

**FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Therapeutic Products
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Division of Pharmacology/Toxicology 2
Pharmacology/Toxicology Branch 4**

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PRODUCT: FESILTY (Fibrinogen BT524)

APPLICANT: Grifols Therapeutics, LLC

PROPOSED INDICATION: For treatment and prophylaxis in pediatric and adult patients with congenital hypo- or afibrinogenemia with bleeding tendency.

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EXECUTIVE SUMMARY:

This memorandum summarizes the review of the toxicological risk assessment (TRA) of extractables and leachables in FESILTY, a lyophilized fibrinogen concentrate supplied in a glass vial container closure system. In this original Biologic License Application (BLA), the applicant submitted results from an extractables and leachables evaluation conducted on the final reconstituted product at time point 0, representing the starting time point immediately after process performance qualification (PPQ). The applicant identified 15 organic compounds and 10 elemental compounds detected above analytical thresholds. The TRA incorporated worst-case exposure scenarios, bioavailability adjustments for parenteral administration, and conservative safety factors. Compounds without established exposure limits were assessed based on data from structurally similar compounds and regulatory guidance thresholds. The applicant has committed to evaluate potential leachables over FESILTY's intended shelf life of 36 months plus an (b) (4), with ongoing studies planned at 12-month, 36-month, and (b) (4) timepoints. Based on the review of the TRA, there are no deficiencies identified at the initial time point, and the data provide sufficient support for the safety of FESILTY in the proposed container closure system.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:

Based on the TRA for extractables and leachables of lyophilized fibrinogen concentrate reconstituted in the co-packaged diluent with the supplied transfer device and stored in a glass vial with a bromobutyl stopper, there are no deficiencies identified in this submission. The data provide sufficient support for the safety of FESILTY in the proposed container closure system at time point 0.

Formulation and Chemistry:

FESILTY is a lyophilized, heat-treated fibrinogen concentrate in which 1 g is supplied in type (b) (4) borosilicate glass vials closed with type (b) (4) bromobutyl stoppers, which are held in place with metal crimps covered with flip-off plastic caps. Sterile water for reconstitution is packaged separately in single-dose containers consisting of 20 mm neck type (b) (4) glass vials stoppered with a chlorobutyl rubber stopper, which is protected by an aluminum flip-off cap. 1 g of fibrinogen lyophilisate is dissolved in 50 mL water for injection (WFI). The vials contain no antimicrobial agent or other added substance. The device supplied for reconstitution is the nextaro v, 20/20 5 µm, manufactured by SFM medical devices GmbH. Extractable and leachables evaluation was performed on the final reconstituted product in the contained closure system.

Abbreviations

ADI	Acceptable daily intake
AET	Analytical evaluation threshold
(b) (4)	
BLA	Biologics license application
CMC	Chemistry, manufacturing, and controls
DNEL	Derived no effect level

DP	Drug product
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EPA	Environmental Protection Agency
ICH	International Council for Harmonisation
IR	Information request
LOQ	Limit of quantification
MoS	Margin of safety
NIH	National Institutes of Health
NOAEL	No observed adverse effect level
PDE	Permitted daily exposure
PPQ	Process performance qualification
PQRI	Product Quality Research Institute
P/T	Pharmacology/toxicology
QT	Qualification threshold
RfD	Reference dose
SCT	Safety concern threshold
STN	Submission tracking number
TDI	Tolerable daily intake
TRA	Toxicological risk assessment
TTC	Toxicological threshold of concern
USPI	United States Prescribing Information
WFI	Water for injection

INTRODUCTION

FESILTY is a lyophilized, heat-treated human fibrinogen concentrate indicated for treatment and prophylaxis of bleeding in pediatric and adult patients with congenital hypo- or afibrinogenemia with bleeding tendency. Fibrinogen is critical to the coagulation cascade in which thrombin converts fibrinogen to fibrin resulting in clot formation. Normal blood fibrinogen concentration is between 2.0 and 4.5 g/L, although this range can vary among individuals. In cases of fibrinogen deficiency, blood coagulation does not occur properly and can result in severe hemorrhagic events.

The final drug product (DP) is contained in type (b) (4) borosilicate glass vials closed with type (b) (4) bromobutyl stoppers and is reconstituted with the supplied diluent, sterile WFI, using the nextaro v transfer device. FESILTY is to be administered intravenously, and the applicant notes that (b) (4) g is to be administered initially with subsequent infusions as required. In cases of severe hemorrhage, (b) (4) of fibrinogen may be required. Given that individuals may require a maximum dose of up to (b) (4) (equating to (b) (4) vials), the applicant considered this as the worst-case dosing regimen in their TRA.

Based on the analysis of the study protocols and chemical characterization conducted by

reviewer Dr. Andrey Sarafanov, the information provided for the risk assessment of extractables and leachables from the container closure system was determined to be acceptable. As summarized in this memo, the TRA of the organic compounds and elemental impurities identified in these analytical studies did not present significant safety concerns.

NONCLINICAL STUDIES

Study Number	Study Title	Report Number
1	Leachables Study of Fibrinogen Concentrate (BT524) drug product	BE-219-24/01
2	Screening Risk Assessment of Leachables in Stability Samples of Drug Product Fibrinogen Concentrate (BT524)	BE-218-24/01

Study #1

Methods:

The leachables study of FESILTY (fibrinogen concentrate BT524) drug product was evaluated at timepoint 0 (T0), representing the starting time point immediately after PPQ was conducted at commercial scale across (b) (4) production sites.

Reconstitution of FESILTY was performed using the co-packaged diluent, WFI and the transfer device according to the United States Prescribing Information (USPI) to ensure an overall leachable profile of the final, ready-to-use product. (b) (4) batches of reconstituted FESILTY underwent leachables analyses via various (b) (4) methods to detect volatile, semi-volatile, non-volatile, and elemental leachables. Following a risk evaluation of extractables and leachables during manufacturing and storage that detected no direct leachable risk, the applicant conducted a leachable screening study of the final reconstituted product. Compounds detected above established limit values, as described below, were identified for TRA.

The safety concern threshold (SCT) was based on (b) (4) guidelines on assessment and control of mutagenic impurities in pharmaceuticals to limit potential carcinogenic risk. Since FESILTY can be administered over a maximum of (b) (4), an SCT of (b) (4) was considered, as indicated for a treatment duration of less than (b) (4). In a worst-case scenario dosing regimen, up to (b) (4) of FESILTY may be administered. Thus, the limit value for mutagenic impurities per vial was calculated to be (b) (4). The analytical evaluation threshold (AET) incorporated an uncertainty factor of (b) (4) to address measuring inaccuracies. Therefore, the final AET for mutagenic impurities was determined to be (b) (4) corresponding to (b) (4) for the reported (b) (4) values (see equations below).

(b) (4)

AET= analytical evaluation threshold; TC= threshold of concern; D= daily dose; U_f= uncertainty factor, here (b) (4) since the relative standard deviation (RSD) is assumed to be (b) (4)

Source: BE-219-24/01, Section 3, pg. 8

(b) (4)

Source: Response to P/T IR #5 (IR #26), pg. 1

Compounds detected above the limit of quantification (LOQ) of the (b) (4) analyses but below the calculated AET were included in the TRA as a conservative safety measure.

The margin of safety (MoS) was calculated based on the established exposure limit divided by the maximum exposure to the patient. The established exposure limits were derived from various regulatory sources including (b) (4)

Results:

Using worst case scenario exposure assumptions and reporting compounds above LOQ and/or AET, a total of 15 organic compounds and 10 elemental compounds were detected in the FESILTY DP at T0 (Table 6). In line with the worst-case scenario, all identified compounds were identified as potential leachables and underwent a toxicological risk assessment, which are further reviewed in Study #2.

Table 6: Summary of maximal exposure values and limits as well as the resulting margin of safety

(b) (4)

(b) (4)

Source: BE-219-24/01, Section 5, Table 6, pg. 12

Reviewer's Comment:

- In response to information request (IR) #22 (P/T IR#4), question 3, the applicant acknowledged 2 errors regarding the intake values for (b) (4) in Table 7 of study report BE-218-24 that included inconsistent values within the table and a mathematical error converting grams to micrograms. Correction of these errors increased the MoS for (b) (4) as well as (b) (4). The applicant corrected these errors in BE-218-24, but not in BE-219-24/01, however the corrected values also apply to Table 6 in BE-219-24-01.
- In response to IR #26 (P/T IR #5), the applicant provided justification for: a) their calculated thresholds and b) the conversion factor and methodology used to convert µg/g and µg/mL.

- *The applicant notes that risk assessments for carcinogens assume that cancer risks correlate with cumulative exposure. Given that FESILTY is administered for up to (b) (4), the applicant established an acceptable daily intake of (b) (4), in accordance with (b) (4) guidelines.*
 - *Regarding non-mutagenic compounds (e.g., local irritants), the applicant used the same safety threshold of (b) (4) as mutagenic compounds. The applicant justified this approach by noting that if they extrapolated from the (b) (4) threshold of (b) (4) (as for mutagenic compounds) rather than the (b) (4) qualification threshold (b) (4) of (b) (4) (for intake of non-mutagenic substances), the extrapolated PDE for non-mutagenic leachables in FESILTY would exceed the established (b) (4). However, because the QT is informative of sensitization and local irritation which do not accumulate throughout a lifetime, it is inappropriate to extrapolate for lifetime exposure. While the applicant did not consider a QT of (b) (4), it is in this reviewer's opinion that the applicant's assessment of compounds detected above both the LOQ and AET levels provides comprehensive coverage of potential leachables.*
 - *The applicant provided additional information pertaining to the conversion of $\mu\text{g/g}$ to $\mu\text{g/mL}$. The AET of (b) (4) is equal to (b) (4) (1 vial contains 1 g of FESILTY), which is reconstituted in 50 mL of WFI, therefore (b) (4).*
- *In response to IR #27 (P/T IR #6) the applicant clarified that the reported leachable concentrations refer to the final LOQ which is the detection limit in the ready-to-use product following reconstitution. This incorporates dilution factors used in reconstituted samples for (b) (4) analyses.*

Study #2

Methods:

A TRA was performed to evaluate the safety of the leachable compounds identified above the LOQ or AET in the FESILTY DP. For each identified leachable, the applicant conducted a literature search for previously established compound exposure limits. For compounds without established limits, the applicant referred to other regulatory and/or health-based exposure limits available for structurally similar compounds. For compounds without known structurally similar analogs, an IR was sent to the applicant requesting additional database searches to obtain toxicological profile information for the unidentified compounds.

Established regulatory/health-based exposure limits were available for oral routes of exposure, however FESILTY is intended for parenteral administration. Extrapolation of the data from oral

to parenteral was calculated using a bioavailability adjustment factor using the following formula, where intravenous bioavailability is 100%¹:

$$\text{Bioavailability factor} = \frac{\text{bioavailability by intravenous route}}{\text{bioavailability by oral route}}$$

Source: BE-218-24/01, Section 4.1.1, pg. 15

The applicant determined bioavailability factors based on available bioavailability data. For compounds with high oral absorption rates (e.g., (b) (4)), a bioavailability factor of 1 was applied. For the (b) (4), a bioavailability factor of ^{(b) (4)} was also applied based on read across from (b) (4) data. For compounds with oral absorption rates ranging from 64.4%-99.9% (e.g., (b) (4)), or for compounds where read-across data suggested oral absorption, but specific bioavailability data were unavailable (e.g., (b) (4)), the applicant applied a conservative assumption of 50% oral bioavailability, resulting in a bioavailability factor of ^{(b) (4)}. For polysorbate degradation products for which bioavailability data were not available, a conservative default bioavailability factor of ^{(b) (4)} was applied.

The bioavailability factors were then applied to known oral exposure limits to derive parenteral exposure limits. For compounds with no established exposure limits, regulatory/health-based exposure limits available for structurally similar compounds were used in the applicant's risk assessment.

To determine the level of risk, a MoS was determined by comparing the estimated worst-case patient exposures with the established limits which incorporated bioavailability calculations. The applicant considers a MoS ≥ 1 acceptable given: a) the worst-case scenario assumptions used in

^(b) (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

their analyses, and b) the short-term exposure of the product. However, this reviewer has provided additional information in the results section for compounds with a MoS ≤ 10 .

Results:

The applicant identified 2 organic leachable compounds, (b) (4), with a MoS of 3.0 and 7.0, respectively.

- (b) (4) The applicant notes this is a non-genotoxic compound. A no observed adverse effect level (NOAEL) of (b) (4) with 100% absorption in rats following oral administration has been established.⁹ To address human exposure, the applicant applied an extrapolation factor of (b) (4) resulting in a PDE of (b) (4) for humans. While the (b) (4) guideline recommends a rat-to-human extrapolation factor of (b) (4) the applicant used a more conservative factor of (b) (4) when establishing the exposure limit for the risk assessment. Additionally, (b) (4) was detected in only (b) (4) analytical replicates, suggesting it may not represent a consistent leachable risk.
- (b) (4) This compound is similar in structure and a metabolite of (b) (4). The (b) (4) panel notes an oral ADI of (b) (4) (b) (4), equating to (b) (4) for a 70 kg adult. Since (b) (4) oral bioavailability data is not available, the applicant assumed 50% oral bioavailability. To address systemic exposure following parenteral administration, the parenteral dose is (b) (4) (50% of the oral dose to account for the difference in bioavailability). The applicant applied an additional safety factor of (b) (4) to address uncertainties in the read-across approach between (b) (4) and (b) (4) (i.e., accounting for potential differences in toxicological profiles due to structural differences, intraspecies variation⁹), resulting in a final parenteral ADI of (b) (4). This compound was detected above the established AET in (b) (4) replicates in the applicant's (b) (4) analysis, with a calculated maximum exposure of (b) (4) µg/patient, but below the calculated parenteral ADI of (b) (4). Therefore, it is in this reviewer's opinion that (b) (4) does not pose a significant safety risk.

(b) (4)

⁹ Masuda-Herrera, M., H. T. Rosen, A. Burild, T. Broschard, T. Bell, J. Graham, T. Griffin, J. Hillegass, P. Leavitt, B. Huta, P. Parris, U. Bruen, M. Cruz, and J. Bercu. "Harmonisation of Read-across Methodology for Drug Substance Extractables and Leachables (E&Ls)." Regul Toxicol Pharmacol 145 (Dec 2023): 105494. <https://dx.doi.org/10.1016/j.yrtph.2023.105494>.

The applicant identified 4 unknown or partially unknown compounds with a MoS ranging from 2.7 to 3.0 compared to the (b) (4) TTC threshold of (b) (4) . In response to IR #22 (P/T IR #4), the applicant performed additional database searches and comparisons to structurally similar compounds with known toxicological profiles or daily intake information, as described below.

- (b) (4)

- (b) (4)
- (b) (4)
- (b) (4)

■ (b) (4)

■ (b) (4)

■ (b) (4)

(b) (4)

The applicant identified 2 leachable metals, (b) (4), with a MoS of 4 and 8, respectively. Per (b) (4) guidelines, elemental impurities are compared to established PDE limits that represent the maximum acceptable exposure levels for lifetime daily administration¹³. Since FESILTY is to be administered for a duration of less than (b) (4), it is in this reviewer's opinion that consideration of lifetime daily exposure limits is a conservative approach for this TRA.

Reviewer's Conclusion:

- *Based on the provided information and considering worst case scenario assumptions used to estimate patient exposure, it is in this reviewer's opinion that the identified leachables are below the acceptable exposure and therefore do not pose a significant safety risk immediately following FESILTY reconstitution. Ongoing analyses and risk assessments are to be submitted for timepoints representative of FESILTY shelf-life, with the applicant noting the next timepoint of 12 months.*

CONCLUSION OF RISK ASSESSMENT

Based on the review of the submitted TRA and subsequent IR responses, the leachable compounds identified are unlikely to pose a significant risk to patients under the proposed clinical use.

(b) (4)