

Draft Guidance on Levothyroxine Sodium

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 the 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: Levothyroxine sodium

Dosage Form; Route: Tablet; oral

Recommended Studies: One study

1. Type of study: Fasting
Design: Single-dose, four-way, fully replicated crossover in vivo
Strength: 0.3 mg
Subjects: Healthy males and non-pregnant females, general population
Additional comments:
 1. Females should not be pregnant or lactating, and should practice abstinence or use appropriate forms of contraception during the study.
 2. Levothyroxine has a long elimination half-life, hence adequate washout periods should be ensured between treatments in the crossover study. Measurement of levothyroxine may be truncated to 48 h post-dose.
 3. The dose for R and T administered during the study should be 0.6 mg to ensure adequate measurement of the analyte.
 4. Given the numerous drug-drug interactions for levothyroxine sodium, caution should be exercised in administering concomitant medications during the study.
 5. Post-dose levothyroxine measurements by the baseline levothyroxine value should be corrected in each period for each subject. The baseline value should be obtained from the average of three levothyroxine measurements taken before dosing (i.e., at 0.5 h, 0.25 h, and 0 h pre-dose).
 6. Applicant may consider using the reference-scaled average bioequivalence approach for levothyroxine sodium.

Analytes to measure (in appropriate biological fluid): Levothyroxine in serum

Bioequivalence based on (90% CI): Baseline-corrected levothyroxine

Waiver request of in vivo testing: 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.137 mg, 0.15 mg, 0.175 mg, and 0.2 mg based on: (i) an acceptable bioequivalence study on the 0.3 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Regulatory Filing Recommendations: Note that there are five different reference listed drug (RLD) products for levothyroxine sodium tablets. A separate fasting bioequivalence study (and a

separate fed study, if appropriate) must be conducted against the highest strength of each RLD product for which a sponsor wishes its product to receive an 'AB' rating. However, it is not necessary to submit a separate abbreviated new drug application (ANDA) for each RLD product being referenced. Instead, a sponsor may seek an 'AB' rating for its product against one of the RLD products in the original submission, and then submit one supplement to the original submission per each of the other RLD products against which it wishes its product to obtain an 'AB' rating.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: <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 (ANDA).

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

- The range between serum levothyroxine therapeutic and toxic concentrations is narrow;
- Some levothyroxine-associated toxicities are serious and/or irreversible;
- Sub-therapeutic levothyroxine concentrations result in inadequate treatment and lead to poor clinical outcomes;
- Levothyroxine sodium requires individual dose titration to achieve a satisfactory balance between maximizing efficacy and minimizing serious dose-related toxicity;
- Therapeutic drug monitoring based on serum TSH and total or free-T₄ levels is routinely employed to facilitate levothyroxine dose titration; and
- Levothyroxine 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 product within-subject variability.

For details about Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for narrow therapeutic index drugs, refer to the draft Guidance on Warfarin Sodium.