Our STN: BL 125640/0

BLA APPROVAL
November 1, 2017

Instituto Grifols, S.A.
Attention: Joan Robertson
Vice President, Regulatory Affairs
Grifols Shared Services North America, Inc.
8368 U.S. Highway 70 West
Clayton, NC 27520

Dear Ms. Robertson:

Please refer to your Biologics License Application (BLA) for Fibrin Sealant (Human) dated November 3, 2016, received on November 4, 2016, and submitted under section 351(a) of the Public Health Service Act (PHS Act).

LICENSING

We have approved your BLA for Fibrin Sealant (Human) effective this date. You are hereby authorized to introduce, or deliver for introduction, into interstate commerce Fibrin Sealant (Human) under your existing Department of Health and Human Services U.S. License No. 1181. Fibrin Sealant (Human) is indicated for use as an adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. Fibrin Sealant (Human) is effective in heparinized patients.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: 01662856, 01731938, and 01754480.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Fibrin Sealant (Human) at your facility located in Barcelona, Spain. You may label your product with the proper name FIBRIN SEALANT (Human) and market it in 2-mL, 4-mL, 6-mL, and 10-mL fill sizes as a kit consisting of two packages:

- A package containing one syringe each of human fibrinogen (component 1) and human thrombin (component 2) sterile frozen solutions which are assembled on a syringe holder.

- A package containing an application cannula for drip application of the product.

Under this license, you are approved to manufacture Fibrin Sealant (Human) drug product at Instituto Grifols, S.A., 2 Can Guasch St., Poligono Levante, Parets del Vallès, Barcelona, Spain 08150. This includes the manufacturing of final formulated human fibrinogen and human thrombin components, filling, assembly with the device components, packaging, sterilization, and labeling.

We did not refer your application to the Blood Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for Fibrin Sealant (Human) drug product shall be 24 months from the date of manufacture when stored at a temperature ≤ -18 ˚C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated human fibrinogen and human thrombin components. No reprocessing/reworking at any manufacturing stage or following the final sterile filtration is allowed without prior approval from the Agency.

FDA LOT RELEASE

Please submit final container samples of the product and each kit component in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, 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

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of Fibrin Sealant (Human), or in the manufacturing facilities.

LABELING

We hereby approve the draft package insert labeling submitted under Amendment 63, dated October 27, 2017, and the draft carton and container labeling submitted under Amendment 56, dated October 10, 2017.

Please provide your final content of labeling, including the carton and container labels, in Structured Product Labeling (SPL) format. All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125640, 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 CFR 601.12(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)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80), and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports* at http://www.fda.gov/Drugs/DrugSafety/ucm400526.htm and FDA's Adverse Event reporting System website http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

PEDIATRIC REQUIREMENTS

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 deferring submission of your pediatric study because the product is ready for approval for use in adults, and the pediatric study has not been completed.

Your deferred pediatric study under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a 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.

Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. This required study under PREA is listed below:

1. Instituto Grifols, S.A. commits to evaluating the safety and efficacy of FIBRIN SEALANT (Human) as an adjunct to hemostasis during surgery in pediatric patients < 18 years of age in the deferred pediatric clinical trial under protocol IG1405 entitled "A Prospective, Randomized, Active-Controlled, Single-blind, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during Surgery in Paediatric Subjects." Instituto Grifols, S.A. also commits to conducting a study of the

Human Factors assessment as part of the pediatric trial. The timelines for the combined PREA PMR study are as follows:

Final Protocol Submission Date: March 30, 2018

Study Completion Date: June 30, 2023

Final Report Submission Date: June 30, 2024

Please submit the protocol to your IND 14986, with a cross-reference letter to this BLA, STN BL 125640 explaining that this protocol was submitted to the IND.

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(s)**

POSTMARKETING COMMITMENT NOT SUBJECT TO THE REPORTING REQUIRMENTS UNDER SECTION 506B

We acknowledge your written commitment as described in your letter of October 5, 2017:

2. Instituto Grifols, S.A. commits to providing results from small-scale studies for the (b) (4) The final results will be submitted as a "Postmarketing Study Commitment - Final Study Report" by December 31, 2018.

   Final Report Submission Date: December 31, 2018

We request that you submit information concerning nonclinical and chemistry, manufacturing, and controls postmarketing commitments and final reports to your BLA, STN BL 125640. Please refer to the sequential number for each commitment.

Please use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study commitment as appropriate:

- **Postmarketing Commitment – Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Commitment – Status Update**. The status report for each commitment should include:

- The sequential number for each study as shown in this letter;
- The submission number associated with this letter;
- Description of what has been accomplished to fulfill the non-section 506B PMC; and,
- Summary of any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment – Final Study Report**.

POST-APPROVAL FEEDBACK MEETING

New biological products qualify for a post-approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

/s/

Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research