

Our STN: BL 125640/0

September 29, 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:

Attached is a copy of the memorandum summarizing your August 31, 2017, Late-Cycle Meeting teleconference with CBER. This memorandum constitutes the official record of the teleconference. If your understanding of the teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to BL 125640 in future submissions related to the subject product.

If you have any questions, please contact Yu Do at (240) 402-8343.

Sincerely,

Basil Golding, MD
Director
Division of Plasma Protein Therapeutics
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date/Time: Thursday, August 31, 2017, 10:30 a.m. to 12:00 p.m., EDT
Meeting Location: Teleconference
Application Number: BL 125640/0
Product Name: Fibrin Sealant (Human)
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. Fibrin Sealant (Human) is effective in heparinized patients.
Applicant Name: Instituto Grifols, S.A. (Grifols)
Meeting Chair: Natalya Ananyeva, PhD
Meeting Recorder: Yu Do, MS

FDA ATTENDEES

Yu Do, MS, RPMBI/DRPM/OTAT
Natalya Ananyeva, PhD, HB/DPPT/OTAT
Ze Peng, PhD, HB/DPPT/OTAT
Svetlana Shestopal, PhD, HB/DPPT/OTAT
Andrey Sarafanov, PhD, HB/DPPT/OTAT
Grainne Tobin, PhD, LACBRP/DBSQC/OCBQ
Karla Garcia, LMIVTS/DBSQC/OCBQ
Ritu Agarwal, PhD, LACBRP/DBSQC/OCBQ
Hsiaoling Wang, PhD, LACBRP/DBSQC/OCBQ
Christine Harman, PhD, BI/DMPQ/OCBQ
Deborah Trout, BI/DMPQ/OCBQ
Rong Guo, PhD, DAGRID/ODE/CDRH
Rita Lin, MS, DAGRID/ODE/CDRH
Min (Annie) Lin, PhD, TEB/DB/OBE
Bhanu Kannan, BMB/DIS/OCBQ
Faith Barash, MD, PB/DE/OBE
Alpita Popat, PharmD, APLB/DCM/OCBQ
Wilson W. Bryan, MD, Director, OTAT
Kimberly Benton, PhD, Associate Director for Regulatory Management, OTAT
Basil Golding, MD, Division Director, DPPT/OTAT
Tejashri Purohit-Sheth, MD, Division Director, DCEPT/OTAT
Ilan Irony, MD, Branch Chief, GMB1/DCEPT/OTAT
Renee Rees, PhD, Team Lead, TEB/DB/OBE
Carolyn Renshaw, Branch Chief, BI/DMPQ/OCBQ
Christopher Jankosky, MD, Supervisory Medical Officer, OBE
John (Jay) Eltermann, Division Director, DMPQ/OCBQ
Tim Lee, PhD, Branch Chief (Acting), HB/DPPT/OTAT
Iwen Wu, PhD, Branch Chief (Acting), PTB2/DCEPT/OTAT

Lokesh Bhattacharyya, PhD, Supervisory Chemist, LACBRP/DBSQC/OCBQ

Grifols ATTEENDEES

Sebastián Gascón, VP, Quality, Regulatory Compliance, & Technical Director

Juan Carlos Sánchez, Deputy Qualified Senior Manager

Ricard López, Manager, Quality Control Division

Salvador Grancha, VP, Research & Development

Maite López, Senior Manager, Laboratory and R&D Coordination

Núria Jorba, VP, Manufacturing, Instituto Grifols, S.A.

Helena Alberca, Validations HVAC, Area Manager

Sandra Pérez, Final Processes, Area Manager

Jaume Ayguasanosa, Clinical & Medical Affairs, Senior Manager

Jordi Navarro, Global Clinical Research Leader

Junliang Chen, Director, Biostatistics and Data Management

Carmen Soucheiron, Pharmacovigilance Medical Manager

Antonio Páez, Medical & Technical Director

Sònia Amorós, Director, Global Regulatory Affairs

Joan Robertson, VP, Regulatory Affairs

BACKGROUND

BLA under STN 125640/0 was submitted on November 4, 2016, for Fibrin Sealant (Human).

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. Fibrin Sealant (Human) is effective in heparinized patients.

PDUFA goal date: November 3, 2017

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on August 18, 2017.

DISCUSSION

1. Introductory Comments

FDA welcomed Grifols, stated the ground rules, and outlined the objectives of the Late-Cycle Meeting (LCM).

FDA stated that the LCM is not intended to discuss any information regarding the final regulatory action to the applicant. The primary purpose of LCM is to provide an update on the BLA review in accordance with PDUFA V agreement, discuss substantive review issues and unresolved deficiencies, and develop the objectives for the remainder of the review.

FDA stated that information regarding Advisory Committee meeting, risk management, PREA, labeling, and Postmarketing Commitments/Postmarketing Requirements will also be provided at the LCM.

2. Discussion of Substantive Review Issues/Major Deficiencies

No substantive review issues have been identified to date. The outstanding issues discussed between FDA and Grifols during this meeting are as follows:

Chemistry, Manufacturing, and Controls

a. Validation of SP-Sepharose Resin Lifetime Used in the Manufacture of Thrombin for Commercial Production

FDA acknowledged receipt of the Amendment 30, dated May 30, 2017, with an outline for concurrent full-scale validation of the lifetime of SP-Sepharose resin and Report IG_VS-001435 covering (b) (4) purification runs. FDA found this response inadequate in that the proposed number of uses (n=(b) (4)) were not supported by data or Study Protocol. For the FDA to grant (b) (4) runs for commercial production to allow release of subsequent lots, FDA requested Grifols to submit a detailed Study Protocol based on the approach used in Report IG_VS-001435 and FDA recommendations stated in the August 18, 2017, Information Request (IR). FDA also requested that Grifols submit an updated report IG_VS-001435 no later than October 1, 2017, with subsequent full-scale purification runs to demonstrate the validity of the protocol.

Grifols acknowledged this deficiency and agreed to submit Study Protocol and the updated Study Report by September 18, 2017, and October 1, 2017, respectively.

FDA also stated that additional small-scale studies may need to be submitted later for FDA review in a Prior Approval Supplement if Grifols wishes to increase the maximum number of uses beyond (b) (4) runs for commercial production. Grifols acknowledged this information.

b. Validation of Viral Clearance Capacity of the SP-Sepharose Chromatographic Step

FDA found the validation of viral clearance capacity of the SP-Sepharose chromatographic step to be incomplete. The log reduction factors need to be supported by results from small-scale studies performed with aged resin that had undergone the specified maximum number of cycles for the clearance of relevant and model viruses, as requested in the August 7, 2017, IR. (b) (4)

(b) (4)

(b) (4)

(b) (4)

c. Analytical Issues

FDA stated that the validations of a few analytical methods remain incomplete. For the analytical procedure “(b) (4) in Fibrinogen by (b) (4),” the (b) (4) characterization needs to be validated. Also, there are minor outstanding issues regarding the chemistry assays for excipients in Fibrinogen (Glutamic acid, Polysorbate 80, and TNBP) and Thrombin (Polysorbate 80 and TNBP).

Grifols stated that the requested information would be submitted in response to IRs dated August 3 and 28, 2017.

d. Extractables/Leachables Studies

FDA stated that information on extractable and leachable substances (E & L) from product-contacting surfaces of materials used in the manufacturing process was found deficient. In the August 17, 2017, IR, FDA requested Grifols to provide limits of detection for all analytical methods used, along with the assessment of cumulative effects of E & L from all product-contacting surfaces and their toxicological risks.

Grifols stated that partial information was submitted in Amendment 37, dated August 3, 2017 (eCTD Sequence No. 36). Grifols then agreed to organize systematically and submit a complete package of information by September 13, 2017.

CDRH Review of Device and Human Factors/Usability

e. Design and Functionality of the Application System

FDA acknowledged Grifols’ commitment to verify/adjust the measurements of the syringe holder hook for the 3-mL syringe for a tighter fixation of the syringe in the syringe holder, and to implement changes if warranted (stated in Amendment 30, dated May 30, 2017). FDA asked for an update on the investigation of this design issue, which was noted during both examination of the samples in FDA and the pre-license inspection.

Grifols stated that the measurements of the syringe holder were adjusted and a qualification study is planned to be conducted during the week of September 4, 2017. Grifols confirmed that the investigational report will be submitted for FDA review by October 1, 2017, as originally planned.

FDA also requested information or data on how Grifols demonstrated, or plans to demonstrate, that the device will meet the essential performance requirements at

the end of shelf life. FDA also recommended adding the parameter “*Volume*” in the stability protocol to demonstrate that the syringe can deliver the desired amount of product at expiry. These requests for information are currently in preparation.

f. Human Factors/Usability Studies

FDA stated that several deficiencies were identified about the Human Factors (HF)/Usability studies, including unclear criteria for choosing critical tasks, insufficient number of recruited surgeons, lack of explanations on use environment, participants’ training, and approach in analyzing the performance data. These deficiencies were detailed in the August 28, 2017, IR and will need to be addressed. FDA stated that this new HF study may be performed as part of the planned pediatric study. For planning purposes, FDA requested Grifols to revise the protocol in accordance with FDA recommendations and submit it for FDA review.

Grifols stated that it is feasible to prepare the new HF study protocol during this review cycle and will soon provide a time frame for the protocol submission. FDA noted that this protocol needs to be submitted for review no later than one month before the action due date. FDA also stated that issues regarding *Instructions for Use* will be further elaborated during the labeling negotiation.

3. Updates on Information Requests

Grifols recapped the IRs recently issued by FDA (dated August 3, 7, 14, 17, 18, 28, and 29, 2017) and confirmed their intent to submit the responses by requested dates. The following IRs were discussed further:

- Response to August 3, 2017, IR, regarding the (b) (4) for the analytical procedure “(b) (4) in Fibrinogen by (b) (4)” will be submitted by the new due date of September 18, 2017, as it requires experimentation.
- Response to August 14, 2017, IR, regarding the deaths reported in Study IG1102 after exposure to Fibrin Sealant (Human), was submitted on August 30, 2017.

FDA noted, however, the discrepancy in the number of cases that occurred and patient IDs between those reported in IG1102 and in the hospital record. Information submitted on August 30, 2017, only pertained to four of the seven deaths reported in Study IG1102. A new IR for the missing information and clarifications will be issued to Grifols in the near future.

- August 28, 2017, IR regarding the Human Factors/Usability studies: Grifols will determine a specific time frame for the protocol preparation after internal discussion, but is committed to providing a response to this IR no later than October 1, 2017.

4. Discussion of Upcoming Advisory Committee Meeting

This application will not be presented before the Advisory Committee at this time.

5. Risk Management Actions [e.g., Risk Evaluation and Mitigation Strategy (REMS)]

There is no anticipation that REMS will be needed at this time.

6. Post-Marketing Requirements/Post-Marketing Commitments

- The planned pediatric study required under PREA is considered a Postmarketing Requirement (PMR) study and will be presented at the Pediatric Review Committee (PeRC) meeting on September 6, 2017.

No other PMRs are anticipated at this time.

- A potential PMC for (b) (4)

7. Labeling

FDA stated that recommendations regarding the *Prescribing Information*, *Instructions for Use*, and labels will be provided as part of the labeling review. Labeling negotiations will approximately begin in the middle of September 2017.

The phrase “(b) (4)” should be removed from the proposed indication statement because submission of the pediatric study may be deferred pending a final decision from the PeRC.

8. Action Items

- Grifols will conduct small-scale studies with (b) (4) as a Postmarketing Commitment (PMC) to (b) (4). The language and timeline for this PMC will be proposed by FDA, and agreed upon, by the applicant.
- Grifols will conduct a new Human Factors (HF) study as part of the deferred pediatric study which constitutes a Postmarketing Requirement. The applicant is committed to submitting a protocol of this new HF study for FDA review no later than one month before the action due date.
- Grifols will submit an investigational report regarding the design issue of the 3-mL syringe holder by October 1, 2017.

- Grifols will submit an updated report on full-scale Thrombin purification runs with the use of SP-Sepharose resin by October 1, 2017.
- FDA will soon issue Information Requests related to delivery device, death cases, and stability program.
- FDA plans to issue the first Information Request with labeling comments toward the middle of September 2017.

9. **Post-Meeting Comments**

Information Request with labeling comments will be communicated in late September to early October 2017.

Information Requests related to delivery device, death cases, and stability program, as mentioned in Section 8. *Action Items*, have been issued on September 5, August 31, and September 8 and 18 (2017), respectively.

This application has not yet been fully reviewed by the signatory authorities, Division Directors, and Review Committee Chair; therefore, this meeting did not address the final regulatory decision for the application.

END

Concurrence Page

Application Type and Number: BLA, BL 125640/0

Communication Type: Late Cycle Meeting Summary

Cc: EDR

History: Drafted: Yu Do / September 11, 2017
Revised: Yu Do / September 25, 2017
Revised: Natalya Ananyeva / September 22, 2017
Reviewed: Ze Peng / September 12, 2017
Revised: Andrey Sarafanov / September 12, 2017
Revised: Tim Lee / September 20, 2017
Reviewed: Rong Guo / September 25, 2017
Revised: Rita Lin / September 25, 2017
Reviewed: Renee Rees / September 25, 2017
Reviewed: Min (Annie) Lin / September 27, 2017
Reviewed: Bhanu Kannan / September 26, 2017
Reviewed: Ilan Irony / September 25, 2017
Revised: Lokesh Bhattacharyya / September 27, 2017
Reviewed: Mahmood Farshid / September 28, 2017
Reviewed: Grainne Tobin / September 27, 2017
Reviewed: Karla Garcia / September 27, 2017
Revised: Kimberly Benton / September 27, 2017

Concurrence:

Office/Division	Name	Date
OTAT/DRPM	Yu Do	
OTAT/DPPT	Nataly Ananyeva	
OTAT/DPPT	Basil Golding	
OTAT	Wilson W. Bryan	
OCBQ	Mary Malarkey	