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Draft Guidance on Metoprolol Succinate

May 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.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

In November 2018, FDA issued a draft product-specific guidance for industry on generic metoprolol succinate. We are now issuing revised draft guidance for industry that replaces the previously issued guidance

Active Ingredient:	Metoprolol succinate
Dosage Form; Route:	Capsule, extended release; oral
Recommended Studies:	Three in vivo bioequivalence studies with pharmacokinetic endpoints
1.	Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo Strength: EQ 200 mg tartrate Subjects: Males and non-pregnant, non-lactating females, general population Additional comments: None

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: EQ 200 mg tartrate
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: None

3. Type of study: Fasting, sprinkle-in-applesauce
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: EQ 200 mg tartrate
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: None

Analyte to measure: Metoprolol in plasma

Bioequivalence based on (90% CI): Metoprolol

Additional strengths: Bioequivalence of the EQ 25 mg, 50 mg, and 100 mg tartrate strengths to the corresponding reference product strengths may be demonstrated based on principles laid out in the most recent version of the FDA guidance for industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.^a

Dissolution test method and sampling times: For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's Dissolution Methods database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each strength of the test and reference products. Specifications will be determined upon review of the ANDA.

In addition to the method above, submit dissolution profiles on 12 dosage units for each strength of the test and reference products generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (e.g., pH 1.2, 4.5 and 6.8 buffer). Agitation speeds may be increased if appropriate. It is acceptable to add a small amount of surfactant if necessary. Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released to provide assurance against premature release of drug (dose dumping) from the formulation.

Alcohol dose dumping studies: Due to concerns of dose dumping of drug from this product when taken with alcohol, conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: 500 mL, 0.1N HCl, USP Apparatus 2 (paddle) at 50 rpm, with or without alcohol

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl) with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Conduct testing on both test and reference products accordingly, and provide data on individual unit, means, range and %CV.

Product-specific testing conditions for in vitro feeding tube studies: The approved labeling for the reference product states that the product may be administered by a nasogastric (NG) tube (12 French or larger). Conduct the in vitro feeding tube studies including comparative recovery testing, sedimentation volume and redispersibility testing, particle size distribution study, and comparative dissolution testing. For general procedures of in vitro feeding tube studies, refer to the most recent version of the FDA guidance for industry on *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations*.^a

Testing tube: NG tube (12 French)

Testing strengths: EQ 200 mg Tartrate

Dispersion medium: 15 mL water with different pH values (e.g., pH 5.5, 7.0 and 8.5)

Revision History: Recommended November 2018; Revised May 2022

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^a For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>