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Draft Guidance on Liothyronine Sodium

February 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 August 2021, FDA issued a draft product-specific guidance for industry on generic liothyronine sodium. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Liothyronine sodium

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, four-way, fully replicated crossover in vivo
   Strength: EQ 50 mcg Base at the dose of EQ 100 mcg Base (2 x EQ 50 mcg Base)
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Measure baseline concentrations of liothyronine at -0.5 h, -0.25 h, and 0 h before dosing. Use the average of three pre-dose concentrations of liothyronine for the baseline adjustment to the post-dose concentrations. Apply baseline correction to the post-dose liothyronine concentrations in each period for each subject. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of liothyronine. A reference-scaled average bioequivalence

approach is recommended for the statistical analysis of liothyronine pharmacokinetic parameters.

2. Type of study: Fed
Design: Single-dose, four-way, fully replicated crossover in vivo
Strength: EQ 50 mcg Base at the dose of EQ 100 mcg Base (2 x EQ 50 mcg Base)
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above.

Analyte to measure: Total (free + bound) liothyronine in plasma

Bioequivalence based on (90% CI): Baseline-corrected total (free + bound) liothyronine

Waiver request of in vivo testing: EQ 5 mcg Base and EQ 25 mcg Base strengths based on (i) acceptable bioequivalence studies on the EQ 50 mcg Base strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths

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 for each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

If any strength of the tablet product has a functional score, additional dissolution profile testing should be conducted for each segment of the split tablet after manual and mechanical splitting as per the most recent FDA guidance for industry on *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*.[a]

Explanation: FDA has concluded that liothyronine sodium is a narrow therapeutic index (NTI) drug based on the following evidence:

- The range between plasma liothyronine therapeutic and toxic concentrations is narrow
- Some liothyronine-associated toxicities are serious and/or irreversible
- Sub-therapeutic liothyronine concentrations result in inadequate treatment and lead to poor clinical outcomes
- Liothyronine sodium requires individual dose titration to achieve a satisfactory balance between maximizing efficacy and minimizing serious dose-related toxicity
- Therapeutic drug monitoring based on plasma thyroid-stimulating hormone and total or free-triiodothyronine concentrations is routinely employed to facilitate liothyronine dose titration
- Liothyronine has small-to-medium within-subject variability

The study design should be a fully replicated crossover approach in order to

- Scale bioequivalence limits to the variability of the referenced product; and compare test and referenced products within-subject variability.

For details about methods for statistical analysis using the reference scaled average bioequivalence approach for NTI drugs, refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application.*[a]

Revision History: Recommended February 2006; Finalized May 2008; Revised December 2012, August 2021, February 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