



Filing Meeting Summary

Application: BL 125640/0
Product: Fibrin Sealant (Human), Fibrin Sealant (FS) Grifols
Proprietary Name: VERASEAL (currently under review)
Proposed Indication: An adjunct to hemostasis for mild to moderate bleeding in adults (b) (4) undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. VERASEAL is effective in heparinized patients.
Applicant: Instituto Grifols, S.A.
Meeting Date & Time: Wednesday, December 14, 2016, 11 AM to 12 PM, EST
Meeting Chair: Natalya Ananyeva, PhD
Meeting Recorder: Yu Do, MS

Background:

Instituto Grifols, S.A. submitted a Biologics License Application for Fibrin Sealant (Human), FS Grifols, for use as an adjunct to hemostasis in surgery. The FS Grifols meets the legal definition of a biologics/device combination product according to 21 CFR Part 3 with the primary mode of action being provided by the biologics (human fibrinogen and human thrombin). A 513(g) Request for Information was submitted to CBER to determine the regulatory classification of the system components, and an FDA decision was issued on June 30, 2016.

FS Grifols is provided as a kit comprised of two pre-filled syringes containing sterile frozen solutions of Human Fibrinogen (component 1) and Human Thrombin with calcium chloride (component 2), which are assembled on a single syringe holder, intended for topical use. The syringe plungers are connected by a plunger link to ensure simultaneous application of the biologics. When applied, the solutions generate a cross-linked fibrin clot in a process that mimics the last stage of the human coagulation cascade. One application cannula (Class I device) is co-packaged with the product for application by dripping. An optional spray applicator (Class II device), which has been 510(k)-cleared by FDA, is supplied separately.

Both Human Fibrinogen and Human Thrombin are isolated from Source Plasma of U.S. origin, followed by a fractionation process based on the Cohn method. To ensure product safety, both Drug Substance components are subjected to treatment with organic solvent and detergent and double nanofiltration through 35 nm and 20 nm, demonstrated to inactivate or remove enveloped and non-enveloped viruses.

Along with Integrated Summary of Efficacy and Integrated Summary of Safety, three clinical studies to assess the safety and efficacy of FS Grifols were submitted for review: IG1101 in vascular surgery, IG1102 in parenchymous tissue (hepatic) surgery, and IG1103 soft tissue surgery. For the nonclinical section, 8 pharmacological and 6

toxicological studies, performed on two different animal models, were submitted in this application for review.

REVIEW COMMITTEE AND DISCIPLINES:

- a. Regulatory Project Manager (RPM) - Yu Do (RPMBI/DRPM/OTAT)
- b. Chair (CMC, Product) - Natalya Ananyeva (HB/DPPT/OTAT)
- c. CMC, Adventitious Agents Safety - Ze Peng (HB/DPPT/OTAT)
- d. CMC, Analytical Methods/Raw Materials - Svetlana Shestopal (HB/DPPT/OTAT)
- e. QC, Test Methods - Grainne Tobin (LACBRP/DBSQC/OCBQ)
- f. QC, Test Methods - Ritu Agarwal (LACBRP/DBSQC/OCBQ)
- g. Product Quality, Lot Release Protocol/Testing Plan - Varsha Garnepudi (QAB/DBSQC/OCBQ)
- h. QC, Bioburden/Sterility/Endotoxin - Karla Garcia (LMIVTS/DBSQC/OCBQ)
- i. Facilities and Inspection, Reviewer and Inspector – Christine Harman (BI/DMPQ/OCBQ)
- j. DMPQ Consultant, Delivery Device – Deborah Trout (BI/DMPQ/OCBQ)
- k. DMPQ RPM – Sarah Lee (ARB/DMPQ/OCBQ)
- l. CDRH Consultant, Engineering (Delivery Device) – Rong Guo (DAGRID/ODE/CDRH)
- m. Pharmacology/Toxicology – John Jameson (PTBII/DCEPT/OTAT)
- n. Clinical Safety and Efficacy – Agnes Lim (GMBI/DCEPT/OTAT)
- o. Biostatistics – Min (Annie) Lin (TEB/DB/OBE)
- p. Pharmacovigilance/Epidemiology – Faith Barash (PB/DE/OBE)
- q. Bioresearch Monitoring (BIMO) – Bhanu Kannan (BMB/DIS/OCBQ)
- r. Labeling - Alpita Papat (APLB/DCM/OCBQ)
- s. Labeling, Proprietary Name Review – Oluchi Elekwachi (APLB/DCM/OCBQ)

Other participants:

Chava Kimchi-Sarfaty (HB/DPPT/OTAT), Ilan Irony (GMBI/DCEPT/OTAT), Becky Robinson (PTBI/DCEPT/OTAT), Mercedes Serabian (PTBI/DCEPT/OTAT), Renee Rees (TEB/DB/OBE), and Carolyn Renshaw (BI/DMPQ/OCBQ).

REGULATORY CONCLUSIONS/DEFICIENCIES:

1. Does the application, on its face, appear to be suitable for filing?

There is a consensus among the discipline reviewers at this time that this application is complete and suitable for filing. [Review Committee]

2. If suitable for filing, list any substantive deficiencies or issues that have significant impact on the ability to complete the review or approve the application.
 - a. Information related to the device components of the combination product is not adequate for a meaningful review. Specifically, information on Design Inputs & Outputs with acceptance criteria, Design Review planning, Design Verification, and Design Validation was not provided in the BLA. The Applicant has been contacted via Information Request to provide Design Controls information including all elements as per 21 CFR 820.30. The Applicant is committed to submitting the Design History File and Design Control data by February 15, 2017. [Deborah Trout/Rong Guo]
 - b. At this time, there is only one Drug Product (DP) lot (i.e., IBND6L3MP1) available for CBER's in-support testing, which is within the shelf life. Although six conformance DP lots covering all fill sizes were manufactured and described in the BLA, these lots are not suitable for in-support testing because they have exceeded the shelf-life period. During the December 7, 2016, teleconference, the Applicant stated its commitment to manufacture two additional DP lots, provide their release information, and make them available for CBER's in-support testing by March or April of 2017. [Natalya Ananyeva/Svetlana Shestopal].
 - c. Information related to the Human Factors/Usability study is not available in this BLA for review. However, product usability information can be gleaned from the three pivotal Clinical Studies which consist of two parts in which Part I provided opportunities for the appropriate personnel to become acquainted with the product and its application procedures. The BLA also includes results of Risk Analysis which assessed risks to the patient. It is unclear whether any use-related concerns were raised during review of the associated INDs, or addressed in BLA review of other fibrin sealant products. Additionally, the Applicant will be contacted via Information Request to submit reports from the Human Factors studies *or* any other safety-related assessments of the combination product user interface conducted in lieu of Human Factors studies. The need of any additional Human Factors study will be determined based on the review of the Applicant's response, reports from Design Validation and Clinical Studies, results of Risk Analysis, and description of the administration procedure in the labeling. [Ilan Irony, Agnes Lim, Natalya Ananyeva, and Faith Barash].

Post-meeting comments:

- Information Request regarding the Human Factors studies was communicated to the Applicant on December 15, 2016, with

responses due by December 27, 2016. Per consultation with clinical reviewers of the associated INDs, the Grifols delivery system functions on the same principles as devices for other approved fibrin sealant products (e.g., EVICEL), and potential for error in product administration by surgeons, as qualified and trained staff, was assessed as low at the IND stage.

- d. To facilitate ease of review, the information on manufacturing (development and consistency) and characterization of the biological components of Drug Product should have been organized under *Module 3.2.S Drug Substance* rather than *Module 3.2.P.2 Pharmaceutical Development*. This, however, is not a substantive issue. [Natalya Ananyeva/Deborah Trout]
3. If RTF, list any issues that would make this application unsuitable for filing.

There is no need for an RTF or deficiencies-identified letter at this time. [Review Committee]

FILING MEETING DISCUSSION, IF FILED:

4. Indicate any comments on the status of the proprietary name review (PNR).

PNR request for VERASEAL was submitted on November 15, 2016, and is currently under review. The due date for this review is February 14, 2017.

5. Indicate whether the product would be subject to lot release, surveillance, or exempt from lot release.

Since it is derived from human plasma, this product would be subject to CBER lot release requirements. [Yu Do]

6. Review classification of this application

Standard status is granted for review of this application. [Yu Do]

7. A decision regarding the need for an Advisory Committee

There is no need at this time to present this application before an Advisory Committee: Fibrin sealants have a long history of use as an adjunct to hemostasis, and their mechanism of action is well studied and understood. Also, no waiver memo would be necessary since this product is not considered to be a New Molecular Entity.

8. Indicate whether the submission triggers PREA.

Since this BLA has no orphan designation, the submission does trigger PREA for a new indication, and the PeRC review has been scheduled for September 6, 2017.

9. Is a comprehensive and readily located list of all clinical sites included or referenced in the application?

The tabular listing of all clinical sites is included under Module 5.2.
[Yu Do]

The phone number and site ID of each investigator for all three studies are not readily available in the application, so the Applicant will be contacted via Information Request to provide such information. [Bhanu Kannan/Yu Do]

10. Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?

Yes. [Yu Do]

11. Indicate any updates since the first committee meeting on pre-license inspection, pre-approval inspection, or identification of BIMO sites requiring inspections.

No sites for BIMO inspection have been identified thus far. These sites will be identified in consultation with the clinical reviewer by the end of January 2017.
[Bhanu Kannan/Agnes Lim]

DMPQ is currently working on scheduling the pre-license inspection which will occur at the Barcelona, Spain facility sometime around the Mid-Cycle depending on the IG's production schedule.

12. If the application is affected by the Application Integrity Policy (AIP), has the Division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

This application is not affected by the Application Integrity Policy.

13. Is the product an Original Biological Product or a New Molecular Entity (NME) for NDAs only?

This product is subject to review as an original Biologics License Application under the PDUFA V "Program."

FOR APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs), IF FILED

14. Confirm that any late-submission components were submitted within 30 days.
List any late-submission components that arrived after 30 days.

There were no agreements regarding the late-submission components with regard to this application.

15. Was the application otherwise complete upon submission?

Proprietary name review request had to be requested as it was not included in the original submission.

Information regarding design controls for the device components was inadequate and had to be requested.

ADMINISTRATIVE DETAILS, IF FILED:

16. Review the milestone schedule and indicate if there are any issues with the schedule.

There are no issues brought forth with regard to the following schedule:

Receipt Date: November 4, 2016
Filing Checklist:
Supervisory concurrence - December 23, 2016
EDR upload – December 29, 2016
Filing Date: January 03, 2017
Day-74 Deficiencies Identified Letter: January 17, 2017
Proprietary Name Review: February 14, 2017
PeRC Date: September 06, 2017
Mid-Cycle Meeting: April 13, 2017
Mid-Cycle Communication: April 27, 2017
Late-Cycle Internal Meeting: June 20, 2017
Late-Cycle External Meeting: July 20, 2017
PDUFA Action Due Date: November 03, 2017

Drafted: Yu Do/December 19, 2016
Revised: Natalya Ananyeva/December 20, 22, 2016
Reviewed: Deborah Trout/December 21, 2016
Reviewed: Rong Guo/December 27, 2016
Reviewed: Bhanu Kannan/December 27, 2016
Revised: Carolyn Renshaw/December 19, 2016

Page 7 - BL 125640/0 Filing Meeting

Reviewed: Renee Rees/December 19, 2016

Reviewed: Karla Garcia/December 19, 2016

Reviewed: Annie Lin/December 19, 2016

Revised: Chava Kimchi-Sarfaty (on behalf of Tim Lee)/December 27, 2016