



MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies

To: BLA STN 125640/0
From: Andrey Sarafanov, PhD, DPPT/HB
Applicant: Instituto Grifols, S.A.
Product: Fibrin Sealant (Human)
Indication: An adjunct to hemostasis for patients undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical
Subject: Review of information on Leachables & Extractables
Through: Tim Lee PhD, DPPT/HB
Basil Golding MD, DPPT
CC: Natalya Ananyeva PhD, DPPT/HB & Yu Do, DRPM/RPMBI

EXECUTIVE SUMMARY

This memorandum summarizes the review of product-related information in the original biologics license application (BLA), submitted by Instituto Grifols, S.A. (Grifols) for Fibrin Sealant (Human). I reviewed information on analytical methodology used to quantitate extractables and leachables (E&L) in the drug product (DP). Dr. Evi Struble, as consult, reviewed the associated information from the safety perspective. During the review cycle, both of us requested additional information, which was provided by the company. Upon review of all information, I found that the data are acceptable and Dr. Struble also agreed with that from the toxicological perspective. I recommend approval of the BLA.

BACKGROUND

Fibrin Sealant (Human) [FS] consists of two components, fibrinogen and thrombin, which are purified from human plasma and supplied as sterile frozen solutions in separate pre-filled syringes. The proposed indication is to support local hemostasis in patients during surgery, when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical, using topical route of administration. The product kit also contains an applicator (cannula) for mixing both solutions and may contain (optionally) a spray device to apply the mix onto the patient's tissue. Each FS component is provided in either a 3-mL pre-filled syringe with 1 or 2 mL of solution; or in a 5-mL pre-filled syringe with 3 or 5 mL of solution, per the dosage strength. The whole container closure system consists of syringe barrel (made of (b) (4) glass), and tip cap with plunger stopper (made of bromobutyl rubber). These materials comply with European Pharmacopoeia specifications.

3.2.P.3.3. Description of manufacturing process

Fibrinogen

Fibrinogen (component 1) is purified from fraction I (a precipitate) in the following process (protocol IG_MP-000026_ING).

(b) (4)

In further process, the (b) (4) fraction I undergoes solvent/detergent treatment and repeated glycine precipitations. Fibrinogen is purified in sequence in each of the recovered glycine precipitates. After three precipitation steps, the last precipitate is (b) (4). It is then (b) (4) nanofiltered through 35 nm and 20 nm pore size filters. Subsequently, the solution is (b) (4). The bulk undergoes sterile filtration and then filling to the syringes (protocol IG_MP-000033_ING). The respective process steps are as follows.

2.1. (b) (4)

2.2 TREATMENT WITH SOLVENT-DETERGENT

2.3 FIRST GLYCINE PRECIPITATION

2.4 SECOND GLYCINE PRECIPITATION

2.5 THIRD GLYCINE PRECIPITATION

2.6 (b) (4) OF THE THIRD GLYCINE PRECIPITATE (b) (4)

2.7 DILUTION AND NANOFILTRATION

The solution is filtered consecutively through (b) (4), 35 nm and 20 nm filters.

2.8 (b) (4) AND FINAL FORMULATION

The solution is (b) (4)

2.9 BULK FILTRATION AND ASEPTIC FILLING

The solution is (b) (4) filtered through (b) (4).

2.10 ASSEMBLING THE SYRINGES OF FIBRINOGEN FOR FIBRIN SEALANT

2.11 STERILIZING WITH (b) (4)

2.12 FINAL PACKAGING AND FREEZING

MATERIALS

- (b) (4) or equivalent (b) (4) filters.
- (b) (4) and (b) (4) filters or equivalent.
- (b) (4) filters or equivalent.
- (b) (4) filters (b) (4) or equivalent.
- (b) (4) filters (b) (4) or equivalent.
- (b) (4)
- Nanofilter 35 nm and 15-nm nominal pore size, (b) (4) 35N & (b) (4) 15N.
- (b) (4) glass 3-ml and 5-ml syringes.
- Butyl rubber stoppers.

Thrombin

Thrombin (component 2) is obtained from the supernatant of fraction I. This solution is purified using (b) (4). Prothrombin (in the (b) (4)) is (b) (4) and the solution is treated by tri-n-butyl phosphate and polysorbate-80 for virus inactivation, and further purified by cation-exchange chromatography on SP-Sepharose. The (b) (4) is (b) (4), formulated and filtered through two 15 nm filters (b) (4). (b) (4) the final sterile

filtration through (b) (4) and aseptic filling into syringes is performed (protocol IG_MP-000026). The respective process steps are as follows.

- 2.1 (b) (4) OF THE PROTHROMBIN COMPLEX BY (b) (4)
- 2.2 (b) (4)
- 2.3 TREATMENT WITH SOLVENT-DETERGENT
- 2.4 PURIFICATION BY SP-SEPHAROSE ION-EXCHANGE CHROMATOGRAPHY
- 2.5 (b) (4) AND (b) (4)
- (b) (4)

2.6 BULK (b) (4)
The solution is (b) (4) and (b) (4).

2.7 NANOFILTRATION
The solution is filtered through two 15 nm filters (b) (4).

2.8 BULK FILTRATION AND ASEPTIC FILLING
A sterilizing filtration through (b) (4) is performed into syringes, which are stoppered.

2.9 ASSEMBLING THE SYRINGES OF THROMBIN FOR FIBRIN SEALANT

2.10 STERILIZING WITH (b) (4)

2.11 FINAL PACKAGING AND FREEZING

MATERIALS

- Membranes of sterile filtration of (b) (4) or equivalent.
- (b) (4)
- (b) (4) filter up to (b) (4) pore size, (b) (4) or equivalent.
- Nanofilter 15-nm nominal pore size "(b) (4) 15N".

REVIEW OF INFORMATION

Extractables & leachables in drug product

Evaluation of E&L was provided in two reports from section 3.2.P.2.4 (Container closure system) for each of the components of the DP.

- Report IG_ITEC-002265_ING v2, Fibrin Sealant (FS) Grifols. *Leachables study on syringe with tip cap (b) (4) and plunger stopper (b) (4).*
- Report IG_ITEC-002201_ING v1, Fibrin Sealant (FS) Grifols. *Leachables study on syringe with tip cap (b) (4) and plunger stopper (b) (4).*

In both studies, leachables were evaluated based on the identification of the extractables, the evaluation of which was provided by the manufacturers of the respective materials. Samples of both components of DP were tested.

Report IG_ITEC-002201_ING v1.

This study evaluated leachables from the syringe with tip cap (b) (4) and plunger stopper (b) (4). The extractables identified by the manufacturer of the tip cap and the plunger stopper were as follows.

(b) (4)

Reviewer's comment

(b) (4)

Leachables were analyzed in samples from the ongoing stability study. The samples were as follows.

- Stored between 12 and 20 months at -21 °C (three lots of DP).
- Stored under accelerated stability conditions at (b) (4) (a worst-case condition, three lots of DP).
- Filled in a (b) (4) vial (inert material) and stored at -21 °C to serve as a negative control for the container's leachables.

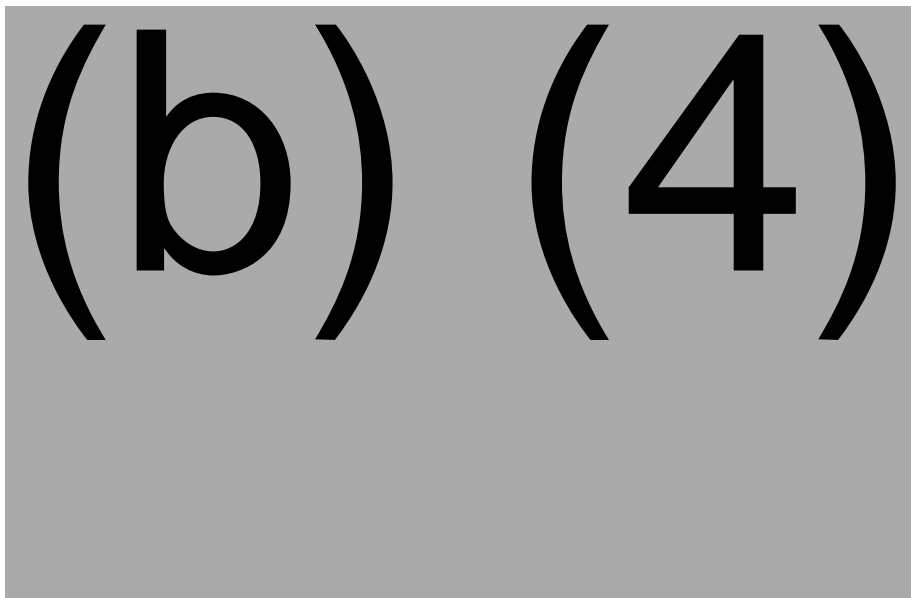
Analytical METHODS used were as follows.

(b) (4)

In most cases, the analyzed compounds were undetectable or presented at trace levels. Toxicological assessment indicated no risk.

Report IG ITEC-002265_ING v2.

This study evaluated leachables from the syringe with tip cap (b) (4) and plunger stopper (b) (4). Extractables identified by the manufacturer of the tip cap and the plunger stopper were as follows.



Leachables were analyzed after one month of storage of the DP at -21 °C (three lots) and at (b) (4) (three lots of DP, accelerated conditions) in horizontal position. The analytical methodology was the same as that in the above study. In most cases, the analyzed compounds were undetectable or presented at trace levels. Toxicological assessment indicated no risk.

As a result of both studies, no risk for patients associated with the determined levels of the leachables was found. Both types of containers for the DP were considered compatible with the filled compounds.

COMMUNICATION FOR ADDITIONAL INFORMATION

I. On 07/25/2017, an informational request (IR) was sent to the company as follows:

1. Under section 3.2.P.2.4 Container closure system (reports IG ITEC-002201_ING v1 and IG ITEC-002265_ING v2) for both fibrinogen and thrombin, you stated that (b) (4) were analyzed “according to IG_MA-000678”, and (b) (4) were analyzed “according to TO-MA-0174-1”. However, you did not include the referenced documents. Therefore, please submit the documents IG_MA-000678 and TO-MA-0174-1 to the BLA.

Response (08/02/2017, Amendment 37)

a) The provided document IG_MA-000678 is a protocol to analyze (b) (4) in aqueous solutions. It is stated that these compounds were typical leachables from polypropylene. The analytical procedure involves the preparation of standards for these compounds in organic solution ((b) (4)), and spiking them at different amounts to solutions with (b) (4). This was followed by (b) (4) in the samples by (b) (4) and analysis of the supernatants by (b) (4) with (b) (4) versus the standards.

Reviewers' Comment

It is unclear why only propylene was selected to evaluate potential leachables, but not other materials (membranes, filters, etc.) used in close proximity to the filling step. It was also not stated what were the limits of detection (LOD) of the assays for each compound, and whether those were sufficient for assessment of risk to patients. The response is incomplete.

b) The provided document TO-MA-0174-1 is a protocol to analyze (b) (4) in plasma. The principle is based on (b) (4). As an internal standard, (b) (4) was used.

Reviewers' Comment

The response is partially acceptable, as it does not describe how the (b) (4).

2. In your submission, you provided risk assessments on extractables and leachables (E&L) only for the final drug product (FDP) containers (for each of its components, fibrinogen and thrombin). However, you did not provide risk assessments on the E&L from materials, such as columns and resins, filters and membranes, etc., used at the various manufacturing steps before the filling of the product into the final container. Therefore, please provide results of studies to assess the levels of E&L in the FDP, and risk assessments of the leachables, which may be present in the FDP, from materials used at the different unit operations of the manufacturing process.

Response (08/02/2017, Amendment 37)

The company provided reports for the assessment of extractables for the materials considered to pose a risk based on their proximity to the filling step, contact time and temperature, extraction capacity and contact surface to volume ratio. For both components of the DP, the data included assessment of 26 materials (filters, bags, chromatography resins and hoses) provided in reports from the respective manufacturers ((b) (4)).

Reviewers' comment

The response is acceptable for the evaluation of extractables. Regarding the assessment of leachables, the response is incomplete.

II. On 08/17/2017, a second IR was sent to the company as follows:

Your response to our July 25, 2017 information request does not address our question about the assessment of leachables in both components of the Final Drug Product (FDP). The provided study report IG_MA-000678 describes the assessment of four organic compounds as potential leachables from polypropylene. This assessment is insufficient because it does not include the assessment of other materials (filters, membranes, etc.), which are used in close proximity to the respective filling steps when no further purification to remove them is present. Also, the referenced document does not include data about the limit of detection of the assays for each of analyzed compounds. Hence, we have the following requests for additional information:

1. For each component of the FDP, please provide an assessment of the leachables from all materials used in the following steps of the manufacturing process for (1) Fibrinogen - starting from step 2.6 to the FDP, and (2) Thrombin - starting from step 2.5 to the FDP. In this study, please also include an assessment of extractables and leachables from the applicator device (cannula).

Response (09/13/2017, Amendment 44)

a. The company provided additional membrane extractables reports Valrpt2634 and 16-4140-TFF-P2B1 and assessment of leachables for the applicator device (report IG_ITEC-002666_ING). The analytical procedure involved extraction of aqueous solutions by (b) (4) followed by combining the fractions and analysis by (b) (4) for volatile, semi-volatile and non-volatile compounds, respectively. Quantitation was performed using three calibration curves with compounds commonly used in the industry: (b) (4). (b) (4) leachables were detected. Toxicological evaluation concluded that the levels present in the DP are safe.

Reviewer's comment

Evaluation of leachables in the application device is acceptable. However, leachables were not assessed for all listed materials.

2. Please provide an assessment of the cumulative leachables in the final containers of each component of the FDP performed at the end of its shelf-life stored under either real-time or accelerated conditions.

Response (09/13/2017, Amendment 44)

The data were not provided. The company just stated that it is unlikely that leachables will appear in the drug product.

Reviewer's comment

The response is not acceptable and needs to be followed-up.

3. Please list the detection limit of the assays for all analyzed leachables, and justify that these assays are sufficiently sensitive to assure safe levels of these compounds in the FDP.

Response (09/13/2017, Amendment 44)

The company provided LODs for leachables from the tip caps (b) (4) and (b) (4) and plunger stopper (b) (4), and justification that these limits ((b) (4)) are sufficient to ensure toxicological safety of the found compounds ((b) (4)).

Reviewer's comment

It is still unclear why the LODs were so high ((b) (4)) indicating insufficient sensitivity of the methods. Typically, the LODs for most of compounds by (b) (4) are around (b) (4), which is about (b) (4) more sensitive. Therefore could have missed from the analysis. The company needs to comment on it.

4. Please explain how you (b) (4) of (b) (4) in the analyses of samples described in document TO-MA-0174-1.

Response (09/13/2017, Amendment 44)

The company explained that (b) (4) was based on (b) (4).

Reviewer's comment

The response is acceptable.

5. Please provide more details on the procedure used in your extractable/leachable studies (reports IG_ITEC-002265_ING and IG_ITEC-002201_ING). In particular:

a) Clarify if fibrinogen and thrombin components were in contact with the stopper during storage at -20°C (to create a worst-case condition), or only with the tip (representing normal storage conditions),

b) in Report IG_ITEC-002265_ING, you state: "one (b) (4) tip cap and one (b) (4) plunger stopper were soaked, separately, in a 10 mL (b) (4) syringe, with different volumes of each product separately." Please clarify the duration and temperature condition for the soaking step.

Response (09/13/2017, Amendment 44)

The company confirmed that the whole surface of the tip cap and plunger stopper was in contact with the product during storage. During the study, the samples were kept frozen for one month at -21 °C (normal storage conditions) and (b) (4) (accelerated conditions).

Reviewer's comment

The response is acceptable.

III. On October 5, 2017, a third IR was sent to the company as follows.

1. You study reports for assessment of leachables in the product containers and application device do not have information about assessment of recovery of organic compounds from aqueous solutions upon the extraction into the organic phase for further analysis, and whether the respective factors were applied to calculate the concentrations in the parental samples. In particular, a low recovery factor can result in underestimation of the respective leachable in the drug product, which in turn, would result in incorrect assessment of the risk for patients. Therefore, please provide such information for each potential leachable and confirm that the respective correction factors were applied for respective quantitation and safety assessments.

Response (October 10, 2017, Amendment 55)

The company provided recovery data for the analyzed compounds, (b) (4). These values were in the range of (b) (4) and the respective factors were applied for safety assessment. In case of (b) (4), no data for recovery were available from the external contractors. However, due the wide safety margin determined for those compounds (response to question 3, Amendment 43, September 13, 2017), their presence was deemed safe. Regarding the quantitation of organic compounds present in the application device, the company explained that an internal standard was used for that (report IG_ITEC-002666_ING). This standard was spiked in the blank (aqueous) solution, thus, was subjected to the same extraction process as the samples that ensured correctness of calculations.

Reviewer's comment

The response is acceptable.

2. In your response on our question 3 (on 09/13/2017, Amendment 44), you stated that the detection limits of (b) (4) identified organic leachables from final containers were (b) (4) (i. e. (b) (4), Table 4, page 14); which was likely applicable for other (non-detected) organic compounds. From our experience, using (b) (4)-based methods for analysis of organic compounds, the detection limits are typically (b) (4) (i. e. (b) (4)) that generally results in detection of significantly higher number of leachables. Indeed, in your study of leachables from application device, the concentrations of identified compounds were in the range of (b) (4) (report IG_ITEC-002666_ING, Tables 8-11). Therefore, please comment on relevance of your analytical methodology to the intended purpose, in particular, possible missing other leachables from detection in studies performed for final containers.

Response (October 10, 2017, Amendment 55)

The company agreed that the methods used should have been much more optimized. However, the respective safety margin was still sufficient.

Reviewer's comment

Dr. Evi Struble also confirmed the safety of these compounds at the level of the LODs. Thus, the response is acceptable.

3. It appears that you have applied the correction factor twice for the non-volatile leachables. According to pages 13 and 14 out of 31 in report IG_ITEC-002666_ING, the calculation of (b) (4) was performed by applying a (b) (4). However, in table 11 (page 18/31), a "Corrected concentration (ug/L)" an additional correction factor due to pre-concentration is applied. Please check the calculations for accuracy.

a) If the amounts are adjusted upwards, please submit a complete toxicological assessment of the leachables identified. Links to peer reviewed publications should be accompanied by critical assessment of the studies performed by qualified toxicologist(s).

Response (October 10, 2017, Amendment 55)

The company confirmed that the correction factors were applied only once. Based on this, the values provided in report IG_ITEC-002666_ING were correct.

Reviewer's comment

Dr. Evi Struble, who reviewed this response, found that this information is acceptable. Her review memo in the form of email correspondence is attached. From my perspective, the response is also acceptable.

REVIEW SUMMARY

Leachables in the DP were assessed for the container closure system, applicator device (cannula) and in filled solutions in stability study. This study is ongoing and involves testing the product under real-time storage conditions at multiple time-points throughout the product shelf-life. However, for some materials such as filters and membranes, leachables were not evaluated. On 10/03/2017, the review committee additionally discussed this issue and concluded that absence of specific information for selected materials does not pose a concern for the product safety, based on the following reasons:

- Fibrin sealant is for topical use and is expected to be used once per surgery. The requirements for this class of products are less stringent compared to coagulation factors or other products that are administered intravenously.
- The product containers, (b) (4) syringes and (b) (4) stoppers, are not new materials and have a long history of use in the pharmacological industry.
- Although separate studies were not performed for some materials (nanofillers, sterile filters *etc*), these materials have short contact time with the product, and are used in the same manner as the manufacture of other licensed products by Grifols (IV immunoglobulin and Albumin). Besides, Grifols' risk assessment based on extractables qualifies these materials as non-risk. Therefore, additional studies with these materials are not needed to support product safety.
- Low sensitivity of methods used ((b) (4)) implies that the actual levels of leachables are lower than the LOD. Therefore, for risk assessment, LOD represents the worst-case scenario, the levels of which do not raise safety concerns. Thus, even if Grifols repeat the leachable studies using more sensitive methods, the detected levels will not change the outcome of risk assessment.

CONCLUSION

Dr. Evi Struble, who reviewed the information on leachables from the toxicological perspective, found that this information is acceptable. Her review memos are attached (in the form of email correspondence). In conclusion, the levels of leachables from the manufacturing process in the final drug product will not affect its safety profile. Approval is recommended.