DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 006488/S-090
NDA 006488/S-095

SUPPLEMENT APPROVAL

Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, IL 60047

Attention: John McNally
Senior Regulatory Specialist

Dear Mr. McNally:

Please refer to your Supplemental New Drug Applications (sNDAs) dated April 3, 2015 (S-090), and August 24, 2017 (S-095), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xylocaine (Lidocaine hydrochloride; Lidocaine Hydrochloride and Epinephrine) Injection.

We also acknowledge receipt of your amendments dated December 5, 2017, for S-090, and December 12, 2017, for S-095.

Supplement S-090, submitted as a "Changes Being Effected" supplement, provides for adding "HCl" after "lidocaine" throughout the label, and revisions to the **ADVERSE REACTIONS** section of the Package Insert to include language on allergic reactions and cross-sensitivity.

Supplement S-095, was initially submitted as a "Changes Being Effected" supplement to provide for a change in the adhesive from (b) (4) used to attach the ampoule label to the (b) (4) ampoules. You were notified in a letter dated September 26, 2017, that changes of this kind cannot be put into effect prior to approval of a supplement. Therefore, this supplement was reviewed as a Prior Approval Supplement.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Xylocaine was approved on November 19, 1948, we have become aware of limited data on extractables and leachables from only one batch of a new adhesive on stability study. Per USP <1664> "Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems, at least three study batches are required. Without these additional studies, we cannot assure that all extractables and leachables are identified and meet specifications. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risk of potential neurotoxicity, genotoxicity, reproductive toxicity, or carcinogenicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3321-1 Conduct a simulation study to characterize the potential leachables profile from your drug product container closure system that employs the (b) (4) adhesive that will be used on the (b) (4) labels that are placed on the (b) (4) ampoules (b) (4) 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 accelerated storage conditions in order to identify trends in potential leachable levels over time. Batches for each of your drug product presentations that employ this new adhesive should be tested unless you can justify that there would be no difference in leachable profile across the drug product presentations or that the presentations chosen represent the worst-case scenario. The materials tested should include any secondary container closure systems, if present, and be subjected to the same to-be-marketed (b) (4) as appropriate. Establish an AET of (b) (4) mcg/day. Based on these results, provide a revised toxicological risk assessment for any leachable above (b) (4) mcg/day that addresses both systemic and local tissue effects, including the potential for neurotoxicity if the product is inadvertently administered via the intrathecal route.

The timetable you submitted on December 21, 2017 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2018
Study Completion:	01/2019
Final Report Submission:	02/2019

3321-2 Conduct a long-term leachables study to adequately characterize the leachables profile from your drug product container closure system that employs the (b) (4) adhesive that will be used on the (b) (4) labels that are placed on the (b) (4) ampoules (b) (4) 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, through the proposed expiry duration, in order to identify trends in leachable levels over time. Batches for each of your drug product presentations that employ this new adhesive should be tested unless you can justify that there would be no difference in leachable profile across the drug product presentations or that the presentations chosen represent the worst-case scenario. The materials tested should include any secondary container closure systems, if present,

and be subjected to the same to-be-marketed (b) (4), as appropriate. Establish an AET of (b) (4) mcg/day. Based on these results, provide a revised toxicological risk assessment for any leachable above (b) (4) mcg/day that addresses both systemic and local tissue effects, including the potential for neurotoxicity if the product is inadvertently administered via the intrathecal route. Submit annual reports over the course of this study that discuss trends in the leachable profile to date.

The timetable you submitted on December 21, 2017 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2018
Study Completion:	07/2021
Annual Interim Report #1:	1/2019
Annual Interim Report #2:	1/2020
Annual Interim Report #3:	1/2021
Final Report Submission:	08/2021

Submit the protocol(s) to your IND, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Taiye Ayoola, PharmD, Regulatory Project Manager, at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Rigo Roca, MD
Deputy Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

RIGOBERTO A ROCA
12/22/2017