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Draft Guidance on Protamine Sulfate

May 2026

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Active Ingredient:	Protamine sulfate
Dosage Form:	Solution
Route:	Intravenous
Strengths:	50 mg/5 mL (10 mg/mL) | 250 mg/25 mL (10 mg/mL)
Reference Listed Drug:	NDA 006460
Recommended Studies:	Request for waiver of in vivo bioequivalence study requirements and comparative characterization studies to support active ingredient sameness

Waiver request of in vivo bioequivalence study: To qualify for a waiver from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b)(1), a generic protamine intravenous solution product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

An applicant may seek approval of a drug product intended for parenteral use that differs from the RLD in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the test product.[3]

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the RLD.
[3] 21 CFR 314.94(a)(9)(iii).

Recommendations to support active ingredient sameness and impurity assessment:
To ensure active ingredient sameness, conduct the following comparative analyses between the proposed generic protamine (test) and the designated reference standard (RS). Testing should be performed on no less than three batches of the test product and RS.

1. Demonstrate comparable identity, quantity, and higher order structures of the four main protamine peptides to the RS. The primary sequences for the four protamine peptides are:

   Peptide 1-PRRRRRSSSRPIRRRRRPRASRRRRRGGRRRR
   Peptide 2-PRRRRSSRRPVRRRRRPRVSRRRRRRGGRRRR
   Peptide 3-PRRRRSSSRPVRRRRRPRVSRRRRRRGGRRRR
   Peptide 4-PRRRRASRRIRRRRRPRVSRRRRRGGRRRR

2. The total amount of phosphorylated peptides, and the total amount of other peptide impurities, in the proposed product should not exceed those in the RS.

3. Demonstrate comparable innate immune response risk for the proposed test product and RS.
   - Demonstrating comparable innate immune activities can be accomplished through analyzing aggregates and non-peptide process-related impurities, which may alter the product's immunogenicity profile. Differences found in comparability studies assessing aggregates should be mitigated using manufacturing strategies. Levels of non-peptide process-related impurities including particulate matter, microbial contaminants, endotoxins, residual organic solvents, elemental impurities and leachables, residual DNA and RNA should meet compendial acceptance criteria and toxicological limits.
   - If non-peptide process-related impurities meet these criteria and limits, and aggregation profiles are comparable to that of the RS, applicants do not need to conduct in vitro innate immune testing.

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