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Draft Guidance on Aprepitant

February 2024

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Active Ingredient:	Aprepitant
Dosage Form:	Emulsion
Route:	Intravenous
Strengths:	32 mg/4.4 mL (7.2 mg/mL), 130 mg/18 mL (7.2 mg/mL)
Recommended Studies:	Two in vitro bioequivalence studies and supportive comparative characterization studies

To demonstrate bioequivalence using the studies recommended in this guidance, the test product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same reference listed drug (RLD).

Two in vitro bioequivalence studies:

1. Type of study: Globule size distribution (GSD)
   Design: In vitro bioequivalence study on three batches of both test and reference standard (RS) products
   Strengths: 32 mg/4.4 mL (7.2 mg/mL), 130 mg/18 mL (7.2 mg/mL)[3]
   Additional comments: The sample preparation method and selected particle sizing methodology should be adequately optimized and validated to demonstrate the adequacy of the selected method in accurately and reliably identifying and measuring the size of the

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[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 reference product.
[3] Testing of a strength(s) other than the designated reference standard (RS) strength, or a portion of the strength (i.e., part of a vial), and waiving of other strengths may be acceptable. Justification may include, but is not limited to, why testing of another strength(s), or a portion of the strength, is representative of the designated RS strength.

drug particles. Prospective applicant should perform size characterization at different dilution conditions as part of method development to demonstrate the impact of dilution. Full GSD profiles representative of all test product and RS product batches tested should be submitted as supporting information.

Parameters to measure: Z-average size and polydispersity index (PDI) or D_{50} and SPAN [$(D_{90}-D_{10})/D_{50}$], as appropriate

Bioequivalence based on (95% upper confidence bound): Population bioequivalence (PBE) analysis of the Z-average and PDI, or D_{50} and SPAN. Prospective applicants should provide no less than 10 datasets from three batches each of the test and RS products to be used in the PBE analysis. For additional information on PBE statistical analysis, refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929).[a]

2. Type of study: Comparative in vitro release testing (IVRT) of aprepitant
Design: Should be performed on three batches of both test and RS products using at least 12 units from each batch
Strengths: 32 mg/4.4 mL (7.2 mg/mL), 130 mg/18 mL (7.2 mg/mL)[3]
Additional comments: The IVRT method study should include information on the method development and validation to detect potential formulation differences and capture the complete release profile of aprepitant.

Bioequivalence based on: Comparative analysis of dissolution profiles should be established using an appropriate statistical method (e.g., model independent approach using similarity factor (f_2)). For more information on calculation of f_2 factor, refer to the most recent version of the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.[b]

Comparative characterization studies:

Comparative physicochemical characterization of the test product and the RS product. The comparative studies should be performed on a minimum of three exhibit batches of the test product[4] and three batches of the RS product and should include but not limited to, the following:

a. Viscosity
b. pH
c. Zeta-potential
d. Osmolality

[4] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

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[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

[b] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.