CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209511Orig1s000

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Cross-Discipline Team Leader and Division Director Summary Review

Date	August 28, 2020
From	Renee Petit-Scott, M.D.; Rigoberto Roca, M.D.
NDA Number	209511
Applicant	Innocoll Pharmaceuticals
Date of Original Submission	February 2, 2018
Date of Complete Response Submission	February 26, 2020 Complete Response Letter issued November 30, 2018
PDUFA Goal Date	August 26, 2020
Proprietary Name	Xaracoll
Established or Proper Name	Bupivacaine HCl collagen implants
Dosage Form	Implants
Applicant Proposed Indication	For placement into the surgical site in adults to produce postsurgical local analgesia following open inguinal hernia repair
Applicant Proposed Dosing Regimen	300 mg (3 x 100 mg implants) implanted into the surgical site
Regulatory Action	Approval
Indication	For placement into the surgical site in adults to produce postsurgical analgesia for up to 24 hours following open inguinal hernia repair
Dosing Regimen	300 mg (3 x 100 mg implants) implanted into the surgical site

Materials Reviewed, Teams Consulted	**Discipline Reviewers**
Statistical Review Team	Yi Ren, PhD; Jinglin Zhong, PhD
Pharmacology Toxicology Review Team	Gary Bond, PhD; Jay Chang, PhD; R. Dan Mellon, PhD
OPQ Review	Valerie Amspacher, PhD; Tarun Mehta, PhD; Yan Zheng, PhD; Elizabeth Bearr, PhD; Julia Pinto, PhD
Clinical Pharmacology Review	David Lee, PhD; Suresh Naraharisetti, PhD; Yun Xu, PhD
CDRH	Lixin Liu, PhD
OSI (initial review cycle)	Roy Blay, PhD; Phillip Kronstein, PhD; Kassa Ayalew, PhD
OSE/DMEPA	Cameron Johnson, PharmD; Otto Townsend, PharmD

CDRH=Center for Devices and Radiological Health
Division of Medication Error Prevention and Analysis
OPQ=Office of Pharmaceutical Quality
OSE= Office of Surveillance and Epidemiology
OSI=Office of Scientific Investigations

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1. Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Integrated Assessment

This is the second review cycle for NDA 209511. The previously identified nonclinical and product quality issues have been adequately addressed such that the benefit:risk profile supports the safe administration of INL-001 (proposed tradename Xaracoll®) into the surgical site in adults for postsurgical analgesia for up to 24 hours following open inguinal hernia repair. The Applicant has modified the proposed indication to include only the surgical procedure extensively evaluated during Phase 3 clinical development. As discussed in detail in Section 2, Background, the deficiencies that resulted in issuance of a Complete Response Letter (CRL) during the first review cycle included inadequate systemic safety data, invalid in vivo micronucleus assay, inadequate extractable/leachable assessment for the container closure system, and inadequate (b) (4) (b) (4) specification.

INL-001 is a sterile, resorbable, biodegradable (b) (4) porous bupivacaine collagen-matrix implant comprised of 100 mg bupivacaine HCl (bupivacaine) and 75 mg Type I bovine collagen in each of three implants measuring 5 cm x 5 cm x 0.5 cm. The maximum recommended dose of bupivacaine is 300 mg for patients undergoing open inguinal hernia repair. Upon placement into the surgical site, bupivacaine is solubilized, by absorption of fluid from the surrounding tissues into matrix, and released over time. Nonclinical studies indicate that approximately 57% of the bupivacaine is released within the first hour, 81% is released by eight hours, and 99% released by 24 hours.

The collagen, obtained from the Achilles tendons of (b) (4) closed herds certified as transmissible bovine spongiform encephalopathy-free (b) (4), undergoes chemical and enzymatic hydrolysis resulting in soluble peptides and amino acids, which are absorbed into the surrounding tissues. The Applicant states that the collagen confers no therapeutic benefit and that its only purpose is support the slow release of bupivacaine. Nonclinical data indicate the collagen implant is degraded and absorbed by Day 56 post-implantation. In response to Information Requests sent during the first review cycle, the Applicant provided additional data indicating that the collagen matrices do not appear to change size (specifically increase) during the dissolution process, a potential clinical concern if administered in surgical locations other than the inguinal hernia wound.

The Applicant's Phase 3 clinical development program included two studies conducted in patients undergoing open inguinal hernia repair, Study INN-CB-014 and INN-CB-016. In each study, approximately 300 patients were stratified by gender and history of previous inguinal hernia repair with mesh and randomized in a 2:1 ratio to receive either INL-001 (300 mg bupivacaine) or placebo collagen matrices. The primary efficacy endpoint in both studies was timeweighted sum of pain intensity from 0 to 24 hours (SPI24), and key secondary efficacy endpoints included total opioid use (i.e., TOpA24, TOpA48, TOpA72) and SPI (i.e., SPI48, SPI72) through different time points. As discussed in both Dr. Renee Petit-Scott's primary clinical review and Dr. Martha Van Clief's cross discipline team leader review, the combined analysis of the primary efficacy endpoint was statistically significant for the INL-001 treatment group compared to the placebo group. Specifically, there appeared to be approximately a 22% reduction in SPI24 in patients treated with INL-001 compared to those treated with placebo implants. The limitation of these studies, however, is that there was no active comparator, such that the observed improvement in postsurgical pain would likely be less clinically meaningful when compared to bupivacaine, the most commonly administered local anesthetic for postsurgical analgesia, administered

either as wound infiltration or for peripheral nerve blockade.

In Study INN-CB-014, none of the key secondary SPI efficacy endpoints reached statistical significance, but in Study INN-CB-016, SPI48 was significant with a p-value of 0.027. Some of the key secondary total opioid use efficacy endpoints did reach statistical significance, including TOpA24 in both studies, and TOpA48 in Study INN-CB-016. The median values presented by the Applicant, however, were more impressive than the mean values, and overall differences in post-operative opioid use were small and likely not clinically significant. Analysis of TOpA48 in Study INN-CB-014 and TOpA72 in Study INN-CB-016 demonstrated p-values of 0.0248 and 0.0016, respectively, however, these were not statistically significant due to hierarchical testing. An evaluation of the proportion of patients opioid-free in the INL-001 and placebo treatment groups for both studies demonstrated differences of unknown clinical significance. Specifically, in Study INN-CB-014, 36% of patients who received INL-001 were opioid-free through 72 hours, compared to 22% of patients treated with placebo matrices. In Study INN-CB-016, 28% of patients treated with INL-001 were opioid-free through 72 hours, compared to 12% of patients treated with placebo matrices. The time to first opioid rescue in patients treated with INL-001 compared to patients treated with placebo matrices was likely clinically meaningful in both studies. Specifically, the median time to first opioid rescue analgesia in INL-001 and placebo treatment groups was 11 hours and 1 hour, respectively, in Study INN-CB-014, and 6 hours and 1 hour, respectively in Study INN-CB-016.

As described in Dr. Petit-Scott's primary clinical review, the safety issues of most clinical significance associated with administration of INL-001 are the development of local anesthetic systemic toxicity (LAST) and adverse events related to impaired or delayed wound healing. The risk of developing LAST after administration of INL-001 is related to the variable pharmacokinetic (PK) profile, the fact that the pharmacodynamic (PD) effect is unrelated to the systemic bupivacaine concentration, patients will likely be in an unmonitored setting at the time of maximum concentration (T_{max}), and the total dose of bupivacaine exceeds that recommended for the reference drug, Marcaine™. The Applicant's clinical development program evaluated 612 patients who received a dose of INL-001 and 469 patients received that maximum recommended dose, 300 mg bupivacaine. There was a single patient in a Phase 2 study who developed presumed LAST after receiving INL-001 150 mg during bladder sling surgery. This patient developed chest pain, ECG changes, including QT prolongation, and refractory hypotension post-operatively and was treated with IV fluids, vasopressor agents, electrolyte replacement, lipid emulsion, and ultimately removal of the matrices. Her maximum bupivacaine plasma concentration (C_{max}) was 900 ng/mL measured 22 hours post-operatively, about the time the patient returned to the operating room for removal of the matrices. During the evaluation and treatment of chest pain, the patient received a "GI cocktail", which included lidocaine. The additional lidocaine may have contributed to on-going symptoms of LAST. The Applicant has suggested this may have been a case of drug allergy, either to antibiotic or neuromuscular blocking drugs, versus LAST. This is unlikely given the absence of typical allergic symptoms, such as wheezing, urticaria, or angioedema; normal IgE levels measured during the hypotensive episode; and improvement in the patient's symptoms after removal of the matrices. There were no reported cases of LAST in patients who received the maximum recommended dose of INL-001 during the Phase 3 studies, and review of the neurological assessment data and the 24-hour ECG data captured via Holter monitoring did not identify clinically significant differences between the INL-001 and placebo treatment groups.

Risk mitigation strategies for the development of LAST after administration of INL-001 include the following:

1. Limited postsurgical use. The product label recommends administration of INL-001 in the surgical population for which the safety and

efficacy data were thoroughly evaluated, open inguinal hernia repair. In this review cycle, the Applicant has modified the indication.
2. Adequate neurological and cardiac monitoring, and resuscitative medications and airway equipment must be immediately available in all facilities where INL-001 is administered.
3. Because a large number of patients will be in an unmonitored setting during C_{max}, patient and caregiver post-operative instructions must include adequate education regarding signs and symptoms of LAST.
4. Because the toxic effects of local anesthetics are additive, additional local anesthetic administration should be avoided for 96 hours after administration of INL-001. This information is including in the prescribing information.

The potential for adverse would healing after administration of INL-001 was extensively evaluated by Dr. Petit-Scott during the initial review cycle. There did appear to be an increased incidence in some wound-related adverse events, such as incision site pain and incision site swelling, in patients who received INL-001 or the placebo matrices compared to patients who received comparator treatments, including immediate-release bupivacaine. More concerning wound-related adverse events, such as dehiscence and post-procedural discharge, were also observed with increased frequency in patients treated with either INL-001 or placebo matrices; however, the overall incidence was low and consistent with reports in the published literature for patients undergoing the same surgical procedure. Additionally, there did not appear to be any long-term adverse events related to impaired healing. Dr. Petit-Scott concluded that the amount of collagen in INL-001, history of previous inguinal hernia repair, or other surgical procedure performed did not impact the overall incidence of wound-related adverse events.

There are two advantages of bupivacaine administration using the INL-001 technology, resulting in an improved safety profile over other injectable bupivacaine products. First, the unique route of administration obviates the risk of catastrophic intravascular injection. High bupivacaine plasma concentrations may still be observed in the case of administration during highly vascular surgeries, but limited surgical indications can adequately mitigate this risk. And second, in the event of LAST, INL-001 can be surgically removed, as was done in the single patient who developed LAST during clinical development. This is a unique mitigation strategy not currently available for any other marketed bupivacaine product.

In conclusion, INL-001 has been shown to be a safe and efficacious treatment for the management of postsurgical pain following open inguinal hernia repair. The duration of analgesic benefit appears to be 24 hours, possibly longer as demonstrated in Study INN-CB-016. While some of the TOpA efficacy endpoints (i.e., TOpA24 for Study INN-CB-014, and TOpA24 and TOpA48 for Study INN-CB-016) did demonstrate a statistically significant reduction in median post-operative opioid use, the mean values were relatively small and likely not clinically significant. The clinical significance of the observed differences in the proportion of patients opioid-free may be unclear; however, the increased time to first opioid rescue in patients treated with INL-001 compared to those treated with placebo matrices likely provides additional clinical benefit, and enhances the favorable benefit:risk profile of this medication.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Inguinal hernia repair is a commonly performed soft tissue surgical procedure, particularly in men. Many of these procedures are performed using minimally invasive techniques, such as laparoscopy or robot-assisted, in an attempt to minimize postsurgical pain, improve recovery time, and improve patient outcome. However, there are still a large number performed via the open technique due to patient body habitus, history of previous abdominal or hernia surgery, size of the inguinal hernia, or surgeon/patient preference. • Postsurgical pain after open inguinal hernia repair is more severe than that observed after minimally invasive hernia surgery, resulting in the need for longer-acting local anesthetics to minimize postsurgical opioid use. • Many inguinal hernia repairs are performed in outpatient ambulatory surgical centers in an attempt to lower healthcare costs and improve efficiency, which involves adequate management of postsurgical pain. • Efficacious, rapidly-acting, and extended duration of action are the goals of all postsurgical pain management strategies and while there are a number of opioid analgesics that meet these criteria, the large numbers of opioid-related adverse events and deaths are a clear indication that alternate treatment options are needed.	**While exposure to bupivacaine may be low in the general population, patients undergoing a surgical procedure have a high likelihood of receiving bupivacaine. Due to the disease process and anatomic pathology, the development of an inguinal hernia is more common in male patients, suggesting the post-market exposure to INL-001 will be primarily in males.** **Inguinal hernias can be bilateral and can recur, potentially resulting in repeat exposure to bupivacaine products, either in the same location or a new location.**
Current Treatment Options	• Current treatment options for postsurgical pain include the following: – opioid analgesics – non-opioid analgesics – local anesthetics for wound infiltration, peripheral nerve blockade, or neuraxial anesthesia • For acute postsurgical pain that develops into a chronic or neuropathic condition, antidepressants, gabapentanoids, and anti-seizure medications can also be used.	**While there are several marketed, approved bupivacaine products for use in the management of postsurgical pain, none have an extended release profile that reliably prolong postsurgical analgesia beyond that observed after administration of immediate release bupivacaine. Extended release formulations of local anesthetics may address an unmet need if the duration of analgesia is able to reliably cover the period of moderate to severe**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Non-traditional therapeutic strategies have also been employed, including acupuncture and massage therapy. Physical therapy can be used for a variety of musculoskeletal disorders, as well as other painful conditions, including post-operative neuropathy and disability. • Of the local anesthetics available for postsurgical pain management, lidocaine, ropivacaine, and bupivacaine, with and without epinephrine, are the most commonly used. Ropivacaine and bupivacaine are considered longer-acting than lidocaine and may provide up to eight hours of postsurgical pain relief when administered via wound infiltration. • There are currently no approved local anesthetics with an extended release or slow release profile that have demonstrated reliable prolonged postsurgical analgesia. A continuous infusion of a dilute concentration of bupivacaine or ropivacaine via a peripheral nerve or neuraxial catheter appears to be the only available mechanism to prolong the duration of action of bupivacaine.	**postsurgical pain.** **Approval of INL-001 would provide clinicians an additional, potentially longer-acting bupivacaine product for use in the management of postsurgical pain. The results from the Applicant's Phase 3 studies have demonstrated improved sum of pain intensity over 24 hours after INL-001 administration when compared to placebo treatment.** **While some total opioid use efficacy endpoints reached statistical significance, the differences were small and the clinical significance was less clear. There were, however, clinically significant differences in the proportion of patients opioid-free and time to first opioid rescue in patients treated with INL-001 compared to placebo in open inguinal hernia repair.**
Benefit	• The Applicant conducted two placebo-controlled Phase 3 studies (INN-CB-014 and INN-CB-016) in patients undergoing open inguinal hernia repair. In each study, approximately 300 patients were stratified by gender and history of previous hernia repair, and randomized in a 2:1 ratio to receive either INL-001 (three 100 mg collagen matrices for a total of 300 mg of bupivacaine) or placebo collagen matrices. • The results from both studies demonstrated a statistically, and clinically, significant difference in the timeweighted sum of pain intensity from 0 to 24 hours, the primary efficacy endpoint. Several key secondary efficacy	**The Phase 3 studies demonstrated statistically, and clinically, significant differences in sum of pain intensity over 24 hours between the INL-001 and placebo treatment groups. Therefore, the evidentiary standard for approval has been met. Additionally, while the clinical significance of the differences in the proportion of patients opioid-free between the INL-001 and placebo treatment groups is unknown, the increased time to first opioid rescue in patients treated with INL-001 likely provides additional clinical benefit to individual patients.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	endpoints also reached statistical significance, including total opioid analgesic use; however, the clinical significance of the observed differences in opioid use between the treatment groups is unclear. • Observed differences in the proportion of patients opioid-free and time to first opioid use between treatment groups were clinically significant. • INL-001 would provide clinicians with an additional bupivacaine product for use in the management of postsurgical pain following open inguinal hernia repair. • Two clear advantages of INL-001 over other injectable bupivacaine products are the route of administration, such that there is no risk of catastrophic intravascular injection, and the ability to remove the matrices in the event of LAST.	**Approval of INL-001 would offer clinicians an additional bupivacaine product to administer for the management of postsurgical pain after open inguinal hernia repair. It may provide longer postsurgical analgesia than currently approved products.** **Additional benefits of INL-001 include the following:** **– Bupivacaine is a widely-used local anesthetic with a long history of clinical use and a large safety database.** **– While each matrix is a standard size, they can be cut to accommodate a variety of surgical sites.** **– The route of administration, implantation without a needle, eliminates the risk of intravascular injection.** **– In the event of LAST, the matrices can be surgically removed, as was the case in one patient during clinical development.**
Limitations, and Risk and Risk Management	• A limitation of the Applicant's Phase 3 studies is the use of a placebo control versus an active comparator. Bupivacaine, administered either as wound infiltration or for peripheral nerve or neuraxial block, is considered standard of care for the management of postsurgical pain, suggesting that the comparison to a placebo treatment is clinically meaningless. However, while the Division recommends Sponsors of potentially extended-release local anesthetic formulations use active comparators in Phase 3 development, the regulatory threshold requires superiority over a placebo. • The two safety concerns associated with administration of INL-001 are LAST and wound-related adverse events. Dr. Petit-Scott evaluated both concerns extensively during the	**Despite the bupivacaine dose in INL-001 being greater than the maximum recommended dose in the Marcaine drug product label, there were no reported cases of LAST in the Applicant's Phase 3 studies, which evaluated the maximum proposed dose. The only case of presumed LAST was reported for a female patient who received 150 mg during bladder sling surgery, a procedure for which INL-001 is not indicated.** **Review of the neurological assessment data and the 24-hour ECG data captured via Holter monitoring did not identify other cases of bupivacaine toxicity. Risk mitigation strategies for the development of LAST after treatment**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	initial review cycle and concluded the following: – While the dose of bupivacaine administered with INL-001 is higher than that recommended in the Marcaine drug product label, the risk of LAST appears low, and adequate mitigation strategies are described in the INL-001 label (i.e., limited surgical population, monitoring, availability of resuscitative medications and equipment, and patient education). – While there was an increased incidence of wound-related adverse events in patients who received either INL-001 or the placebo collagen matrix when compared to patients who received a comparator treatment, the adverse events which occurred with the highest incidence, incision site pain and swelling, are not unexpected given the size of the matrices. Additionally, of the adverse events considered more clinically concerning, wound dehiscence and drainage, the reported incidences are consistent with reports in the published literature in patients undergoing open inguinal hernia repair.	**with INL-001 include the following:** – **Limited surgical population; i.e., open inguinal hernia repair.** – **Continuous intra- and post-operative monitoring.** – **Immediate availability of resuscitative medications, including lipid emulsion, and equipment.** – **Patient and caregiver education regarding signs and symptoms associated with LAST.** – **Avoid additional local anesthetic administration for 96 hours following administration of INL-001.**

2. Background

This document will serve as the Cross-Discipline Team Leader (CDTL) and Division Director Summary review of new drug application (NDA) 209511 for the decision on regulatory action following resubmission on February 26, 2020.

NDA 209511 was initially submitted for approval through the 505(b)(2) regulatory pathway on February 2, 2018, for Xaracoll®, also referred to as INL-001, a bupivacaine collagen-matrix, indicated for the management of postsurgical pain. The Applicant, Innocoll Pharmaceuticals (Innocoll), was relying on the Agency's previous findings of safety and efficacy for Marcaine (NDA 016964). Based on unresolved issues regarding the systemic safety of the proposed bupivacaine dose, a valid in vivo micronucleus bupivacaine assay, the extractables/leachables evaluation to support the safety of the container closure system, and the proposed specification for (b) (4) in the drug product formulation, the application received a Complete Response Letter (CRL) on November 30, 2018. The following is a summary of the identified deficiencies, by discipline, and the information needed to adequately address them (refer to the CRL for additional information).

Nonclinical

1. The characterization of the systemic safety of bupivacaine exposures via the INL-001 formulation was inadequate. Specifically, based on the existing human pharmacokinetic data, administration of INL-001 results in an area under the curve $(AUC)_{0\text{-last}}$ that is twice that of the referenced product. The existing toxicology data in the rat model did not provide coverage for the human exposures via INL-001.

   To address this deficiency
   Conduct adequate toxicology studies in two species that provide adequate coverage for the proposed human exposures via INL-001 or provide clinical data to support the safety of the proposed exposure.

2. The in vivo micronucleus assay for bupivacaine was invalid. Specifically, the high dose selected for the assay did not result in frank toxicity.

   To address this deficiency
   Repeat the in vivo micronucleus assay for bupivacaine testing doses that results in frank toxicity in accordance with the ICH guidance document: *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use.*

3. The extractables/leachables evaluation to support the safety of the proposed container closure system was inadequate. Specifically, while the extraction study submitted was capable of detecting compounds at the requested safety concern threshold of (b) (4) mcg/day, many of the compounds detected above this safety threshold were not described. Further, the leachables data from multiple batches at release with compounds identified in the extraction study targeted using validated methods was not adequate.

To address this deficiency
Identify the compounds detected in the extraction studies completed to date and evaluate the drug product stability batches for the presence of any extractable detected at (b) (4) mcg/day or higher. Provide a toxicological risk assessment for any leachable compound present in the drug product at (b) (4) mcg/day or greater.

4. The justification for the proposed specification for (b) (4) in the drug product formulation was not adequate.

   To address this deficiency
   Either reduce the specification for (b) (4) to NMT (b) (4) mcg/day or provide an adequate toxicological risk assessment for this compound to justify the proposed specification in accordance with the ICH guidance document: *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.*

Product Quality

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

   To address this deficiency:
   a. From the robust extractables profiles of both primary and secondary packaging, identify and determine the target leachables.
   b. Develop methods which can detect these leachables in the drug product.
   c. Test 3 batches of drug product at multiple time-points on stability with emphasis on (b) (4) manufactured product that includes ink labeling on individual blisters as planned for commercial product.

During the initial review cycle, Dr. Petit-Scott, clinical reviewer, recommended approval of INL-001 300 mg for the management of postsurgical pain following open inguinal hernia repair, and there were no clinical concerns that impacted the approvability of INL-001; however, Dr. Petit-Scott did include an additional comment in the CRL regarding the proposed indication and the unlikelihood of a broad postsurgical analgesic indication. She determined that INL-001 should be indicated for only those procedures in which the drug product was tested and demonstrated to be safety and effective.

Regarding the efficacy of INL-001, Dr. Petit-Scott concluded that when formulated in the collagen matrix, bupivacaine did appear to demonstrate an extended release profile, which resulted in statistically and clinically significant postsurgical analgesia through 24 hours. In addition to a reduction in sum of pain intensity post-operatively, Dr. Petit-Scott noted that administration of INL-001 resulted in a reduction in total opioid analgesic use through 24 hours for both Phase 3 studies, and through 48 hours in one Phase 3 study, and an increased

percentage of patients who were opioid-free through 72 hours compared to patients treated with placebo collagen matrices. Additionally, the time to first opioid analgesic rescue was clinically meaningful in patients treated with INL-001.

The regulatory history and Applicant interactions following issuance of the CRL are summarized in the following table.

Meeting/Communication/Date	Event/Key Issues Identified
Complete Response Letter, November 30, 2018	– No clinical issues identified that contributed to the CR action; however, the Applicant was again advised that INL-001 would likely be indicated for only those surgical procedures in which it was demonstrated to be safe and effective. – Nonclinical and product quality issues described in the CRL included inadequate systemic safety data, invalid in vivo micronucleus assay, inadequate extractable/leachable assessment for the container closure system, and inadequate (b) (4) specification.
Type A, Post-Action Meeting, May 28, 2019	– The Applicant submitted additional PK information, using nonparametric superimposition (NPS) methods with various dosing regimens, to establish a scientific bridge between INL-001 300 mg and Marcaine 400 mg. The Division indicated that the proposal dosing regimens are not clinically relevant and exceed the recommended bupivacaine dose of 2.5 mg/kg. Additional information was submitted post-meeting to support the PK bridge from INL-001 300 mg to Marcaine 400 mg, using data from Study INN-CB-022 in which Marcaine 175 mg was administered. The Division stated that the PK results after administration of INL-001 300 mg demonstrated similar systemic exposure to that predicted after administration of a single Marcaine 400 mg dose using NPS estimation. – The Division advised that if the NPS method did not provide adequate systemic safety information, toxicology studies in two species would be required. Dog would be an acceptable nonrodent animal to evaluate the proposed clinical dosing of INL-001. – The Applicant proposed the limited indication of postsurgical analgesia after open inguinal hernia repair. The Division stated that the data from the Phase 3 studies would likely support this indication. – Information required for the safety update, nonclinical summary, and clinical summaries were discussed.
Type C, Written Responses Only, October 29, 2019	Information needed to resolve the extractable/leachable CR deficiencies was discussed.
NDA 209511 Resubmission, February 26, 2020	The Division determined the submission was a complete response and acceptable for review. A PDUFA goal date of August 26, 2020, was set.

For information regarding the regulatory history and communications that were reviewed during the first cycle, refer to the clinical review completed by Dr. Petit-Scott on November 30, 2018.

3. Product Quality

Based on evaluation of the information included in the NDA resubmission, the Applicant adequately addressed the outstanding product quality issues that contributed to the CR action during the initial review cycle. The following is a summary of the product quality review, adapted from the quality review team.

Product Overview

INL-001 is supplied as three sterile surgical implants (5 cm x 5 cm x 0.5 cm), each containing 100 mg of bupivacaine HCl and 75 mg of Type I purified collagen in individually sealed blister packs. Type I purified collagen serves as an inert delivery system and releases the bupivacaine through dissolution and diffusion from the porous implant. As described in Section 6, Clinical Microbiology, of this review, the implant consists of purified Type I bovine collagen containing (b) (4)% of bupivacaine HCl. (b) (4)

(b) (4)

Facilities Review/Inspection

Per the OPQ review, there are no changes in facilities since the first review cycle, and all facilities are in Approve status.

Quality Assessment Overview

Drug Product

The Applicant has adequately responded to the identified extractable/leachable deficiency and provided additional stability data, including supportive data for the 24-month expiry and temperature storage conditions.

Biopharmaceutics

The Applicant submitted all requested stability dissolution data, including individual values through the proposed expiry period, and the team concluded this assessment was adequate.

Microbiology

The Type I collagen contained in each INL-001 matrix is purified from bovine Achilles tendons (b) (4)

(b) (4) The Applicant stated that the tendons are obtained from closed herds, which have been certified as transmissible (TSE) and bovine (BSE) (b) (4) spongiform encephalopathy-free

(b) (4)

[redacted] The microbiology review team concluded the information and official statement provided were adequate to ensure all products are TSE- and BSE-free. For additional information regarding the bovine collagen processing, refer to the review completed by Drs. Elizabeth Bearr and Yan Zheng.

The product presentation, container closure system, manufacturing site, [redacted] validation data, manufacturing process, product release specification and testing methods for sterility and endotoxins were unchanged and found to be adequate during the first review cycle.

I concur with the conclusion of the product quality review team that the previously identified extractable/leachable deficiency has been adequately addressed and there are no outstanding issues that would prevent approval.

4. Nonclinical Pharmacology/Toxicology

Based on evaluation of the information included in the NDA resubmission, the Applicant adequately addressed the outstanding nonclinical issues that contributed to the CR action during the initial review cycle. The following is a summary of the conclusions from the pharmacology-toxicology review (adapted).

The Applicant provided information to address each of the four deficiencies noted in the CR Letter. To address the systemic safety of bupivacaine, the Applicant provided clinical PK information to demonstrate that the systemic exposure to bupivacaine after administration of Xaracoll at the maximum recommended human dose (MRHD) is within the range of exposure after administration of the MRHD of the reference product, Marcaine 400 mg. As noted in the clinical pharmacology review completed by Dr. Naraharisetti, discussed in Section 5, the additional PK information extends the scientific bridge between Xaracoll and Marcaine, and addresses the first CR nonclinical deficiency.

The Applicant provided new data to adequately address the remaining three deficiencies from a nonclinical perspective. Specifically, an adequate in vivo micronucleus study was submitted which demonstrated that bupivacaine is negative for clastogenicity under the conditions of the test. New extractable/leachables data, including a sufficiently robust extractables study and sufficient leachables stability methodology and testing, were submitted to adequately justify the safety of the container closure system. The Applicant reduced the specification for [redacted] so that the potential daily exposure would be within the acceptable daily intake as per ICH M7 for potentially genotoxic impurities.

The pharmacology-toxicology review team concluded that all of the previously identified deficiencies have been adequately addressed, and I concur that there are no additional nonclinical concerns that would prevent approval of Xaracoll. The team did note, however, that results from a GLP bone healing study in rats subjected to an osteotomy procedure, which evaluated torsional strength testing, radiologic evaluations, microCT data, and

histopathological evaluations, suggested that the bupivacaine collagen implant inhibited bone healing compared to control treatments, including immediate-release bupivacaine. An additional non-GLP study was conducted in sheep, however, the endpoints used to evaluate bone healing were inadequate. While there were no clinical studies evaluating the effect of this drug product on bone healing, there is concern that Xaracoll may be used off-label during orthopedic procedures, such as total joint arthroplasty. Therefore, the pharmacology-toxicology review team recommends the following language be included in Section 13.2 of the label:

> Bupivacaine collagen implants delayed bone healing in a rat osteotomy model compared to saline, bupivacaine, or placebo-collagen matrix alone. The clinical significance of these delays is not known.

I concur with this recommendation, and the following Limitations of Use statement is included Section 1:

> Safety and efficacy have not been established in other surgical procedures, including orthopedic and boney procedures.

5. Clinical Pharmacology

There were no new clinical pharmacology data submitted to support approval of INL-001; however, the Applicant provided additional information from nonparametric superposition (NPS) methods to extend the PK bridge to a Marcaine 400 mg/day dose to support the clinical use of bupivacaine 300 mg.

During the first review cycle, the clinical pharmacology review team did not identify any deficiencies that would have prevented approval; however, the pharmacology-toxicology review team included inadequate characterization of the systemic safety of bupivacaine exposure via Xaracoll as a deficiency. To address this, the Applicant utilized nonparametric superposition (NPS) method to bridge the systemic exposure of Xaracoll, determined during the completed PK study, to that of Marcaine 400 mg/day, the listed drug. As noted in Dr. Naraharisetti's review, this method of bridging is acceptable, and the following was included in his review.

> "The rate and extent of bupivacaine absorption, as assessed by C_{max} and AUC_{inf} following implantation of 300 mg of XARACOLL were lower by ~25 to 54% and ~ 12%, respectively compared to those predicted for three different 400 mg dosage paradigms of MARCAINE. These results extend the scientific bridge between XARACOLL and MARCAINE, and addresses CRL nonclinical deficiency #1 regarding inadequate characterization of the systemic safety of bupivacaine exposure via XARACOLL."

Refer to the clinical pharmacology review completed by Dr. Naraharisetti for additional information regarding the PK profile of the proposed 300 mg dose of Xaracoll.

I concur with Dr. Naraharisetti's conclusion that there are no clinical pharmacology concerns that would prevent approval of Xaracoll.

6. Clinical Microbiology

INL-001 is not a therapeutic antimicrobial agent, therefore, clinical microbiology data were neither required or submitted.

7. Clinical/Statistical- Efficacy

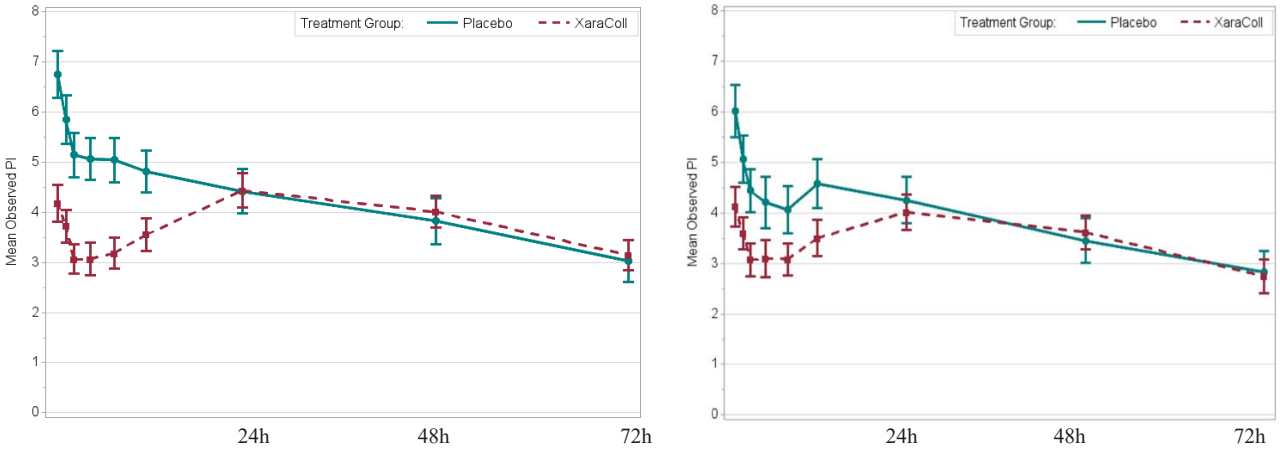
There were no deficiencies related to the efficacy of INL-001 identified during the initial review cycle, therefore, the Applicant did not submit additional efficacy data from completed clinical studies in the NDA resubmission. Clinical efficacy data reviewed during the initial NDA review cycle included results from two adequate and well-controlled Phase 3 studies in adult patients undergoing open inguinal hernia repair with mesh. Exploratory Phase 2 clinical studies were conducted in the same surgical model, as well as in patients undergoing total abdominal hysterectomy, other benign gynecological and abdominal procedures, and laparoscopic cholecystectomy. The following will be a high-level discussion of the efficacy data submitted during the initial review cycle. For additional information, refer to the clinical review completed by Dr. Petit-Scott, and the Division Summary Review for Regulatory Action and the Cross-Discipline Team Leader Review completed by Drs. Roca and Van Clief.

The Applicant evaluated the efficacy (and safety) of INL-001 300 mg (three 100 mg matrices) compared to three placebo collage matrices in patients undergoing open inguinal hernia repair with mesh in two Phase 3 studies, INN-CB-014 and INN-CB-016. Results from the primary efficacy endpoint analyses indicated a statistically and clinically significant improvement in post-operative pain, assessed using time-weighted sum of pain intensity from 0 to 24 hours (SPI24), in patients treated with INL-001 compared to those treated with placebo. In a combined analysis of the primary efficacy endpoint, there appeared to be a 22% reduction in SPI24 in patients treated with INL-001.

While the results of the primary efficacy endpoint analyses demonstrated statistically significant differences through 24 hours post-operatively, the Division is most interested in sustained analgesia through 72 hours for newer formulations of local anesthetic products. Therefore, Dr. Yi Ren, statistical reviewer for this application, calculated mean pain intensity scores and plotted those through the 72-hour post-operative period. For both Phase 3 studies, there does not appear to be any benefit INL-001 after the 24-hour time point. In fact, the mean pain intensity curves for INL-001 and placebo appear to converge at exactly the 24-hour time point, as indicated in the following figures.

Mean Pain Intensity Scores Through 72 Hours

Study INN-CB-014 **Study INN-CB-016**



Source: Dr. Yi Ren, statistical reviewer analyses, internal correspondence.

Additional statistically significant efficacy endpoints included reduction in total opioid use through 24 hours (TOpA24) in Study INN-CB-014. In the same study, analysis of the TOpA48 endpoint had a p-value of 0.0248; however, due to hierarchical testing, this was not considered statistically significant. In Study INN-CB-016, the secondary efficacy endpoints of TOpA24, SPI48, and TOpA48 were statistically significant between the INL-001 and placebo treatment groups. Regarding percentage of patients who were opioid-free, 36% of INL-001-treated patients in Study INN-CB-014 and 28% of INL-001-treated patients in Study INN-CB-016 were opioid-free through 72 hours compared to 22% and 12% of placebo-treated patients, respectively. Time to first opioid rescue analgesia was statistically and clinically significantly different between the INL-001 and placebo treatment groups for both studies. Specifically, the median time to first opioid rescue analgesia was 10.7 hours in INL-001-treated patients and 1 hour in placebo-treated patients in Study INN-CB-014, and 6.2 hours and 0.9 hours, respectively, in Study INN-CB-016.

In conclusion, INL-001 administered during open inguinal hernia repair is an efficacious postsurgical analgesic through 24 hours. Evaluations in other soft tissue surgical procedures in Phase 2 studies did not consistently demonstrate a clinical benefit over an active comparator or placebo treatment, depending on the study. Based on communications during the initial filing and NDA review, the Applicant has modified the proposed indication to include only patients undergoing open inguinal hernia repair.

8. Safety

The Applicant did not submit additional safety information for adult patients, as there are no ongoing clinical studies in adults. The following information is adapted from Dr. Petit-Scott's clinical review.

The safety database for the INL-001 development program included patients from one Phase 1 study, six Phase 2 studies, two PK/BA studies, and two Phase 3 studies. A total of 944 patients were enrolled in the clinical studies; 892 patients received the collagen-matrix implant, 612 received INL-001 and 280 received the placebo implant, and 52 patients received a comparator treatment. Of the 892 patients who received a collagen-matrix implant, 816

underwent inguinal hernia repair, 69 subjects underwent hysterectomy, and 7 underwent other types of soft tissue surgeries, including benign gynecological procedures. The bupivacaine doses administered via the INL-001 matrices ranged from 100 mg to 300 mg. Of the 52 patients who received a comparator treatment, 12 patients received bupivacaine 150 mg with epinephrine wound infiltration, 16 patients received bupivacaine 175 mg wound infiltration, 13 patients received the ON-Q® PainBuster System (900 mg bupivacaine infused over 72 hours), and 11 patients received standard of care which did not include bupivacaine administration.

The two main safety concerns surrounding the clinical use of the bupivacaine collagen-matrix product that were extensively evaluated during review of this NDA included the risk of the development of LAST and the potential adverse impact on wound healing.

The risks of developing LAST after administration of INL-001 are related to the following.

- The variable PK profile for INL-001, as determined in the Applicant's PK/BA studies. Specifically, C_{max} ranged from approximately 663 ng/mL to 1230 ng/mL and T_{max} ranged from approximately 1.5 to 24 hours.
- The pharmacodynamic response does not correlate with systemic bupivacaine concentrations, suggesting patients could develop symptoms of LAST without meaningful analgesia.
- Open herniorrhaphy is often performed on an outpatient basis, such that many patients will be in an unmonitored setting during the time of peak systemic exposure and potential toxicity.
- The total maximum dose of bupivacaine delivered via the collagen-matrix, which is greater than that recommended in the Marcaine product label.

Despite these known risks, the totality of the data support approval of INL-001 for administration during open inguinal hernia repair for five reasons. First, there were 612 patients exposed to a dose of INL-001 and 469 patients received the maximum recommended dose, 300 mg bupivacaine HCl, and there was only a single patient who experienced what appeared to be LAST (refer to Dr. Petit-Scott's clinical review completed during the initial review cycle for additional information). Second, a comprehensive evaluation of adverse events likely associated with early neurotoxicity, including dysgeusia and tinnitus, indicated that the incidence was similar in both the INL-001 and placebo treatment groups. Furthermore, a larger number of placebo-treated patients in Study INN-CB-016 experienced both dysgeusia and tinnitus when compared to INL-001-treated patients. Third, the evaluation of continuous 24-hour Holter data from the PK/BA studies did not suggest an increased incidence of ECG changes indicative of bupivacaine-induced cardiotoxicity. Additionally, there were no ECG changes or cardiac adverse events reported for the patient with the highest observed plasma concentration, 1230 ng/mL, after INL-001 administration. Fourth, the risk of developing LAST can be mitigated by adequate safety monitoring and limited use of INL-001 in the surgical population most extensively evaluated, open inguinal hernia repair. And lastly, while not an ideal risk mitigation strategy for presumed LAST, surgical removal of the matrices is a unique option that is not available for other bupivacaine-containing formulations. The single patient who experienced LAST during bladder sling surgery did return to the operating room for removal of the matrices, which likely contributed to her clinical improvement.

The potential adverse impact on wound healing is the other main safety concern associated with administration of INL-001. Initial review of the Applicant's Phase 1, 2, and Phase 3 studies indicated an increased incidence of wound-related adverse events in patients treated with the collagen implant, either as INL-001 or as the placebo collagen-matrix, when compared to patients treated with a comparator, such as bupivacaine. Incision site pain and incision site swelling were reported with the highest incidences; however, the more concerning adverse events of wound dehiscence and post-procedural discharge were also reported with a higher incidence in collagen-matrix-treated patients. While the increased incidence is concerning, the overall numbers were low and consistent with reports in the published literature after the same surgical procedure without the implanted collagen matrix. Additionally, there did not appear to be any long-term adverse events related to impaired healing.

During the initial review cycle, Dr. Petit-Scott evaluated wound-related adverse events by surgical procedure, amount of Type I collagen per matrix, and history of previous ipsilateral hernia repair. She concluded that only history of previous ipsilateral hernia repair with mesh appeared to result in a higher incidence in wound-related adverse events, specifically incision site swelling and pain, when compared to patients without this history. This is not surprising, however, given the increased surgical dissection typically required during repeat procedures, resulting in increased swelling and pain. The incidence of more clinically significant wound-related adverse events such as post-procedural discharge and dehiscence was similar for patients with and without a history of previous hernia repair. Surgical procedure and amount of Type I collagen did not appear to influence the incidence of wound-related adverse events.

A final consideration regarding administration of INL-001 is the potential for scar tissue or adhesions to develop and the potential impact on future surgical dissection. The Phase 3 studies did not the evaluate the ease or difficulty of surgical re-exploration after administration of INL-001; however, the results of the non-clinical studies have indicated complete dissolution of the implant at Day 56 post-implantation and did not suggest an increased amount of fibrotic tissue at the time of necropsy on either Day 35 or Day 56.

The safety concerns of LAST and wound-healing have been adequately evaluated during the Applicant's drug development program. The risks of LAST can likely be mitigated with use of the strategies discussed above, and the adverse events related to wound healing appear consistent with reports from the published literature in patients undergoing open inguinal hernia repair. Therefore, INL-001 is a safe alternative for the management of postsurgical pain after open inguinal hernia repair with mesh and will be approved for use in this surgical population.

Per the most recent Annual Report, for reporting period April 1, 2019, to March 31, 2020, the Applicant indicated there was no new safety information acquired in adult patients, as there are no ongoing clinical studies in adults. New interim safety data from the ongoing pediatric study, Study INN-CB-020, was included and will be discussed briefly. As of April 2020, there have been 14 pediatric patients treated during open inguinal hernia repair; 13 patients aged 12 to <17 years and one patient aged 6 to <12 years. Of the 14 patients, nine received INL-001 in

the PK cohort; the remaining five were treated in the blinded cohort. There were no deaths and no serious adverse events reported. Adverse event information for the nine patients who received INL-001 is summarized in the following table.

Table 1. Treatment-Emergent Adverse Events Reported During Study INN-CB-020

MedDRA System Organ Class Preferred term	Number (%) of patients
	INL-001 [a] N=9
Patients reporting with any TEAE	9 (100)
Eye disorders	3 (33.3)
Vision Blurred	3 (33.3)
Gastrointestinal disorders	5 (55.6)
Hypoesthesia oral	1 (11.1)
Nausea	5 (55.6)
Paranesthesia oral	2 (22.2)
Vomiting	1 (11.1)
Infections and infestations	2 (22.2)
Upper respiratory tract infection	1 (11.1)
Viral upper respiratory tract infection	1 (11.1)
Injury, poisoning, and procedural complications	5 (55.6)
Delayed recovery from anaesthesia	1 (11.1)
Hand fracture	1 (11.1)
Incision site erythema	1 (11.1)
Incision site haemorrhage	1 (11.1)
Incision site swelling	1 (11.1)
Procedural haemorrhage	0
Procedural pain	1 (11.1)
Venomous sting	1 (11.1)
Wound secretion	0

Nervous system disorders	6 (66.7)
Altered state of consciousness	2 (22.2)
Dizziness	3 (33.3)
Dysgeusia	4 (44.4)
Headache	1 (11.1)
Incoherent	2 (22.2)
Poor quality sleep	0
Somnolence	5 (55.6)
Tremor	0
Psychiatric disorders	3 (33.3)
Restlessness	2 (22.2)
Sopor	1 (11.1)
Respiratory, thoracic and mediastinal disorders	1 (11.1)
Oropharyngeal pain	0
Respiratory disorder	0
Stridor	1 (11.1)
Skin and subcutaneous tissue disorders	1 (11.1)
Rash generalised	1 (11.1)
Skin burning sensation	0
Surgical and medical procedures	0
Wound drainage	0
Vascular disorders	1 (11.1)
Hypotension	1 (11.1)

MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
[a] Includes 9 patients (6 to <17 years) known to have received INL-001 (in part 1/open-label): 8 patients 12 to <17 years, 1 patient 6 to <12 years.
Source: Summary of Safety Information, Annual Report (April 1, 2019, to March 31, 2020), pp. 3-4 (PDF), IND 77127.

The most commonly reported adverse events were in the Nervous System Disorders MedDRA System Organ Class (SOC), including somnolence. While this is not surprising given the administration of general anesthesia during open inguinal hernia repair, it makes the detection of cases of neurotoxicity due to LAST challenging. There were no cardiac-related adverse events reported and it appears no patient demonstrated signs or symptoms consistent with bupivacaine toxicity. The incidence of wound-related adverse events appears consistent with the incidence reported in the Phase 3 studies in adult patients; however, the low number of treated pediatric patients makes definitive conclusions difficult.

In conclusion, there was no new safety information included in the NDA resubmission or in the most recently reviewed Annual Report that adversely impacts the benefit:risk profile of INL-001 when administered during open inguinal hernia repair.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

The safety and efficacy of INL-001 has not been evaluated in pediatric patients. The Applicant submitted an initial pediatric study plan (iPSP) on January 27, 2016, and it was agreed upon on September 23, 2016. An amended iPSP for revision of the milestone dates was submitted on December 9, 2019, and was agreed to on June 17, 2020. Refer to Section 13 for additional information regarding the ongoing and planned pediatric studies.

11. Other Relevant Regulatory Issues

Because the collagen component of INL-001 is considered an implantable drug delivery device, a consultation response was provided by the review team in the Center for Devices and Radiological Health during the first review cycle. The team concluded that the collagen component of INL-001 is non-cytotoxic, non-irritant, non-sensitive, non-pyrogenic, non-genotoxic, and non-toxic for short-term use. There were no deficiencies identified to prevent approval.

Refer to Dr. Petit-Scott's review completed during the first cycle for a discussion regarding financial disclosures and the results of the clinical site inspections.

12. Labeling

Prescribing Information

The following is a high-level summary of the recommendations and rationale for critical changes to the Applicant-proposed full prescribing information (FPI) that was most recently submitted. Because other reviews will address discipline-related labeling issues, detailed edits are not included here.

- INDICATIONS AND USAGE:
  - As discussed previously, the label submitted by the Applicant during this review cycle included open inguinal hernia repair as an indicated surgical procedure. This was the surgical procedure evaluated during Phase 3 development and the revised indication is supported by the safety and efficacy data submitted. Inclusion of a Limitations of Use statement was included in the label to inform clinicians of the limited safety and efficacy evaluations, with a cross reference to information in Section 13 regarding the possibility of delayed bone healing, as noted in the nonclinical review.

  - The additional descriptive term "(b) (4)" was deleted from the product description throughout the label, such that Xaracoll is described as a bupivacaine collagen implant.
  - A time limit for expected postsurgical analgesia was included; i.e., "…for up to 24 hours…"
- DOSAGE AND ADMINISTRATION:
  - Most edits and additions made to this section focused on instructions for safe administration of bupivacaine-containing products, such as Xaracoll. Specifically, information regarding administering providers, clinical monitoring, and availability of resuscitative medications and equipment was included.
  - Based on data from the PK studies, information regarding additional use of local anesthetics was included in this section and others.
  - Additional edits were made to clarify and improve the organization of the administration instructions.
- CONTRAINDICATIONS:
  - Hypersensitivity reactions to amide-type local anesthetics or any component of Xaracoll, and obstetrical paracervical blocks were included in this section.
- WARNINGS AND PRECAUTIONS:
  - Substantial edits were made to this section to be consistent with information included in the revised Marcaine label. Several subsections were added, including Methemoglobinemia, Risk of Toxicity in Patients with Hepatic Impairment, and Risk of Use in Patients with Impaired Cardiovascular Function.
  - Because Xaracoll is not administered via injection, not all warnings and precautions included in the Marcaine label were included in this section.
- ADVERSE REACTIONS:
  - Edits made to this section clarified adverse reactions that were observed across drug development and those specifically observed in the Phase 3 studies in patients undergoing open inguinal hernia repair.
  - Table 1 was edited by the Applicant, per our request, to include adverse events that occurred with an incidence of 2% and greater and higher in the Xaracoll treatment group than the placebo treatment group.
  - Postmarketing information for bupivacaine and relevant to Xaracoll was included in Section 6.2.
- DRUG INTERACTIONS:
  - Drugs associated with the development of methemoglobinemia were included in this section.
- OVERDOSAGE:
  - Relevant information from the revised Marcaine label was included in this section.
  - Removal of Xaracoll was added as a management strategy.
- CLINICAL STUDIES:

  - Edits to this section included the presentation of the primary [redacted] endpoints; i.e., removal of [redacted]
  - Clinically relevant secondary and other endpoints were included in this section of the label. Specifically, information regarding proportion of patients opioid-free and median time to first opioid rescue was included to inform prescribers of the overall benefit of Xaracoll administration and guide expectations in patients undergoing open inguinal hernia repair.
- PATIENT COUNSELING INFORMATION:
  - Allergic-type reactions and methemoglobinemia were included in this section.

Other Labeling

During the first review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) provided recommendations regarding the container label, pouch labeling, and carton labeling. The Applicant incorporated those recommendations into the proposed labeling, and included additional packaging configurations, a four-pack carton labeling, and a ten-pack carton labeling in the NDA resubmission. The additional configurations and labeling were reviewed and found to be acceptable. DMEPA has not identified any outstanding issues from a medication error perspective. Refer to the review completed by Dr. Cameron Johnson for additional information.

13. Postmarketing Requirements

The Pediatric Research Equity Act (PREA) applies to this NDA. Under PREA, the Applicant is required to conduct studies to assess safety, efficacy, and appropriate dosing. The Applicant submitted an initial pediatric study plan (iPSP) on January 27, 2016, and it was agreed upon on September 23, 2016. An amended iPSP for revision of the milestone dates was submitted on December 9, 2019, and was agreed to on June 17, 2020. Innocoll cites challenges in patient enrollment as the main reason for the amended protocol milestone dates. Specifically, the age-group order of enrollment, the use of an open surgical approach, and the necessity for inpatient care have resulted in longer times to reach enrollment goals.

The proposed pediatric studies evaluating INL-001 and the associated dates are as follows.

Study INN-CB-020 (ongoing)
A Multicenter, Randomized, Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Analgesic Effect of the INL 001 Bupivacaine Hydrochloride (HCl) Collagen Matrix Implant in Children 2 to <17 Years of Age Following Open Inguinal Hernia Repair.

- Final protocol submission: February 2016 (complete)
- Study completion: January 2024
- Final report submission: May 2024.

Study INN-CB-021

A Multicenter, Randomized, Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of the INL-001 Bupivacaine-Collagen Bioresorbable Implant in Children 0 to <2 Years of Age Following Open Inguinal Hernia Repair.

- Draft protocol submission: April 2021
- Final protocol submission: July 2021
- Study completion: March 2023
- Final report submission: August 2023.

14. Decision/Action/Benefit:Risk Assessment

Regulatory Action
Approval.

Benefit: Risk Assessment
As noted above, the Applicant has adequately addressed the deficiencies discussed in the Complete Response Letter issued on November 30, 2018, and the application can be approved.

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/

RENEE L PETIT-SCOTT
08/28/2020 04:48:39 PM

RIGOBERTO A ROCA
08/28/2020 07:40:35 PM