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Draft Guidance on Defibrotide Sodium

May 2023

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Active Ingredient:	Defibrotide sodium
Dosage Form; Route:	Solution; Intravenous
Strength:	200 mg/2.5 mL
Recommended Studies:	Comparative characterization studies to support active ingredient sameness and request for waiver of in vivo bioequivalence study requirements

This guidance provides recommendations for developing generic defibrotide sodium intravenous solution containing defibrotide sodium as the active ingredient. It includes recommendations for supporting active ingredient sameness and for requesting waiver of in vivo bioequivalence study requirements.

Recommendations to Support Active Ingredient Sameness:

For characterization to support sameness between the active ingredient of the test product and the active ingredient from the reference listed drug (RLD), FDA recommends that the potential applicants develop and use appropriately validated orthogonal analytical methods, as applicable, to perform side-by-side comparative testing, especially when unambiguous results cannot be obtained by using a single analytical method. A minimum of three batches of the test active ingredient and three batches of the active ingredient from the RLD should be characterized to assess active ingredient sameness and robustness in the manufacturing process.

In general, the comparative studies of finished product should be performed on samples of at least three exhibit batches of test product, tested minimally at release and at the end of the proposed shelf life, and at least three batches of the RLD of different ages prior to expiry (as available, stored under conditions consistent with the labelled storage conditions). Defibrotide

double-strand or high order structure content in the test and RLD products, if present, should be comparable. For studies that may be impacted by the defibrotide double-strand or high order structure content, if “denatured” samples are included as part of the studies, the denaturation process should not lead to degradation of defibrotide. For studies that may be impacted by dilution, samples evaluated should include “as is” product solutions and diluted product solutions per the product labeling.

The active ingredient sameness can be established by evaluating the equivalence in the following:

1. Source of the starting material

The starting material (animal source and organ tissue) used to manufacture the test active ingredient should be equivalent to that used to manufacture the active ingredient for the RLD.

2. Mode of depolymerization

Depolymerization method used in the test active ingredient manufacturing process should be equivalent to that used in the RLD active ingredient manufacturing process.

3. Chemical structure, molecular weight distribution and composition

Evaluation of test active ingredient and the active ingredient from the RLD should be performed to demonstrate comparable chemical structure, molecular weight distribution and composition. These could include but not be limited to the following:

- a. Elemental composition
- b. Nucleic base composition including purines/pyrimidines ratio
- c. Nucleic phosphorus content including sodium/phosphorus and phosphorus/base ratios
- d. Fingerprint structural features using diverse spectroscopic technologies
- e. Molecular weight and distribution, including mean molecular weight and polydispersity, point-to-point comparison and multiple fractions comparison (e.g., 3 – 6 kDa, 6 – 12 kDa, > 12 kDa, and > 41 kDa) of the molecular weight distribution curve

4. Physicochemical properties

Side-by-side comparative physicochemical characterizations of the test and RLD products should be performed to include high order structures (e.g., through CD, melting temperature) and aggregation of the active ingredient in the drug product.

5. Biological activity

Comparative biological activity should be assessed for both the active ingredient and the drug product. Both fibrinolytic activity/plasmin assay and euglobulin assay are recommended for the comparative studies of the test active ingredient and the active ingredient from the RLD, while at least one of such comparative studies is recommended for the test and RLD products. In addition, an assessment demonstrating that the innate immune and inflammatory response elicited by the test product is reproducible and comparable to that of the RLD is recommended.

A comparative profile analysis should be performed for product-related impurities and process-related impurities, including impurities derived from mucosa of the animal source. Innate immune modulating impurities derived from the mucosa of the animal or the manufacturing process as well as higher order structures or aggregates in the drug product should be assessed as part of the immunogenicity risk assessment. The risk of residual DNA, RNA or other contaminants should be assessed, and it should be demonstrated that there is no added risk present compared with the RLD.¹

Waiver of in vivo bioequivalence study requirements:

To qualify from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b), a generic defibrotide sodium intravenous solution product should be qualitatively (Q1)² and quantitatively (Q2)³ the same as the RLD.

An applicant may seek approval of a drug product that differ from the RLD in preservative, buffer or antioxidant if the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.⁴

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¹ See Questions and Answers on Current Good Manufacturing Practice Requirements | Control of Components and Drug Product Containers and Closures website (<https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practice-requirements-control-components-and-drug>).

² Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.

³ Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within $\pm 5\%$ of those used in the RLD product.

⁴ 21CFR 314.94(a)(9)(iii)