SUPPLEMENT APPROVAL
PMR Release/Replacement

OUR STN: BL 125392/163

Ethicon, Inc.
Attention: Sally K. Wixson, VMD
Route 22 West
PO Box 151
Somerville, NJ 08876

Dear Dr. Wixson:

We have approved your request dated December 18, 2015, to supplement your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (42 U.S.C. 262) for Fibrin Sealant Patch [EVARREST], to expand the clinical indication of EVARREST to include use with manual compression as an adjunct to hemostasis in adult patients undergoing surgery, when control of bleeding by conventional surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical.

The review of this supplement was associated with the following National Clinical Trial (NCT) numbers: NCT01902459 and NCT02040428.

We hereby approve the draft package insert labeling submitted under amendment 21, dated September 30, 2016, and the draft carton and container labeling submitted on December 18, 2015.

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. In addition, please submit three original paper copies for carton and container final printed labeling. All final labeling should be submitted as Product Correspondence to your BLA, STN 125392, at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling: Technical Qs & As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

Please submit an amendment to all pending supplemental applications for this BLA that include revised labeling incorporating a revised content of labeling that includes these changes.

RELEASE/REPLACEMENT OF POSTMARKETING REQUIREMENT

Your approval letters dated December 5, 2012, and March 26, 2015, for your biologics license application (BLA) STN 125392/0 and STN 125392/33, respectively, for Fibrin Sealant Patch [EVARREST] included the following pediatric postmarketing requirements #1 and #1 in descending order:

1. Deferred pediatric study under PREA for use of EVARREST as an adjunct to hemostasis in patients 1 month to 17 years undergoing intra-abdominal, retroperitoneal, pelvic, and non-cardiac thoracic surgical procedures.

   Final Protocol Submission: December 2013

   Study Completion Date: December 2016

   Final Report Submission: March 2017

1. Deferred pediatric study under PREA for use as an adjunct to hemostasis for control of bleeding during liver surgery in the pediatric study for ages 30 days to 18 years.

   Final Protocol Submission: June 30, 2014

Study Completion Date: June 30, 2016

Final Report Submission: March 31, 2017

We have reviewed your submissions and determined that you are released from the above postmarketing requirements for the following reason:

> Data from an ongoing, randomized, controlled study in the E.U. among pediatric subjects undergoing liver/soft-tissue surgery (study 400-12-004 with N=40) will be integrated with data from a proposed, open-label, prospective, non-controlled, multicenter clinical study in the U.S. among the same population (study BIOS-16-001 with N=35).

As a result, the above PREA postmarketing requirements are now considered closed and will be replaced by the new pediatric postmarketing requirement described below.

NEW REQUIRED PEDIATRIC ASSESSMENT

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to less than 1 month because there is evidence suggesting that the biological product would be ineffective and unsafe in this pediatric group. Because of small body size and limited access in this pediatric population, it is not technically feasible to apply EVARREST to the target bleeding site and apply pressure for 3 minutes, as required for correct application of EVARREST. Inability to apply EVARREST correctly may result in continued blood loss and/or delayed bleeding which, given a small child's sensitivity to blood volume reduction, represents a safety concern.

We are deferring submission of your pediatric study for ages 1 month to less than 18 years for this application because this product is ready for approval for use in adults, and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Please label your annual report as an **Annual Status Report of Postmarketing Study Requirement/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of the approval of STN BL 125392 until all

Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are fulfilled. This required study is listed below:

1. Deferred pediatric study under PREA for use with manual compression as an adjunct to hemostasis in pediatric patients aged 1 month to less than 18 years undergoing surgery, when control of bleeding by conventional surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical.

   Final Protocol Submission: June 30, 2016

   Study Completion Date: December 31, 2018

   Final Report Submission: March 31, 2019

Please submit the protocol to your IND 15098, with a cross-reference letter to STN BL 125392, explaining that this protocol was submitted to the IND. Please refer to the sequential number for each study/clinical trial and the submission number as shown in this letter.

Please submit final study reports to this BLA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated as:

- **Required Pediatric Assessment**

The status report for this study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21

CFR 601.70. We remind you that to comply with section 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 periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

We will include information contained in the above-referenced supplement in your biologics license application file.

Sincerely,

Basil Golding, MD
Acting Director
Division of Hematology Clinical Review
Office of Blood Research and Review
Center for Biologics Evaluation and Research