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Draft Guidance on Dantrolene Sodium

August 2022

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This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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In October 2017, FDA issued a draft product-specific guidance for industry on generic dantrolene sodium. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient:	Dantrolene sodium
Dosage Form; Route:	For suspension; intravenous
Recommended Study:	In vitro bioequivalence studies including drug particle size and size distribution test, rapid dissolution study, and supportive characterization studies

To qualify for the in vitro option for this drug product, the following criteria should be met:

1. The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)¹ and quantitatively (Q2)² the same (Q1/Q2).

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.

2. Acceptable comparative physicochemical characterizations of the test and Reference Standard (RS) products. Comparative analysis should be performed on at least three batches of both test and RS products and should include:
 - a. pH, osmolality, and soluble fraction of dantrolene after reconstitution according to label instructions

In vitro bioequivalence study 1:

Drug particle size and size distribution of dantrolene sodium.

Additional comments: The particle size distribution should be compared using the population bioequivalence (PBE) statistical analysis procedure (95% upper confidence bound) based on D50 and SPAN [i.e. (D90-D10)/D50]. Refer to the most recent version of FDA product-specific guidance on *Budesonide Inhalation Suspension*^a for additional information regarding PBE. Information on the instrument, analysis mode (if applicable), dilution medium, and level of dilution used for particle size measurements should be submitted along with full profiles of the particle size distribution upon serial dilution.

In vitro bioequivalence study 2:

Acceptable comparative study to demonstrate rapid dissolution of dantrolene sodium from the test and RS products.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

Revision History: Recommended October 2017; Revised August 2022

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^a For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>.