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Draft Guidance on Levothyroxine Sodium

August 2026

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Levothyroxine sodium
Dosage Form:	Capsule
Route:	Oral
Strengths:	0.013 mg | 0.025 mg | 0.0375 mg | 0.044 mg | 0.05 mg | 0.0625 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 | 0.2 mg
Reference Listed Drug:	NDA 021924
Recommended Study:	One in vivo bioequivalence study with pharmacokinetic endpoints

1. Class of study: Bioequivalence
   Type of study: Fasting
   Design: Single-dose, two-treatment, two-sequence, four-period, fully replicated crossover in vivo
   Strength: 0.2 mg
   Dose: 0.6 mg (3 x 0.2 mg)
   Subjects: Healthy males and non-pregnant, non-lactating females
   Safety recommendation:
   - Exclude geriatric subjects due to increased risk of cardiac adverse reactions.

   Study design recommendations:
   - Levothyroxine has a long elimination half-life, hence adequate washout periods should be ensured between treatments in the crossover study. Measurement of levothyroxine maybe truncated to 48 h post-dose.
   - This drug product is classified as a narrow therapeutic index drug (NTI). Refer to the Explanation section for further information.

Analyte to measure: Levothyroxine in serum

Measure baseline levothyroxine at -0.5, -0.25, and 0 hours before dosing. The mean of the pre-dose levothyroxine should be used for the baseline correction. Pharmacokinetics and statistical analyses should be performed on both baseline uncorrected and baseline corrected data.

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

Bioequivalence of additional strengths: Waiver request of in vivo testing of additional strength based on (i) an acceptable bioequivalence study on the 0.2 mg strength, (ii) acceptable comparative in vitro dissolution studies between the additional strengths and the 0.2 mg strength using 12 units per strength, and (iii) proportional similarity of the formulations across all strengths

Dissolution: Dissolution test(s) should be included for quality control and to support a waiver request of in vivo testing of additional strengths. For the quality control dissolution method, provide a dissolution method development report for the test product containing information and data that demonstrate appropriateness of the selected dissolution method[1] and sampling times, such as the discriminating ability to detect changes in critical quality attributes that could potentially impact drug product performance.

Explanation: FDA has concluded that levothyroxine sodium is an NTI drug based on the following evidence:

- The range between the effective levothyroxine concentrations and the concentrations associated with serious toxicity is narrow
- Sub-optimal levothyroxine concentrations lead to severe therapeutic failure or toxicity
- Levothyroxine is subject to therapeutic drug monitoring based on pharmacodynamic measures
- Levothyroxine exhibits low-to-moderate within-subject variability
- Dose adjustments are in small increments in clinical practice

The in vivo bioequivalence study should be of a fully replicate crossover design to:

- Scale bioequivalence limits to the variability of the reference listed drug
- Compare test product and RLD within-subject variability

For details about the method for statistical analysis using the reference-scaled average bioequivalence approach for NTI drugs, refer to the guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.[a]

Document History: Recommended November 2018; Revised August 2026

[a] We update guidances periodically. For the most recent version of a guidance, refer to the FDA guidance webpage at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[1] Applicant-developed, United States Pharmacopeia drug product monograph or Dissolution Methods database, https://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm