

Draft Guidance on Dalteparin Sodium

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Dalteparin Sodium

Form/Route: Injectable/Subcutaneous

The reference product is a parenteral solution. If the test product meets the following five criteria for demonstrating active ingredient sameness, and is qualitatively (Q1) and quantitatively (Q2) the same as the reference product, the waiver request for *in vivo* BE study requirements for all strengths may be granted based on 21 CFR 320.22(b)(1).

The five criteria for demonstrating active ingredient sameness of the test and reference products are:

1. Equivalence of physicochemical properties
2. Equivalence of heparin source material and mode of depolymerization
3. Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species
4. Equivalence in biological and biochemical assays
5. Equivalence of *in vivo* pharmacodynamic (PD) profile

For additional information on Criteria 1, 2, 3 and 4, please refer to the FDA response to Citizen Petition, Docket No. FDA-2003-P-0273.¹

The recommended *in vivo* PD study design (Criterion 5) in support of active ingredient sameness is as follows:

Type of study: Fasting

Design: Single-dose, two-way crossover *in vivo*

Strength: 95,000 IU /3.8 mL (25,000 IU/mL)

Dose: 120 IU/kg of body weight, but not more than 10,000 IU, administered subcutaneously

Subjects: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study.

¹ The FDA response to Citizen Petition, Docket No. FDA-2003-P-0273, was written to address issues related to active ingredient sameness of enoxaparin sodium. However, the general approach described in this response for demonstrating active ingredient sameness of enoxaparin sodium is also applicable for dalteparin sodium. Please note that the FDA response to Citizen Petition Docket No. FDA-2003-P-0273 is available to the public at <http://www.regulations.gov>.

PD endpoints to measure: Anti-Xa and anti-IIa in plasma.

The following PD parameters should be determined for anti-Xa and anti-IIa: peak effect (anti-Xa_{max}, anti-IIa_{max}), area under the effect curve (AUEC_{0-T} and AUEC_{0-∞}), T_{max}, and T_{1/2}.

Equivalence based on (90% CI): Anti-Xa, the 90% CIs for the geometric mean test/reference ratios of AUEC and anti-Xa_{max} must fall within the BE limits of 80-125%.

Please submit the test and reference anti-IIa data as in vivo supportive evidence of active ingredient sameness.