, providing a ratio to the observed AUC for XARACOLL 300 mg (no change in dose). The geometric mean ratio (GMR) and 90% confidence intervals (CIs) for AUC from INN-CB-022 and GMR (90% CIs) for the NPS predicted bupivacaine HCl 400 mg with the 80-125% bioequivalence (BE) bounds are provided.

Figure 3. Predicted AUC Ratio (XARACOLL/Bupivacaine HCl) as a function of a fixed bupivacaine HCl dose (INN-CB-022)

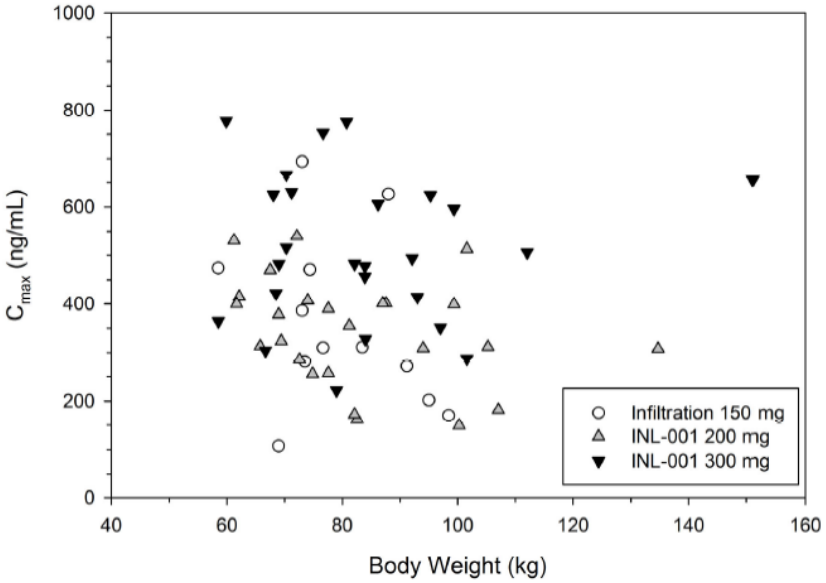


Note: AUC Ratio (%) = AUC ratio of Test/Reference, where Test = XARACOLL 300 mg and Reference is a dose range of 100 to 420 mg bupivacaine HCl.

Appendix A

Figure A1. Distribution of bupivacaine AUC and C_{max} for XARACOLL (INL-001) 200 mg and 300 mg and bupivacaine HCl 150 mg by subject body weight (INN-CB-013)

a) Bupivacaine AUC versus body weight



b) Bupivacaine C_{max} versus body weight

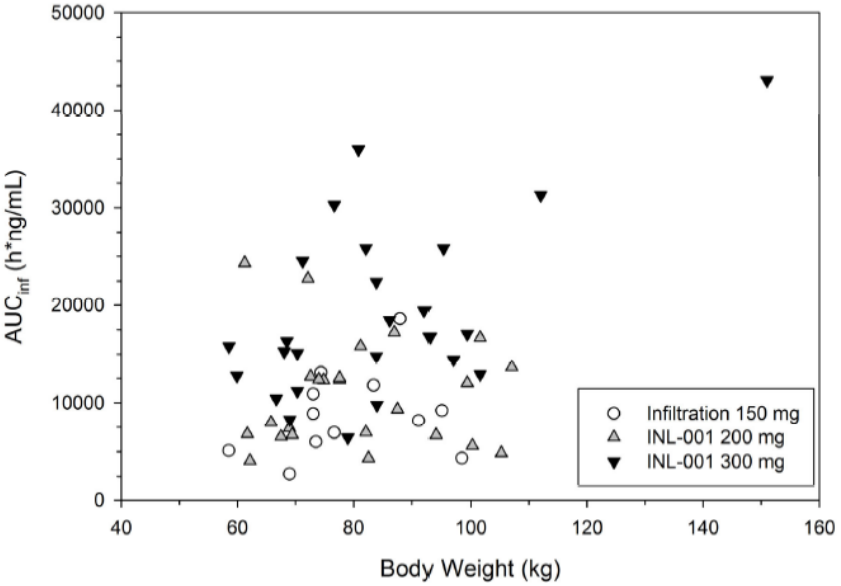
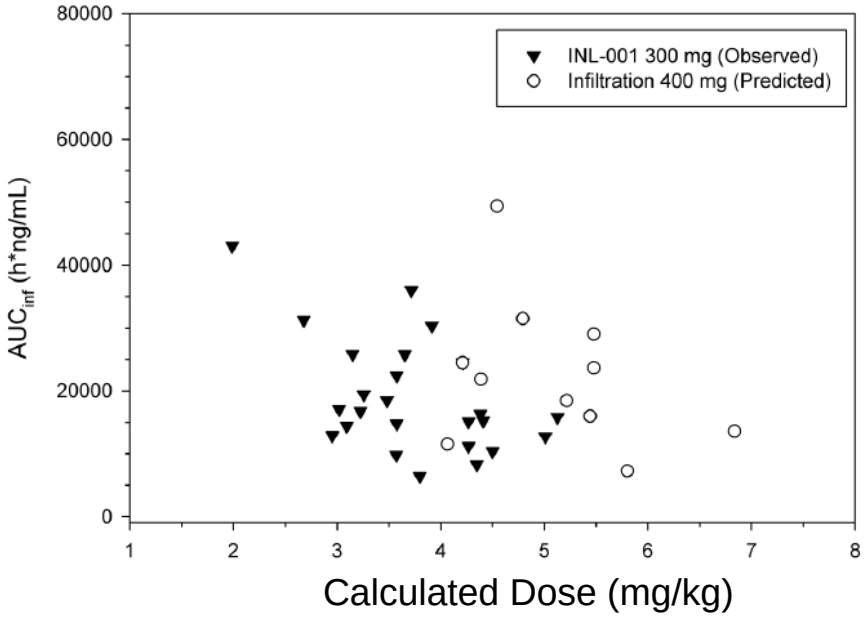
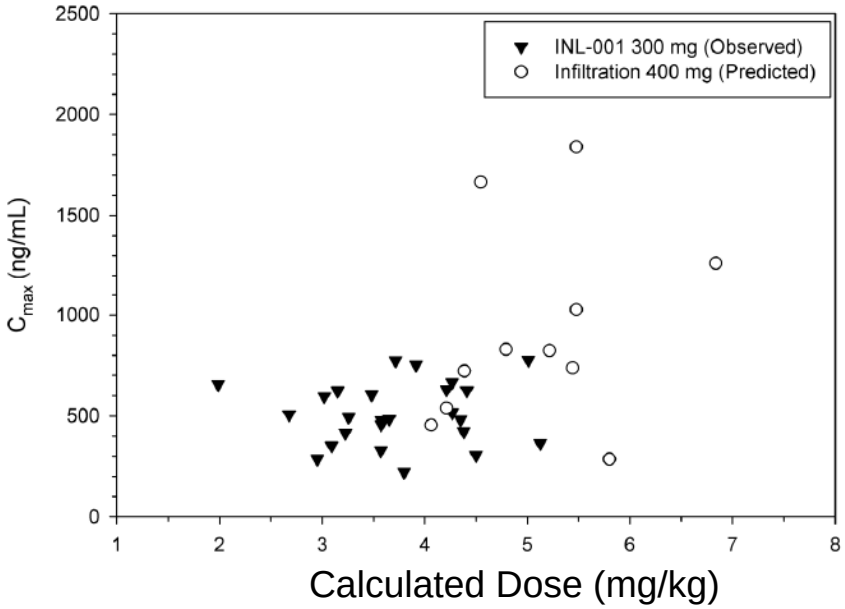


Figure A2. Observed XARACOLL 300 mg and predicted bupivacaine HCl 400 mg infiltration (single dose) AUC and C_{max} by mg/kg dose (INN-CB-013)

a) Bupivacaine AUC versus mg/kg dose



b) Bupivacaine C_{max} versus mg/kg bupivacaine dose



5.0 ACTION ITEMS

1. The Sponsor will submit additional information to support using existing Xaracoll PK data with predicted bupivacaine data using the NPS method. The additional

information should include information based on bupivacaine 2.5 mg/kg dosing, as well as alternate dosing regimens, including single and divided dosing.

2. The Sponsor will submit toxicology protocols for review.

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

/s/

ALLISON MEYER
06/28/2019 10:06:45 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209511

MEETING MINUTES

Innocoll Inc.
c/o Innocoll Pharmaceuticals
3830 West Chester Pike
Newtown Square, PA 19073

Attention: Carol S. Marchione
Vice President, Regulatory Affairs

Please refer to your New Drug Application (NDA) submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xaracoll (bupivacaine collagen implant).

We also refer to the meeting between representatives of your firm and the FDA on February 23, 2017. The purpose of the meeting was to discuss the deficiencies listed in the Agency's Refuse-to-File letter dated December 23, 2016.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

Christopher Hilfiger
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: End-of-Review

Meeting Date and Time: February 23, 2017, 3:30 – 4:30 p.m.
Meeting Location: White Oak Campus, Bldg 22, Room 1309

Application Number: 209511
Product Name: Xaracoll (bupivacaine collagen-matrix implant)
Indication: for single-dose placement into the surgical site to produce postsurgical analgesia
Sponsor/Applicant Name: Innocoll Inc.

Meeting Chair: Rigoberto Roca, MD
Meeting Recorder: Christopher Hilfiger

FDA ATTENDEES

Sharon Hertz, MD	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, MD	Deputy Director, DAAAP
Renee Petit-Scott, MD	Clinical Reviewer, DAAAP
Julia Pinto, PhD	Branch Chief, Office of Pharmaceutical Quality (OPQ), DNDP II
Jay Chang, PhD	Pharmacology/Toxicology Team Leader, DAAAP
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Patricia Love, MD	Deputy Director, Office of Combination Products (OCP)
Robert Kang, MD	Regulatory Officer, CDRH
Cherryn Chang, PharmD	Product Jurisdiction Officer, Office of Executive Programs, CDER
Kristina Lauritsen, PhD	Product Jurisdiction Officer, Office of Executive Programs, CDER
Lixin Liu, PhD	CDRH
Christopher Hilfiger	Sr. Regulatory Project Manager, DAAAP
Parinda Jani	Chief, Project Management Staff, DAAAP
Selma Kraft	Regulatory Project Manager, DAAAP
Maryam Mokhtarzadeh, MD	Senior Medical Officer, OCP
Alla Bazini, MD	Medical Officer, DAAAP

SPONSOR ATTENDEES

Representatives from Innocoll Inc.
Brian Boyd, Vice-President, Quality Assurance
Sue Hobson, Executive Director, Clinical and Regulatory Writing
Charles Katzer, Executive Vice-President, Global Technical Operations
Carol S. Marchione, Vice-President, Regulatory Affairs
Lesley Russell, MBChB, MRCP, Chief Medical Officer
Anthony Zook, CEO

Innocoll Consultants
(b) (4)

BACKGROUND

(i) The purpose of this meeting is to clarify/resolve issues identified by Agency detailed in the RTF letter dated December 23, 2016, and to understand the path forward so that the resubmission of the XARACOLL NDA will result in a positive action.
(ii) XARACOLL is a bupivacaine HCl collagen-matrix implant, a single-use product administered during surgery through placement within multiple layers at the surgical site.
(iii) The Referenced drugs are NDA (b) (4) and NDA (b) (4) /Marcaine, which is an injection.
(iv) Innocoll submitted NDA 209511 for Xaracoll on October 31, 2016. The Agency sent a Refuse to File letter on December 23, 2016. Innocoll submitted a Type A meeting request on January 18, 2017.

DISCUSSION

Regulatory

Question 1:

Many of the issues identified in the RTF letter are a result of the Agency's identification of XARACOLL now being designated a combination product which now elevates collagen from a "non-novel" excipient to a device. The timing of this communication directly contributed to the Agency's refusal to file the NDA. Therefore, Innocoll requests:

a) When did the Division seek guidance from CDRH that XARACOLL is a combination product and when was this officially determined?

b) Has there been a policy change during development that was not relayed?

c) If so, why wasn't the sponsor notified earlier than post-NDA submission?

FDA Response to Question 1:

Product classification is not determined by CDRH. However, because of your question, we contacted the center product jurisdiction officers for CDRH and CDER, as well as the Office of Combination Products. The classification of the bupivacaine-collagen sponge as a combination product is consistent with the classification of other implants for drug delivery as combination products. Such products are also described in the 2005 final rule "Definition of Primary Mode of Action of a Combination Product" accessible athttps://www.gpo.gov/fdsys/pkg/FR-2005-08-25/pdf/05-16527.pdf. (See Section III, example b., Drug Eluting Disc.)

Regarding Xaracoll, as noted in your briefing document, CDRH was consulted as early as 2007. While we acknowledge that the meeting minutes did not expressly identify state that Xaracoll is a combination product, it is considered as such. Should Innocoll disagree with this assessment, you may contact the Office of Combination Products at combination@fda.gov. Also, we refer you to the guidance on How to Prepare a Pre-Request for Designation (Pre-RFD) accessible at http://www.fda.gov/RegulatoryInformation/Guidances/ucm534661.htm

Discussion:

There was no discussion of this question.

Chemistry, Manufacturing, and Controls (CMC)

Question 2:

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

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

Sponsor Response: In the meeting package, Innocoll provided a thorough evaluation of the change in the (b) (4) *of the collagen used in lots of drug product introduced during development. Comparative dissolution and* (b) (4) *data were provided indicating no differences in these parameters between the lots of drug product when the collagen was* (b) (4) *Based on these data Innocoll believes that there has been no significant change to the final drug product between the lot used in the pivotal PK study and the lot used in the phase 3 efficacy and safety studies. Upon review of the information provided does the Agency agree that no additional pharmacokinetic (PK) or toxicology studies are required in the resubmission of the NDA? (please see the entire Sponsor Response in meeting package)*

FDA Response to Question 2

Before we can agree to the following claims you will need to submit additional information/data:

1. **The claim that the implemented changes can be considered minor is based on the assumption that in vitro release is the most critical quality attribute and that your proposed in vitro release test is adequate (e.g., discriminating). In addition, your assertion relies on data provided showing:**

   a) **No differences in the in vitro release profiles between the batches tested in the pivotal PK Study INN-CB-013 and pivotal Phase 3 clinical trial (INN-CB-014).**

   b) **Differences in the in vitro release profiles between new collagen and old collagen batches.**

The additional data needed to support the claims above are as follows:

i) **A list of all the critical material attributes (CMAs) and process parameters (CPPs) for your proposed drug product determined based on your drug product quality risk assessment and/or any DOE studies conducted.**

ii) **Data showing that the in vitro release specifications (method and acceptance criteria) are discriminating toward meaningful changes in the identified CMAs and CPPs. Note that based on your proposed in vitro release acceptance criteria, both batches (i.e., old and new (b) (4) batches) shown in Figure 5 of your submission dated Jan 17, 2017 would be acceptable, as they meet these criteria. This indicates that the specifications are under discriminating.**

   (1) **In general, the testing conducted to demonstrate the discriminating ability of the selected in vitro release method should compare the profiles of the reference drug product (pivotal Phase 3 batch) and the test products that are intentionally manufactured with meaningful variations for the most critical manufacturing variables (i.e., ± (b) (4)% change to the specification ranges of these variables (e.g., (b) (4)).**

- **We remind you that the proposed *in vitro* release acceptance criteria with "no less than **% released" at all time points are not appropriate for MR products. Based on current practice, the acceptance criteria of the in vitro release test are set at multiple time points based on the mean value (i.e., mean value and ± (b) (4)% of labeled drug content and NLT (b) (4)% for the last specification time-point, unless there are clinical BA/BE and/or IVIVC data supporting wider ranges) of n=12 units from batches tested in pivotal clinical Phase 3 studies.**

iii) Data showing that the in vitro release specifications (method and acceptance criteria) are capable of discriminating batches manufactured outside the ranges implemented for the pivotal Phase 3 clinical batches.

We may need additional data (e.g., in vivo data) once we have reviewed all the data in its totality.

Discussion:

The Sponsor stated that they will repeat the BA/BE study. The Sponsor will also conduct a new 56-day GLP toxicology study with the final commercial (to-be–marketed) product.

Nonclinical

Question 3:

RTF issue: There are inadequate nonclinical data in the NDA to adequately qualify the safety of the to-be-marketed drug product. We note that the pivotal nonclinical 56-day bupivacaine collagen implant study (e.g., (b) (4) 134502) did not test the to-be-marketed (b) (4) containing drug product, but rather an earlier development product. To address this issue, you must repeat your pivotal toxicology study testing with the to-be-marketed drug product, or provide justification for how the findings of the conducted study can be extrapolated to support the safety of the to-be-marketed product with respect to the endpoints tested (e.g., bupivacaine release, local toxicity, duration and fate of the inserted sponge).

Sponsor Response: Please see response to Issue #1. Does the Agency concur that the response to #1 addresses the issue of the collagen (b) (4) and that the nonclinical data from (b) (4)-134502 are valid and therefore adequate to meet the requirements of the NDA? (please see the entire Sponsor Response in meeting package)

FDA Response to Question 3

As noted in our RTF comment, you must either repeat the pivotal toxicology study with the to-be-marketed product or provide justification for how findings of the conducted study can be extrapolated to support the safety of the intended product with respect to the endpoints tested. While your responses to Issue 1 (e.g., CMC/Biopharmaceutics) may address the issues regarding bupivacaine release, they do not appear to adequately address our concerns about the fate of the inserted sponge and potential local toxicity. Unless convincing data can be provided that demonstrates that the old and to-be-marketed products are comparable in this regard, an actual toxicity study will be necessary. A final determination of whether any supporting data may preclude the need for a new toxicology study and ultimately support the safety of your product for approval can only be determined after a review of all information submitted.

Discussion:

See the discussion from Question 2.

Clinical Pharmacology

Question 4:

RTF Issue: Multiple formulation modifications [redacted] (b) (4) *were made to the drug product formulation during development. These changes are considered substantial. Therefore, the pharmacokinetic (PK) data obtained with the prior formulation cannot be applied to the commercial formulation. You must conduct an additional PK study similar to Study INN-CB-013 evaluating bupivacaine exposure using the commercial formulation in surgical procedure you plan to include in your product label, i.e., patients undergoing hernia repair. Specify all treatments and provide pertinent information including, lot number, expiration date, NDA or ANDA numbers, etc.*

Sponsor Response: Please see response to #1. Does the Agency concur that the response to #1 addresses the issue of the collagen [redacted] (b) (4) *and that the PK data from INN-CB-013 is valid and therefore adequate to meet the requirements of the NDA? (please see the entire Sponsor Response in meeting package)*

FDA Response to Question 4

See Response to CMC Question 2. The need for additional PK data will be a review issue based on the new data you will be submitting under CMC Question 2.

We have the following comments regarding study INN-CB-013. You have responded that the products used in INN-CB-013 were Sensorcaine (2.5mg/mL) containing epinephrine (1:200,000), which was approved under NDA 018304, and, Marcaine (2.5 mg/mL) containing epinephrine (1:200,000), which was approved under NDA 016964. You also stated that both drugs will be acknowledged as Listed Drugs in the forthcoming resubmission and patent certifications for each will be provided.

In your resubmission, we remind you that you need to provide all necessary information, including revisions to Form FDA 356h in the resubmission, to specify the listed drugs that you are relying upon.

Additionally, since Sensorcaine was utilized in INN-CB-013 as a comparator, you need to re-analyze the study results to compare Xaracoll to both Marcaine and Sensorcaine, as appropriate. Submit all information related to re-analysis, including SAS and WinNonlin program control files, raw outputs from the statistical analyses, etc.

Discussion:

There was no discussion of this question.

Biocompatibility

Question 5:

RTF Issue: The subject product, XARACOLL is a drug/device combination product comprised of bupivacaine and collagen matrix. You did not provide any biocompatibility information regarding the collagen matrix, the device component of XARACOLL. Based on the product description and its intended use provided in current submission, we consider the combination product as an implant in permanent contact with tissue/bone for biocompatibility evaluation purpose. For this evaluation you should provide the following biocompatibility endpoints for a permanent implant final finished combination product: 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.

Sponsor Response: Does the Agency agree that the nonclinical results previously obtained to address cytotoxicity, subchronic toxicity, and implantation along with results from studies to be conducted for sensitization, irritation, acute systemic toxicity and genotoxicity will satisfy the biocompatibility requirements of ISO 10933-1? (please see the entire Sponsor Response in meeting package)

FDA Response to Question 5

In your March 28, 2007, submission, you have stated that "The Bupivacaine Collagen sponge is believed to biodegrade over a period of 3 to 7 days depending on the site of implantation and so falls within the category of prolonged implants (less than 30 days) according to ISO 10993." We do not agree with this conclusion. As the collagen is a protein, the entire product is unlikely to be completely cleared and any residues/leachables in the product may remain in the wound bed or may be absorbed systemically. Therefore, we consider the collagen product has permanent contact for biocompatibility purpose and you need to provide the biocompatibility endpoint evaluations on the final, sterilized combination product as requested. The additional biocompatibility tests recommended for the permanent contact category includes chronic systemic toxicity, genotoxicity, and carcinogenicity. An alternative is to submit a toxicological risk assessment in lieu of the testing to determine if any residuals present in the subject product pose toxicity or carcinogenicity risks, as well as to fully assess if the product is genotoxic. You may provide 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.

Discussion:

The Sponsor stated that they will provide data that will demonstrate the collagen degrades completely between 14 and 28 days, to justify their position that the drug-collagen product would be considered a prolonged device, rather than a permanent device. The Sponsor will

submit these data with their resubmission. Additionally, the Sponsor will provide data with the repeated 56-day GLP toxicology study a long-term (5 year) leachable study and a toxicological risk assessment for carcinogenic potential of the compounds identified.

CDRH stated that they have concerns on the safety of the collagen and the Sponsor must characterize the collagen as well as any residue from the raw products of the collagen.

POST MEETING NOTE:

You propose to conduct the cytotoxicity, sensitization, irritation, acute systemic toxicity, subchronic systemic toxicity, implantation and genotoxicity testing on the final product. However, to mitigate the risk associated with the processing of the materials, the manufacturing methods (b) (4) and any residuals from manufacturing aids used during the process, provide the following biocompatibility endpoint evaluations in addition to the tests you proposed: chronic systemic toxicity, carcinogenicity and material-mediated pyrogenicity. Please be advised, 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.

1. You proposed to conduct a chemical characterization of your 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.

2. You did not propose to conduct the rabbit pyrogenicity test as requested in the RTF letter. 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 your product. Please refer to FDA guidance, “Pyrogen and Endotoxins Testing: Questions and Answers” (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM310098.pdf).

NON-RTF Issues

Clinical

Question 6:

Labeling concerns:
The proposed labeling states the indication for use of this product is postsurgical analgesia. The Phase 3 trials were conducted in one surgical population, open inguinal hernia repair with mesh. The original Phase 2 studies were conducted in patients undergoing abdominal hysterectomy and other abdominal procedures and the results of those studies did not demonstrate efficacy of the XARACOLL matrix. The proposed indication, therefore, is too broad and can only include the surgical population in which the drug product was tested and demonstrated to be safe and effective. Further indications would need to be confirmed with additional Phase 3 studies.

Sponsor Response:

As the Sponsor of two successful adequate and well controlled Phase 3 clinical trials using a model of visceral or soft tissue pain associated with surgery, (i.e., post-surgical pain in hernia repair), an indication of post-surgical analgesia (b) (4) *will be proposed for the XARACOLL indication in the NDA resubmission.*

Does the FDA agree that this indication can be supported by the Phase 3 clinical studies? (please see the entire Sponsor Response in meeting package)

FDA Response to Question 6

We have not determined whether your Phase 3 studies will support the broad labeling indication of postsurgical analgesia or if they will only support a population-specific/narrow pain indication. However, your reference to the FDA guidance for industry *Analgesic Indications Developing Drug and Biologic Products* (2014) fails to consider that your product may behave differently based on implantation site. The final labeling indication for Xaracoll will be determined during the review process.

Discussion:

There was no discussion of this question.

Manufacturing/Facilities:

Question 7:

Provide a summary of the design control system under 21 CFR 820.30 for the device constituent part and combination product. The design control information should include initial design, planning and development, design input, design output, design review, design transfer, design

verification, design validation that meets the proposed intended use of the final combination product, design changes, and design history file. For changes made to the device constituent part of the combination product, the impact of the design changes on the overall combination product performance should be considered and documented. All the design control activities must be documented in the Design History File (DHF) and subjected for design reviews. In addition, the location of DHF should be provided to the Agency for the facility inspection determination.

Sponsor Response: XARACOLL was developed with FDA guidance from the EOP2 Meeting that the collagen component of the formulation was designated as a non-novel excipient. Although the product and process development activities were conducted and documented in accordance with established Quality Systems and Documentation Controls, a formal Design History File (DHF) as defined in 21 CFR 820.30 was not compiled for XARACOLL. The company believes that its historical documentation and controls meet CGMP requirements notwithstanding that the format might not be totally in conformance with the Part 820 design control requirements.

Does the Agency agree that historical design & control documentation will address the intent/requirement of a formal DHF? (please see the entire Sponsor Response in meeting package)

FDA Response to Question 7

The Agency understands that the level of formality with which companies maintain design documentation varies greatly. To that note, the product and process development documentation you describe may address the 21 CFR Part 4 application of requirements of 820.30.

The DHF is intended to act as a repository or archive for documents to show compliance with the design plan, design control procedures, and ultimately, with Part 4. In essence, the DHF provides a complete design history of the device and should provide documentation representative of the actions taken with the device design throughout the design control process to ensure that the combined use of the constituent parts results in a combination product that is safe and effective and performs as expected.

It should be ensured that organization of these documents facilitate efficient retrieval of any particular document throughout the life of the device. Should these conditions be satisfied, the described documentation and controls may satisfactorily address the requirements of maintaining a DHF.

Discussion:

There was no discussion of this question.

Chemistry, Manufacturing, and Controls (CMC)

Question 8:

Section 3.2.P.3.5 of the submission [redacted]

Sponsor Response:
a) As already acknowledged in RTF issues 2, 3, 4, and 5 complete information pertaining to the validation of the [redacted] *process will be included in the NDA resubmission.*

b) In accordance to Compliance Policy Guide (CPG) Sec.490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market, NDAs may be approved by the Center prior to the completion of the initial conformance batch phase of process validation, and further, the manufacture of the initial conformance batches should be successfully completed prior to commercial distribution. This Guide further states, "If a pre-approval inspection is performed, the inspection team should audit and assess any available process validation protocols, activities, data, and information, whether or not completed, and report to the firm any deficiencies". In this regard and for clarification, Commercial Scale Process Validation activities (e.g.,, protocols, data etc.) will be available for audit during the Pre-approval Inspection. In addition, the manufacture of conformance batches will be successfully completed prior to commercial distribution.

Does the Agency agree that Process Validation documentation requirements as described above are not required to be completed and submitted in the NDA? (please see the entire Sponsor Response in meeting package).

FDA Response to Question 8

Please refer to ISO 11135 for the information that should be provided in the NDA resubmission to validate the commercial [redacted] **process.**

Discussion:

There was no discussion of this question.

Clinical

Question 9

Safety database concerns:

The safety database submitted in this NDA may be adequate to characterize the safety of XARACOLL. Specifically, the safety database contains a total of 578 subjects exposed to a dose of XARACOLL, with 435 of those (75.2%) exposed to the proposed marketing dose (including those subjects in the PK study), which may be adequate. If, however, there are signals that are identified concerning the safety of this product in any of the clinical studies, this database may need to be expanded. In the Written Responses document dated, July 16, 2015, you were informed that "any safety signals suggesting local tissue or systemic toxicity could require further evaluation of bupivacaine collagen implant in additional patients to better characterize the risk profile."

Sponsor Response:

Among the 578 subjects who received INL-001 in the Phase 1/2/3 studies, there were no safety signals suggestive of systemic or local tissue toxicity. Therefore, Innocoll believes that the 435 patients exposed to the to-be-marketed dose of XARACOLL are adequate to determine a safety signal, and that none were seen. The safety profile of subjects in the Phase 3 studies were comparable to the full safety database containing over 500 subjects exposed to a dose of XARACOLL. Innocoll requests concurrence by the Agency that the safety dataset is adequate. (please see the entire Sponsor Response in meeting package)

FDA Response to Question 9

The adequacy of your safety database will be determined during the review process. However, it is possible that your evaluation for systemic toxicity may not have been adequate, because your PK/BA study found the mean T_{max} to be at approximately 8.5 h after implantation of the bupivacaine-collagen matrix, a time at which most of the subjects in your Phase 3 studies had been discharged and were evaluated for local anesthetic systemic toxicity via a periodic telephone questionnaire. It is also possible that the 30-day duration of wound healing assessments was not adequate, because your nonclinical data found a higher incidence of necrosis and chronic inflammation within the subcutaneous and deep abdominal tissue when compared to control animals, findings which "generally resolved" by Study Day 56.

Discussion:

The Sponsor understands that a 30-day assessment may not always be adequate and acknowledged that there was a single female rat in their preclinical study noted to have necrosis and inflammation in the deep abdominal tissue layers at 56 days post-implantation. The Sponsor agreed to conduct an additional nonclinical 56-day local tissue toxicity study to specifically address concerns surrounding the potential adverse effects of Xaracoll on adequate wound

healing and to further characterize the time to dissolution of the implant. Additionally, they stated that per protocol, any patient who experienced delayed or incomplete wound healing was followed until resolution of the issue, which could extend beyond the 30-day follow-up visit if necessary. With regard to potential systemic toxicity, the Sponsor agreed to conduct an additional PK/BA study with the to-be-marketed formulation of Xaracoll.

Question 10:

Phase 3 study concerns:

b. In the Written Response document dated June 24, 2014, you were advised that "in the absence of PK/BA data to demonstrate that the levels of systemic exposure are so low that systemic toxicity will not occur with the proposed use of the product, it will be necessary to monitor subjects continuously to assure capture and timely treatment of adverse reactions related systemic toxicity [sic] if they occur." It does not appear that you have fulfilled this request and the safety evaluation for Phase 3 trials may not have been adequate.

Sponsor Response:

In the INL-CB-013 study the systemic exposure of bupivacaine was low with the highest individual exposure reported at 777 ng/mL, well below the threshold of concern for cardiotoxicity and neurotoxicity. Local and systemic toxicities related to XARACOLL were proactively monitored and not seen in the Phase 3 studies.

Does the agency concur that this request has been satisfied? (please see the entire Sponsor Response in meeting package)

FDA Response to Question 10

The PK/BA study does not provide sufficient evidence that plasma bupivacaine levels were so low that systemic toxicity will not occur. Three out of 24 (12.5%) of the subjects in the PK/BA study exposed to the proposed marketing dose of the bupivacaine-collagen matrix had plasma levels greater than 700 ng/mL and there was variability in the T_{max}, with at least one patient having measured plasma levels at or above 700 ng/mL near the 24 h post-operative time point. Therefore, the PK/BA study did not eliminate the need for more thorough monitoring during the Phase 3 studies. Ultimately, the adequacy of the assessments performed during the Phase 3 trials will be determined during the review process.

Discussion:

There was no discussion of this question.

Additional Comments

Nonclinical Comments

1. Extractables/Leachables

In your response to Question 10 from the complete meeting background document (1/18/2017), you agreed to conduct an extractables/leachables study as follows, "Extractables and leachables assessments and a full evaluation of toxicological risk from the closed container/closure system and drug/device product will be provided in the resubmission of an NDA."
This response is generally acceptable as stated, but consider the following in the conduct and assessment of the extractables/leachables study with Xaracoll to provide as complete an NDA package as required:

The NDA submission must contain adequate information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc. Provide justification for the choice of solvents and conditions for the extraction studies (time, temperature, etc). The results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables from the primary or secondary container closure systems and from your analysis of data from any upstream manufacturing processes that suggest the potential for additional leachable compounds in the final drug product formulation. Your analytical evaluation threshold (AET) must be established to be able to detect, identify, and quantitate levels of compounds based on these thresholds or you must provide adequate justification that these thresholds are not possible to be met by current analytical methodology. If you cannot meet these thresholds, safety evaluations will be based on the limits of quantitation (LOQ). Your submission must include a detailed discussion of how you established your AET as well as justification for the limits of detection (LOD) and LOQ for the analytical methods used.

Evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of your stability studies in order to identify trends in leachable levels over time. The materials tested should include any secondary container closure systems, if present, and be subjected to the same sterilization methods, as appropriate. These data are essential to determine the appropriate shelf life of your product.

For all drug products, establish your AET to be able to detect potentially carcinogenic or genotoxic compounds as per ICH M7 qualification thresholds (e.g., not more than (b) (4) mcg/day or up to (b) (4) mcg/day pending during of treatment). However, from a general toxicology perspective, for parenteral products, the AET must be able to detect

and identify any leachable that is present in the product at (b) (4) mcg/day or higher in order, unless justified otherwise, to permit an adequate toxicological risk assessment.

For additional guidance on extractables and leachables testing, refer to the following documents:

- **USP <1663>: Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems**
- **USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems**
- **FDA guidance for industry: *Container Closure Systems for Packaging Human Drugs and Biologics*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf**

The extractable/leachable data must be accompanied by an adequate toxicological risk assessment. Although a toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, evaluate at least three batches of your drug product that have been tested at multiple timepoints over the course of your stability studies, as discussed above, and base the final safety assessment on the maximum predicted levels of leachables identified to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified. Include copies of all referenced studies upon which a safety assessment is based.

- **If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.**

- **Published literature to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your container closure system.**

- **Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the extractable/leachable compound.**

Discussion:

There was no discussion of this statement.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

In addition, your iPSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*, available

at,
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2)

application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*

3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Wrap Up:

1. The Sponsor will conduct a PK study and toxicology study with the to-be-marketed product.

2. The Division will provide a designation of the product as prolonged or permanent in a post-meeting note.

3. The biocompatibility data will demonstrate that carcinogenicity and chronic toxicology are not required. This data will be established with the final finished product.

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

/s/

CHRISTOPHER M HILFIGER
03/27/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209511

REFUSAL TO FILE

Innocoll Inc
c/o Innocoll Pharmaceuticals
3830 West Chester Pike
Newtown Square, PA 19073

Attention: Carol S. Marchione
Vice President, Regulatory Affairs

Dear Ms. Marchione:

Please refer to your New Drug Application (NDA) dated and received October 31, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xaracoll (bupivacaine HCl collagen-matrix implants).

After a preliminary review, we find that your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Chemistry, Manufacturing, and Controls (CMC)

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

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

2. You have not included sterilization validation studies in your submission and you have stated that the studies will be available for review at the time of inspection. This information is required at the time of the NDA submission. Refer to Guidance for Industry: *for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Product,* available at (http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm072171.pdf)

3. The following information is not included in your submission. Either provide this information or provide a letter of authorization (LOA) to a drug master file containing the required information.

    a. Section 3.2.P.2.5 Microbiological Attributes, indicates on page 14 that the secondary packaging to be used for commercial manufacturing will change from that used in clinical development. The Agency's determination of the microbiological quality of the drug product requires review of sterilization validation studies that use the intended commercial packaging. Provide the following information:

        i. A complete description of the intended primary and secondary packaging components intended for the commercial manufacture of the subject drug product.

        ii. The results of successful container closure integrity testing for the intended commercial secondary packaging for the subject drug product.

4. Identify the facility and the (b) (4) that will be used for commercial manufacture of the subject drug product (i.e., manufacturer, model, equipment identification).

5. Provide the following information for the (b) (4) process that will be used for commercial manufacture of the subject drug product.

    a. Describe the routine (b) (4) (b) (4) (b) (4) of the subject drug product.

    b. Describe the pre-conditioning parameters (b) (4)

    c. Indicate whether there will be (b) (4) (b) (4)

    d. Describe the (b) (4) (b) (4)

    e. Describe the (b) (4)

6. Section 3.2.P.3.5 (b) (4) (b) (4)

7. In regard to the intended commercial primary container closure components (i.e., blister and (b) (4) describe the strategy that will be used to control bacterial endotoxins.

8. The drug product facility (Syntacoll GmbH) is not ready for inspection. All facilities must be ready for inspection when the NDA is submitted, in order for the application to be considered as fileable.

Nonclinical

9. There are inadequate nonclinical data in the NDA to adequately qualify the safety of the to-be-marketed drug product. We note that the pivotal nonclinical 56-day bupivacaine collagen implant study (e.g., (b) (4) 134502) did not test the to-be-marketed (b) (4) (b) (4) drug product, but rather an earlier development product. To address this issue, you must repeat your pivotal toxicology study testing with the to-be-marketed drug product, or provide justification for how the findings of the conducted study can be extrapolated to support the safety of the to-be-marketed product with respect to the endpoints tested (e.g., bupivacaine release, local toxicity, duration and fate of the inserted sponge).

10. The NDA did not include an adequate extractables/leachables evaluation per our discussions during development (refer to Meeting Minutes dated January 12, 2012, and Written Responses dated August 10, 2015). We acknowledge your proposal to provide an extractables/leachables evaluation just prior to commercialization since your product is a (b) (4) matrix, which would typically be associated with a low risk of leaching of container closure system components into the drug product. However, an extractables/leachables evaluation is required to file the NDA as it is critical to support the safety of your product.

    To address this issue, your NDA resubmission must contain adequate information on potential leachables and extractables form the drug container closure system and/or drug product formulation, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc. Provide justification for the choice of solvents and conditions for the extraction studies (time, temperature, etc). The results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables from the primary or secondary container closure systems and from your analysis of data from any upstream manufacturing processes that suggest the potential for additional leachable compounds in the final drug product formulation. Your analytical evaluation threshold (AET) must be established to be able to detect, identify, and quantitate levels of compounds based on these thresholds or you must provide adequate justification that these thresholds are not possible to be met by current analytical methodology. If you cannot meet these thresholds, safety evaluations will be based on the limits of quantitation (LOQ). Your submission must include a detailed discussion of how you

established your AET as well as justification for the limits of detection (LOD) and LOQ for the analytical methods used.

Evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of your stability studies in order to identify trends in leachable levels over time. The materials tested should include any secondary container closure systems, if present, and be subjected to the same sterilization methods, as appropriate. These data are essential to determine the appropriate shelf life of your product.

For all drug products, establish your AET to be able to detect potentially carcinogenic or genotoxic compounds as per ICH M7 qualification thresholds (e.g., not more than (b) (4) mcg/day or up to (b) (4) mcg/day pending during of treatment). However, from a general toxicology perspective, for parenteral products, the AET must be able to detect and identify any leachable that is present in the product at (b) (4) mcg/day or higher in order, unless justified otherwise, to permit an adequate toxicological risk assessment.

For additional guidance on extractables and leachables testing, refer to the following documents:

a. USP <1663>: Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems

b. USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems

c. FDA guidance for industry, *Container Closure Systems for Packaging Human Drugs and Biologics*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf

The extractable/leachable data must be accompanied by an adequate toxicological risk assessment. Although a toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, evaluate at least three batches of your drug product that have been tested at multiple timepoints over the course of your stability studies, as discussed above, and base the final safety assessment on the maximum predicted levels of leachables identified to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s)

unless otherwise justified. Include copies of all referenced studies upon which a safety assessment is based.

a. If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.

b. Published literature to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your drug product formulation.

c. Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the novel excipient.

Clinical Pharmacology

11. Multiple formulation modifications (b) (4) (b) (4) (b) (4) were made to the drug product formulation during development. These changes are considered substantial. Therefore, the pharmacokinetic (PK) data obtained with the prior formulation cannot be applied to the commercial formulation. You must conduct an additional PK study similar to Study INN-CB-013 evaluating bupivacaine exposure using the commercial formulation in surgical procedure you plan to include in your product label, i.e., patients undergoing hernia repair. Specify all treatments and provide pertinent information including, lot number, expiration date, NDA or ANDA numbers, etc.

Biocompatibility

12. The subject product, Xaracoll is a drug/device combination product comprised of bupivacaine and collagen matrix. You did not provide any biocompatibility information regarding the collagen matrix, the device component of Xaracoll. Based on the product description and its intended use provided in current submission, we consider the combination product as an implant in permanent contact with tissue/bone for

biocompatibility evaluation purpose. For this evaluation you should provide the following biocompatibility endpoints for a permanent implant final finished combination product: 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. Refer to the guidance for industry and FDA staff, *Use of International Standard ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management*, available at, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM348890.pdf.

Regulatory

13. Your 505(b)(2) application appears to rely upon the Agency's finding of safety and effectiveness for NDA 16964 for Marcaine and (b) (4) Provide a revised Form FDA 356h specifying reliance on NDA 16964 for Marcaine and NDA (b) (4) as the listed drugs that are the basis of your 505(b)(2) application. You must also provide an appropriate patent certification or statement with respect to any relevant patents that claim the listed drug, NDA 16964 for Marcaine and (b) (4) (b) (4), and that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug according to 21 CFR 314.54(a)(1)(vi).

While not issues related to our refusal to file this application, you should address the following review issues if the application is resubmitted.

Clinical

1. Safety database concerns:

   The safety database submitted in this NDA may be adequate to characterize the safety of XaraColl. Specifically, the safety database contains a total of 578 subjects exposed to a dose of XaraColl, with 435 of those (75.2%) exposed to the proposed marketing dose (including those subjects in the PK study), which may be adequate. If, however, there are signals that are identified concerning the safety of this product in any of the clinical studies, this database may need to be expanded. In the Written Responses document dated, July 16, 2015, you were informed that "any safety signals suggesting local tissue or systemic toxicity could require further evaluation of bupivacaine collagen implant in additional patients to better characterize the risk profile."

2. Phase 3 study concerns:

   a. The Phase 3 trials conducted were identical in design and surgical population, therefore, the results obtained are considered to be duplicated. Although potentially supportive of the safety and efficacy of your product in the patient population and

procedure that were studied, these trials may not address questions that trials which were designed to replicate the findings of safety and efficacy would be able to address.

b. In the Written Response document dated June 24, 2014, you were advised that "in the absence of PK/BA data to demonstrate that the levels of systemic exposure are so low that systemic toxicity will not occur with the proposed use of the product, it will be necessary to monitor subjects continuously to assure capture and timely treatment of adverse reactions related systemic toxicity [*sic*] if they occur." It does not appear that you have fulfilled this request and the safety evaluation for Phase 3 trials may not have been adequate.

3. Labeling concerns:

a. The proposed labeling states the indication for use of this product is *postsurgical analgesia*. The Phase 3 trials were conducted in one surgical population, open inguinal hernia repair with mesh. The original Phase 2 studies were conducted in patients undergoing abdominal hysterectomy and other abdominal procedures and the results of those studies did not demonstrate efficacy of the XaraColl matrix. The proposed indication, therefore, is too broad and can only include the surgical population in which the drug product was tested and demonstrated to be safe and effective. Further indications would need to be confirmed with additional Phase 3 studies.

b. There needs to be a statement under the *Drug Interactions* section of the labeling explaining the use of additional local anesthetics with XaraColl. Address the following concerns:

i. The concern of local anesthetic systemic toxicity associated with additional local anesthetic administration, including ester and amide-type local anesthetics.

ii. Subcutaneous infiltration with other local anesthetics (i.e., lidocaine) prior to incision is common in this surgical population. Provide an explanation as to how this may affect the bupivacaine-collagen matrix. If prior local anesthetic use is not recommended, then clearly state this in the labeling.

iii. The labeling will also need to provide clinicians with guidance regarding safe timing and dosing of local anesthetics after XaraColl has been implanted.

c. Any interaction of the bupivacaine-collagen matrix with iodine-containing products, such as those used frequently to cleanse the skin prior to incision, and potential subsequent adverse effects on the matrix must be addressed.

CMC

14. Regarding container closure integrity testing (CCIT) of the commercial secondary packaging, address the following issues:

    a. Provide descriptions of the pressure decay test and seal/peal strength test methods, including the preparation of any positive controls.

    b. Provide the acceptance criteria and limit of detections/sensitivities for the pressure decay test and seal/peal strength test for CCIT of the intended commercial secondary packaging.

15. Regarding the biological indicators for monitoring of the routine production (b) (4) (b) (4) please address the following points:

    a. (b) (4)

    b.

16. Include the following tests on the manufactured collagen which characterize the collagen:

    a. Collagen Content (Hydroxyproline Determination or colorometric assay for collagen, such as Sirius red). The concentration of collagen should be expressed in mass/volume or mass/mass.

    b. Collagen Purity (SDS-PAGE, peptide mapping, and amino-terminal sequencing)

    c. Collagen Type Composition (western blot or enzyme-linked immunosorbent assay (ELISA) analysis)

    d. Amino Acid Analysis (HPLC) and/or Peptide Mapping (CNBr digestion followed by SDS-PAGE, HPLC, mass spectroscopy (MS), matrix-assisted laser desorption/ionization (MALDI), etc.)

    e. Differential Scanning Calorimetry (DSC)

17. Include the following tests on the manufactured collagen that characterize the impurity profile of the collagen:

    a. Elemental Analysis and Trace Metals determination according to ICH Q3D Methods that can detect and quantitate the following:
    (b) (4)

ii. (b) (4)

iii.

iv.

v.

vi. Characterize the presence of collagen-related degradation products

18. Viral clearance should be demonstrated by an appropriately validated viral clearance study protocol (for example USP <1050>).

19. In Form FDA 356h, you have indicated that (b) (4) is responsible for (b) (4) Indicate if any other manufacturing site is involved in API manufacturing and testing activities.

Regulatory

20. In study INN-CB-013, you stated that Sensorcaine (or its ANDA) was also used as a comparator in addition to Marcaine. Sensorcaine and Marcaine were approved under different NDAs. If you plan to use data generated using Sensorcaine, then Sensorcaine also needs to be included as a listed drug for your 505(b)(2) application with appropriate patent certification.

21. In study INN-CB-013, you indicated that ANDA products of Marcaine and Sensorcaine were used. You need to make effort and demonstrate your due diligence to provide the ANDA numbers of these products.

    A 505(b)(2) application contains "full reports of investigations" of safety and effectiveness where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. Therefore, in general, reliance on an approved ANDA is not acceptable to support a proposed 505(b)(2) application. You need to identify the NDA that was the basis for submission for the ANDA you have incorrectly cited as the listed drug relied upon to support your proposed 505(b)(2) application. You must also provide an appropriate patent certification or statement with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)).

Manufacturing/Facilities:

22. Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR Part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR Parts 210, 211) and with the device quality system (QS) regulation (21 CFR Part 820) through a streamlined approach. If utilizing a streamlined approach, you must demonstrate compliance with either the drug CGMPs or the QS regulation in its entirety and also with those provisions specified in Part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). For reference 21 CFR Part 4 is accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products. Preliminary draft guidance is accessible at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf.

23. Identify which approach you use to comply with 21 CFR Part 4.

24. Provide a summary of the management structure with executive responsibility who manage, perform, and assess work affecting quality of the product and related controls to ensure that quality policies are appropriately implemented and followed, and the product appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met as per 21 CFR 820.20.

25. Provide a summary of the design control system under 21 CFR 820.30 for the device constituent part and combination product. The design control information should include initial design, planning and development, design input, design output, design review, design transfer, design verification, design validation that meets the proposed intended use of the final combination product, design changes, and design history file. For changes made to the device constituent part of the combination product, the impact of the design changes on the overall combination product performance should be considered and documented. All the design control activities must be documented in the Design History File (DHF) and subjected for design reviews. In addition, the location of DHF should be provided to the Agency for the facility inspection determination.

26. Provide a summary of information pertaining to the Purchasing Control as per 21 CFR 820.50 to demonstrate controls and documentation for components, products, or services (e.g., sterilization) received at the sponsor's facility for use in the manufacture of the combination product. The summary should include an evaluation process for the suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Notification of changes by the suppliers should be considered in the Purchasing/Supplier agreement as changes to incoming specification that can impact the safety and effectiveness of the final combination product.

27. Provide a summary of information related to Corrective and Preventive Actions (CAPA) as per the requirement of 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of non-conformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions should be documented under the firm's CAPA System as described in 21 CFR 820.100.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.'

If you have any questions, call Ayanna Augustus, PhD, RAC, Sr. Regulatory Project Manager, at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

ELLEN W FIELDS on behalf of SHARON H HERTZ
12/23/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077127

MEETING MINUTES

Innocoll Technologies, Inc.
1 Gate Ct.
Burlington, NJ 08016

Attention: Susan Cusack
US Regulatory Agent

Dear Ms. Cusack:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) Bupivacaine Implant.

We also refer to the meeting between representatives of your firm and the FDA on December 5, 2011. The purpose of the meeting was to discuss your planned Phase 3 development program.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

SPONSOR MEETING MINUTES

MEETING DATE:	December 5, 2011
TIME:	1:30 pm
APPLICATION:	IND 077127
PRODUCT:	(b) (4) Bupivacaine Implant
INDICATIONS:	Post-surgical pain
SPONSOR:	Innocoll Technologies, Inc.
TYPE OF MEETING:	Type B
MEETING CHAIR:	Rigoberto Roca, M.D., Deputy Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
MEETING RECORDER:	Allison Meyer, Senior Regulatory Project Manager, DAAAP

FDA Attendees	Title
Bob A. Rappaport, M.D.	Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, M.D.	Deputy Division Director, DAAAP
Arthur Simone, M.D., Ph.D.	Clinical Reviewer, DAAAP
Brad Harris, M.D.	Clinical Reviewer, DAAAP
Yun Xu, Ph.D.	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCP II)
David Lee, Ph.D.	Clinical Pharmacology Reviewer, DCP II
Adam Wasserman, Ph.D.	Supervisor, Pharmacology/Toxicology
Danae Christodoulou, Ph.D	CMC Lead,ONDQA
Dionne Price, Ph.D.	Team Leader, Biostatistics
David Petullo, Ph.D.	Biostatistics Reviewer
Allison Meyer	Sr. Regulatory Health Project Manager

Innocoll Attendees	Title
Michael Myers	President and CEO
David Prior, Ph.D.	Executive Vice President, Clinical & Regulatory Affairs
Lisa Hemsen	Sr. Director, Clinical Affairs
(b) (4)	

BACKGROUND
On September 22, 2011, the Sponsor requested a Type B meeting. The Division granted this meeting request on October 3, 2011. The Division received a briefing document from the Sponsor on November 1, 2011. The Division sent preliminary comments to the Sponsor on December 1, 2011.

The Sponsor's original questions are in *italics*, the Division's responses in **bold**, and the discussion that took place at the meeting is in normal font.

DISCUSSION
Clinical, Statistics and Pharmacokinetics

Question 1
In comments received from the Division in response to a Type-C meeting request, dated September 22, 2008, the Division indicated that "a broad indication would require that the product also be tested following most, if not all, types of surgeries." During our Phase 2 program, the bupivacaine-sponge was evaluated in hysterectomy and herniorrhaphy, with herniorrhaphy showing the greatest potential for product efficacy in the management of postoperative pain. Therefore, we are proposing to conduct our Phase 3 program on adults undergoing herniorrhaphy and to target our product labeling for NDA submission accordingly. Does the Division agree that (b) (4) *is appropriate to target for our NDA submission?*

Response:
A general indication for postoperative analgesia rather than a more specific indication (e.g., (b) (4) **would be considered based on the findings of the clinical trials. The labeling will reflect the surgical procedure(s) and patient population(s) for which a specific dose of the product has been found to be safe and effective. It will also reflect that dosing, safety, and efficacy have not been established for other surgical procedures and patient populations and may recommend against using the product off label out of concern for patient safety.**

Discussion: There was no further discussion on this question.

Question 2
We are proposing to perform 2 adequately-powered, double-blind, pivotal efficacy and safety studies in our Phase 3 program. The first study will evaluate 2 dose levels in patients undergoing herniorrhaphy; the lower (200 mg) dose corresponding to a dose studied in Phase 2, and a higher dose (300 mg) not yet studied. Both dose levels will be evaluated as independent primary analyses versus placebo and, if the study is successful at one or both dose levels, the results will be used to select the most appropriate dose for a second Phase 3 efficacy study, also in patients undergoing herniorrhaphy. If the second study is similarly successful, we believe that these 2 studies will provide sufficient efficacy data to support an NDA application. Does the Division agree i) with this approach to dose selection in Phase 3, and ii) that if both these adequately powered studies are successful, the efficacy data so obtained would be sufficient to support an NDA with the proposed indication and labeling (b) (4) *?*

Reference ID: 3070863

Response:
Although it is recommended that dosing regimens have been established prior to conduct of the pivotal trials, the proposed approach is acceptable. The independent assessment of efficacy for each (b) (4) dose in the first study could potentially allow the results to qualify as part of the replicated findings of efficacy necessary to support an NDA submission. Approval of the NDA will be a matter of review of all the clinical studies and data submitted.

Discussion: There was no further discussion on this question.

Question 3
Does the Division agree that the proposed primary efficacy endpoint based on the method of Silverman et al, and which integrates total use of opioid analgesia from 0 to 24 hours with the sum of NRS pain intensity from 1 to 24 hours into a single variable (as detailed in Section 12.3.4.1 of the Phase 3 study protocol and rationalized in Section 6.3.6 of the Background Information), is appropriate for our Phase 3 efficacy studies and will support the proposed indication and product label?

Response: Your proposed primary endpoint, an integrated assessment of pain and total use of opioid analgesia, is not one that we customarily use for these clinical trials. It will be necessary to have additional internal discussions before an answer can be provided. If it is not possible to provide a response by the time of the meeting, then a response will be provided either as part of the meeting minutes, in the form of a post-meeting note, or in a separate advice letter.

In addition, see the response to Question 8 regarding claims in the product label.

Discussion: The Sponsor stated that they intend to use the Silverman method for their primary endpoint. The Division stated that further internal discussion were still on-going. A post-meeting note will be included with the minutes. The Sponsor asked if they would be granted a follow-up teleconference to clarify any questions on the post-meeting note. The Division agreed.

Post Meeting Note: The use of an integrated assessment of pain and opioid use is statistically valid and is acceptable as a primary efficacy endpoint.

Question 4
For the first Phase 3 efficacy study where we plan to test 2 dose levels, we are proposing that the primary analysis will be 2-sided and adjusted using Dunnett's method for the 2 pairwise comparisons (1 for each bupivacaine-sponge dose level) against the placebo-sponge. A difference resulting in a p-value of less than or equal to 0.027 will be considered statistically significant, which controls the overall Type-I error rate at 0.05. Does the Division agree that this primary analysis method and use of Dunnett's adjustment is appropriate?

Reference ID: 3070863

Response: Yes, Dunnett's adjustment is an appropriate method to control the overall significance level when there are multiple treatment versus control comparisons. Clarify how you derived the 0.027 significance level.

You define several "key" secondary endpoints. If any of these will form the basis for label claims, then the analysis must account for multiplicity. We also note that you defined the intent-to-treat (ITT) population as all randomized patients who receive treatment and who have at least 1 NRS PI score. The ITT population should not depend on post-treatment efficacy assessments.

Discussion: The Sponsor provided a document that explained how the 0.027 significance level was derived.

Post Meeting Note: The document provided adequately addressed our concern.

Question 5
For the first Phase 3 efficacy and safety study, we are proposing a sample size of 240 patients, randomized 3:3:2 (90 patients in each bupivacaine-sponge group and 60 patients in the placebo-sponge group). Based on the proposed primary analysis, this sample size is calculated to provide 99% power to detect a treatment difference at the 0.027 significance level, and hence has been principally selected by the need for safety data. Does the Division agree that the planned sample size and randomization ratio are appropriate for the first Phase 3 study?

Response: Your sample size appears appropriate based on the information provided from the Phase 2 studies.

Discussion: There was no further discussion on this question.

Question 6
Does the Division agree that our proposed approach for imputation of missing efficacy data, as laid out in Section 12.3.4.3 of the protocol and rationalized in Section 6.3.9 of the Background Information, is appropriate for evaluation of efficacy in Phase 3?

Response: No, it is not appropriate to only impute pain scores for 1 and 72 hours post-dose. This could theoretically result in the computation of an area under the curve (AUC) using only the first and last time points. This may under or over estimate the AUC of pain intensity scores. Your analysis method should account for all time points post-dose. You should also be aware that the National Academy of Sciences (NAS) recently released a report on missing data which was commissioned by FDA. The report does not recommend the use of single imputation methods such as WOCF and LOCF unless scientifically justified. Approaches, consistent with the NAS recommendation, that have the desirable property of not assigning good scores to bad outcomes, should be proposed. Either provide justification or propose a method that is in agreement with the NAS report. In addition, we suggest that you continue to collect data even after discontinuation of treatment as recommended by the NAS report. The report can be found online at: http://www.nap.edu/catalog.php?record_id=12955.

Reference ID: 3070863

Discussion: The Division stated that the comment regarding the NAS report on missing data is being provided to all sponsors to ensure that they are aware of the report. In the current setting, single-dose, acute-indication, missing data should not be an issue and a single imputation approach may be acceptable. The rationale for using the proposed approach along with the appropriate sensitivity analyses should be formally submitted to the Division for review. All early discontinuations should be thoroughly documented and included as a negative finding in your primary analysis.

The Sponsor indicated they would take this approach.

Question 7
In comments received from the Division in response to the Type-C meeting request, the reviewer stated "An alternative approach to monitoring pain levels and assessing the need for postoperative analgesics is to offer analgesics on a fixed schedule with availability of additional analgesics for breakthrough pain." Therefore, in the Phase 3 protocol, we have included a fixed non-opioid analgesic schedule (acetaminophen 1000 mg 3-times daily) with opioid rescue analgesia (morphine 15 mg IR tablets) permitted for breakthrough pain. The fixed analgesic schedule is consistent with the planned revision to the OTC regimen for Tylenol® 500mg, as recently announced by Johnson & Johnson. Does the Division agree that acetaminophen 1000 mg 3-times daily is an appropriate fixed non-opioid analgesic schedule, and that morphine 15 mg IR tablets is an appropriate opioid rescue analgesia for breakthrough pain, for our pivotal Phase 3 safety and efficacy studies?

Response: The selection of acetaminophen and the proposed dosing appear reasonable for the fixed-schedule analgesic medication. The use of an IR morphine is also acceptable for a rescue medication; however, a rationale for the dose (one to two 15 mg tablets every 3-4 hours) should be provided and should take into account the expected level of pain following the procedure. A more fixed regimen, e.g., one tablet every 3 hours, may be more useful for patients and may reduce confounding in the comparisons of the use of rescue between treatment groups.

Note: The protocol should require that a pain assessment be made immediately prior to the use of rescue medication.

Discussion: The Sponsor stated that, in the current Phase 3 program, opioids are only being used for rescue analgesia. Patients are given analgesia as needed for post-cough pain. The patients are asked to cough and assess their level of pain when doing so. The Sponsor is only evaluating pain with cough, not at rest, as this is most likely to demonstrate a treatment effect. The Division expressed concern with this approach as it suggests that the pain following herniorrhaphy is adequately controlled with acetaminophen except with certain types of activity when breakthrough pain occurs. As the study is currently designed, it assesses the ability of (b) (4) to treat breakthrough pain rather than provide post-operative analgesia and would make labeling the product with the proposed indication difficult at best.

Reference ID: 3070863

Question 8
Does the Division agree that the secondary endpoints proposed in the Phase 3 protocol and Section 6.3.8 of the Background Information, are appropriate for our planned Phase 3 efficacy studies?

Response: The proposed secondary efficacy variables are appropriate for the pivotal studies. These will be supportive of a finding of efficacy provided they trend in the direction favoring (b) (4) Note that the use of secondary endpoints for making claims will minimally require:

- **The endpoint is distinct from the primary endpoint in terms of the benefit it assesses and is relevant to the clinical setting in which the product is to be used.**
- **The endpoint used has been appropriately validated.**
- **The statistical analysis plan accounts for the analyses of multiple endpoints.**
- **The study demonstrates that a clinically meaningful difference between treatment groups exists, in addition to a statistically significant difference.**
- **The findings for the endpoint have been replicated.**

For making a claim (b) (4) the study would need to be designed to specifically evaluate the purported benefit, which may require an outcome study. (b) (4)

Discussion: The Sponsor stated that (b) (4)

Question 9
Is the Division aware of any additional efficacy data that would need to be generated in Phase 3 to support the proposed indication and product label?

Response: The proposed efficacy endpoints should be sufficient to determine the benefits of (b) (4) when used following herniorrhaphy.

It is not clear why you have opted not to evaluate the safety and efficacy of (b) (4) for other surgical procedures (e.g., orthopedic procedures, incisional biopsies). As indicated

Reference ID: 3070863

above (and below), this will substantially limit the approved use in the clinical setting. While the Division recognizes the findings of the hysterectomy studies were not encouraging, if there are issues that preclude evaluation of (b) (4) when used following other surgical procedures or concerns for how you wish to market the product, this would be a good time to discuss them with the Division so we may provide guidance at this key juncture in your clinical development program.

Discussion: The Sponsor stated that the current program is the most financially viable. If approved, they plan to do additional studies and submit efficacy supplements to broaden the indication. The Division noted that the limited indication may affect their ability to market the product, but that it is the Sponsor's decision to choose which indication to pursue. The Division also noted that we are not certain at what point enough procedures would be studied so that the product could be labeled in a manner that was less restrictive than for the specific procedures evaluated to date. To some extent, that decision will depend on the efficacy and safety findings from the studies involving single surgical procedures.

Question 10

In addition to the pivotal efficacy and safety studies referred to in Question 2, we are proposing to conduct a randomized, open label, PK/BA study comparing the PK of the bupivacaine-sponge to a local bupivacaine infiltration (150 mg bupivacaine hydrochloride with epinephrine) in 36 patients (24 patients to receive the bupivacaine-sponge and 12 to receive local bupivacaine infiltration). We plan to perform this PK/BA study after the bupivacaine-sponge dose has been selected for further development after the first Phase 3 dose-selection efficacy study (as referred to in Question 2). Does the Division agree that the PK/BA study as proposed in the protocol outline i) will provide sufficient PK data to support an NDA with the proposed indication and ii) can be performed after selection of the bupivacaine-sponge dose intended for NDA submission?

Response: The proposed study design appears to provide the needed relative bioavailability information for a 505(b)(2) submission. The adequacy of the study results will be determined after review of the data. It is not clear which listed drug you will be using in the proposed PK/BA study. Please specify the listed drug you will be using, as you need to use a drug approved via the NDA process in US. Also refer to our "Additional Regulatory Comments."

We recommend that you conduct the proposed PK/BA study prior to the first Phase 3 trial since there is no bupivacaine systemic exposure information, which is a safety concern, from the (b) (4) cm sponge. Due to (b) (4), the newly proposed (b) (4) cm sponge will likely provide (b) (4) bupivacaine systemic exposure compared to the 5 x 5 cm sponge used in previous Phase 1 and 2 studies.

Additionally, we recommend that you obtain dose linearity information from the proposed PK/BA study (200 and 300 mg bupivacaine doses) since the Phase 3 trial(s) will evaluate both dose strengths.

Discussion: There was no further discussion on this question.

Reference ID: 3070863

Question 11

The safety assessments proposed for Phase 3 are detailed in the pivotal Phase 3 efficacy and safety study protocol, and the protocol outline for the PK/BA study. Is the Division aware of any additional safety assessments that will be required in Phase 3 to support an NDA with the proposed indication?

Response: The Division recognizes the long history of use for bupivacaine in the surgical setting and, therefore, the focus will be on the potential risks associated with the method of delivery for a product such as (b) (4) Specifically, the Division is concerned with evaluation of the following risks:

1. **The potential for exposure to high systemic levels of bupivacaine and the associated cardiac and neurotoxicity when (b) (4) is implanted in various tissues**

2. **Adverse effects that (b) (4) may have on wound healing, e.g., inflammation, irritation, infection**

3. **Adverse effects that (b) (4) may have on the integrity of surgically implanted materials, i.e., surgical suture and mesh**

The assessment for cardiac and neurotoxicity needs to include proactive evaluation of patients exposed to the product at appropriate time points following product administration and the time points selected need to include Tmax. This information can be captured in the PK/BA study that needs to be completed before the pivotal studies are initiated. If the PK/BA study is modified to include neurological assessments for possible toxicity related to bupivacaine, in addition to continuous ECG monitoring for dysrhythmias, sufficient data may be captured to adequately characterize the cardiac and neurological risk profiles associated with (b) (4) and, thereby, reduce the need for such intensive and prolonged assessments in the pivotal studies.

Assessments of wound healing and adequacy of the surgical repair of the hernia will need to be performed in the pivotal studies at appropriate time points based on the time for the sponges to be fully resorbed and the expected healing time for the surgical procedure.

The effects of (b) (4) on commonly used suture materials and surgical mesh need to be evaluated, at least in vitro, prior to initiating the pivotal studies.

Discussion: For the Phase 3 and PK/BA studies, the Sponsor is conducting 24-hour cardiac monitoring as well as neurological assessments through patient questioning. The Division stated that this should be sufficient as long as the assessments are made over a period that includes T_{max}. The Division also indicated that the same requirements should be incorporated in studies of additional surgical procedures, as release of bupivacaine may vary based on the characteristics of the surgical site, e.g., vascularity, extent of incision. If it can be demonstrated that there is no systemic exposure to bupivacaine, then the need to monitor for systemic toxicity would be obviated. The Sponsor stated that, for herniorrhaphy, the C_{max} is expected to be at 12 hours.

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The Sponsor explained that they will evaluate the adequacy of surgical repair of the hernia via teleconference with the patients at Day 7 and 30. They will inquire about the incision and follow-up with a clinic visit and doctor assessment. The Division agreed with this approach.

The Division asked if it would be possible to perform in vitro testing to determine the effects of (b) (4) on commonly used suture materials and surgical mesh. The Sponsor indicated that it is possible to perform these types of tests and will investigate further.

Question 12
To date, 114 patients have received the bupivacaine-sponge and we are proposing to include another 24 in our PK/BA study. For our first double-blind, Phase 3 efficacy and study, we expect an additional 180 patients to be treated with the bupivacaine-sponge (over 2 different dose levels) and we plan to study a further 180 patients at the selected NDA dose level in our second Phase 3 efficacy and safety study. This will bring our total patient exposure to approximately 500. Because bupivacaine is a well characterized drug that has an established safety profile, we believe that these safety data will be sufficient to support an NDA application, assuming no significant safety concerns become apparent. Does the Division agree that the extent of safety data obtained from all the proposed Phase 3 studies, when combined with our completed Phase 2 studies, will be sufficient safety to support an NDA provided that no significant safety concerns are identified?

Response: A safety database of 500 patients is likely to be adequate provided:

- **An adequate number of patients were exposed to the to-be-marketed version of the product and the highest to-be-labeled dose to characterize the risk profile of (b) (4) for the intended surgical procedure.**

- **The demographic of the safety database resembles that of the surgical population in whom (b) (4) is likely to be used.**

Discussion: The Division expressed concern that the limitations imposed by the inclusion and exclusion criteria for protocol INN-CB-012 would preclude fully assessing the safety and efficacy of (b) (4) following herniorrhaphy in the population for which it will be used in the clinical setting. It was noted that this study would be used to select the most appropriate dose for a second Phase 3 study. The Sponsor indicated that they understood the Division's concern and that the demographics of the safety database would resemble that of the surgical population presenting for herniorrhaphy in whom (b) (4) would likely be used.

Question 13
Does the Division have any other recommendations on the proposed Phase 3 efficacy and safety study protocol, or the protocol outline for the proposed PK/BA study?

Response:

1. **Complete the PK/BA study before initiating the pivotal studies.**

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2. **Incorporate the neurological and cardiac assessments described above into the PK/BA study to characterize the risk profile associated with the systemic exposures that occur following herniorrhaphy.**

3. **Expand the Inclusion/Exclusion Criteria of the pivotal studies, to the extent possible, so that the demographics from those studies better reflect that of the population in whom (b) (4) is likely to be used, if it is approved.**

Discussion: The Sponsor asked the Division to clarify what appeared to be restrictive language in the entry criteria. The Division noted that the entry criteria for study INN-CB-012 (the Phase 3 study involving open laparotomy herniorrhaphy) and INN-CB-013 (the PK study involving open laparotomy herniorrhaphy) allowed only subjects who were ≤65 years of age and had not used aspirin, antiarrhythmics, antidepressants or a number of other commonly used drugs within days of surgery. These limitations would potentially make the demographics of the subjects in the safety database differ substantially for the population that would be likely to receive (b) (4) if it is approved. The Sponsor assured the Division that the Phase 3 studies would generate a safety database from subjects whose demographics reflect that of the general population presenting for the procedure and for whom their product is likely to be used.

Regulatory

Question 14

Does the Division agree that the proposed PK/BA will meet the requirements for a BA/Bioequivalence (BE) study outlined in the "Guidance for Industry, Applications Covered by Section 505(b)(2)" in support of an NDA filed under 505(b)(2)?

The proposed PK/BA study design appears to address the needed relative bioavailability information for a 505(b)(2) submission For additional recommendations, see Response to Question 10.

Discussion: There was no further discussion on this question.

Nonclinical

Question 15

We plan to file a 505(b)(2) NDA relying on the nonclinical information for bupivacaine hydrochloride injection as well as published literature. Additionally, we plan to perform the following nonclinical studies as rationalized in Section 6.5; a 28-day intraperitoneal implant local toxicity study in male rats, an Ames test, a mouse lymphoma study, and an in vivo micronucleus assay for genotoxicity. Does the Division agree that the proposed nonclinical package is adequate and sufficient in scope to support a 505(b)(2) NDA for the proposed indication, (b) (4)

Response: Your proposed nonclinical package will need to address the following issues in this response, those in our response to your Question 16, and those in Additional Regulatory Comments and Additional Nonclinical Comments.

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You will need to provide a more detailed justification for the nonclinical testing strategy in your NDA submission than what is described in this EOP2 submission. This includes your rationale for the selection of the test species, the rat's comparability/superiority/relevance to other potential nonclinical test species and humans for the pivotal nonclinical local toxicity study, and the adequacy of the 28-day repeat dose implant study to adequately assess potential local toxicity of your drug product (see our response to Question 16 for specific study considerations).

As there is no genotoxicity data for bupivacaine described in the referenced NDA label of Marcaine, we recommend that you test bupivacaine using genotoxicity tests and doses as described in the Guideline for Industry ICH-S2A - Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (Apr 1996) and not your drug product leachate. Leachate-based genotoxicity data is of little value if the dosing material is not characterized as the data will not be used in the product label.

Discussion: The Sponsor asked if it would be acceptable to only perform the genotoxicity studies with the drug substance. The Division agreed with this plan and noted that this evaluation is not a requirement, but a recommendation.

Question 16
Does the Division agree that the outlined study proposed for the 28-day intraperitoneal implant local toxicity study in male rats (refer to Section 6.5, Table 9) is adequate and that the endpoints incorporated (refer to Section 6.5, Table 10) are appropriate to address the Division's concern regarding potential local toxicity?

Response: The 28-day intraperitoneal implant local toxicity study in male rats will only be adequate with some modifications to the existing proposed protocol.

- **If feasible, the testing of sponges with higher formulation strengths than the proposed clinical formulation is recommended in order to identify the presence of a safety margin for local tissue exposure. We note that the sponge formulation used in clinical study INN-CB-010 may be a potential dose group as the sponge has a higher concentration of bupivacaine (4.0 mg/cm^2) and collagen (3.0 mg/cm^2) than the 150 mg sponge proposed for clinical use (3.06 mg bupivacaine/cm^2 and 2.8 mg collagen/cm^2).**

- **Test both genders of rats in the 28-day study as the intraperitoneal anatomy of male and female rats are different. Evaluation of each gender is considered necessary in this single, pivotal toxicity study.**

- **As part of your serial investigations of the dosing site and sponge resorption, assess any impact on wound healing for the different treatment groups that includes macroscopic and microscopic evaluation.**

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- **Unless you are certain about the reversal of any local toxicity and complete resorption of the sponge by 28 days, you should consider including additional test animals to serve as a longer recovery group in the event that reversibility of any local toxicity effects or complete resorption of the sponge is not demonstrated by 28 days after dosing. As you will be conducting serial assessments of the dosing site and sponge throughout the course of the study, your best estimate for the length of any recovery period past 28 days can be justified based on the serial data through 28 days.**

This study must be conducted before any Phase 3 clinical trials are undertaken, since no nonclinical histological assessment for potential human local toxicity has been submitted for your drug product.

Discussion: The Sponsor asked if it would be possible to run the study concurrently with the Phase 3 study, noting the safety demonstrated in completed clinical trials. The Division stated that the Sponsor would need to provide an interim nonclinical report detailing the results of the 28-day implant period to support the safety of the clinical trial. The absence of significant local toxicity based on histopathologic evaluation would allow initiation of the Phase 3 clinical trial program. However, if the result of this interim assessment indicates either unacceptable toxicity or the need for long-term follow-up to evaluate resolution of observed toxicity, this could result in the ongoing clinical trials being placed on Clinical Hold.

If performed, the Sponsor confirmed that genotoxicity tests would be conducted on the drug substance, bupivacaine.

Chemistry, manufacturing and controls

Question 17

We received comments on the chemistry manufacturing and controls (CMC) section of our initial IND. A revised CMC section that addressed these issues and provided the fully updated information was submitted to the IND on September 17, 2010, as serial number 34. Does the Division agree that the CMC issues initially raised have been adequately resolved at this stage of the Product's development?

Response: No, we do not agree.

The September 17, 2010, amendment provides information on the 5 x 5 cm bupivacaine sponge product. A (b) (4) cm bupivacaine sponge will be used in the Phase 3 clinical trials. Submit complete CMC information for the (b) (4) cm bupivacaine sponge for review, prior to the initiation of the Phase 3 trials.

Note that limits of the (b) (4) will be assessed based upon exposures to these impurities from the (b) (4) sponge.

We do not agree with your proposal to exclude in vitro drug release as a part of your product specifications. (See additional biopharmaceutics comments.)

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With respect to the 5 x 5 bupivacaine sponge:
The September 17, 2010 amendment to the IND has been consulted to CDRH and Microbiology. Additional comments from the reviews by the respective disciplines will be communicated at a later date.

Additional Regulatory Comments
We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf . In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision. See Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf .

Note that you may only rely on the Agency's finding of safety and/or effectiveness as it is reflected in the approved labeling for the listed drug(s). You may not reference data in the Summary Basis of Approval or other FDA reviews obtained via the Freedom of Information Act or publically posted on the CDER website to support any aspect of your development program or proposed labeling of your drug product. Reviews are summary data only and do not represent the Agency's previous finding of safety and efficacy.

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Discussion: There was no further discussion on this question.

Additional Biopharmaceutics comments:

1. **An in vitro release test and appropriate acceptance criteria should be included in the product's quality specifications.**

2. **The development report for the in vitro drug release method evaluating the release of the drug from the proposed Bupivacaine Sponge product should be submitted in the NDA, in which the selection of the testing methodology, including the apparatus, rotation speed (if applicable), media and temperature should be fully justified to show the discriminating ability for identifying the quality problems if any. All the raw data**

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should be provided in the report, including the individual value, the mean, the standard deviation and the plots under different conditions. If the above information is available during the IND stage, you are encouraged to submit the development report to the Agency for review and comments.

3. **The in vitro drug release multi-point profile data from the bio-batches (clinical & PK studies) and primary stability batches should be collected and used for the setting of the acceptance criteria (i.e., specification-sampling time points and specification values). The in vitro release profile should encompass the timeframe over which at least (b)(4)% of the drug is being released. At least three specification time-points covering the initial, middle, and terminal phases of the complete release profile data should be set. The acceptance criteria ranges should be based on the overall release data generated at these times. In general, the selection of these ranges is based on mean target value ±(b)(4)% and NLT (b)(4)% for the last specification time-point.**

<u>Additional Nonclinical Comments</u>:
Note that these comments must be considered and addressed for your IND/NDA program. Some of the comments refer to the IND and some to the NDA.

1. **Include a detailed discussion of the nonclinical information in the published literature in your NDA submission and specifically address how the information within the published literature impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.**

2. **The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you will need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label. This bridging data should be submitted with the NDA.**

3. **New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance with the following guidance document: <u>Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005)</u> which is available on the CDER web page at the following <u>http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm</u>.**

As noted in the document cited above, "…the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we

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believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration." (emphasis added).

Discussion: The Sponsor stated that the only excipient that they use is collagen. The Division stated that this is not a novel excipient.

4. **Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in ICH Q3A(R2) and ICH Q3B(R2) guidances at the time of NDA submission.**

Adequate qualification would include:

   a. **Minimal genetic toxicology screen (two in vitro genetic toxicology studies; e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay**

   b. **Repeat dose toxicology of appropriate duration to support the proposed indication**

5. **Genotoxic or carcinogenic impurities, or impurities that contain a structural alert for genotoxicity, must be either reduced to NMT (b) (4) mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative in vitro bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICHS2A guidance document titled "Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals." Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT (b) (4) mcg/day, or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.**

6. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICHQ3A and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.**

7. **The NDA submission must contain complete and definitive safety information on potential leachables and extractables from the drug container closure system and/or drug product formulation as outlined in the FDA Guidance for Industry titled**

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"Container Closure Systems for Packaging Human Drugs and Biologics." The evaluation of extractables and leachables from the drug container closure system must include specific assessments for residual monomers, solvents, polymerizers, etc. Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents "Container Closure Systems for Packaging Human Drugs and Biologics" and "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation." Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf.

8. **Failure to submit adequate impurity qualification, justification for the safety of new excipient use at the time of NDA submission can result in a Refusal-to-File or other adverse action.**

ACTION ITEMS

1. The Sponsor agreed to submit the mathematical derivation of the 0.027 significance level according to Dunnett's method to the IND.

2. The Sponsor agreed to perform in vitro testing to determine the effects of (b) (4) on commonly used suture materials and surgical mesh.

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

/s/

ALLISON MEYER
01/12/2012