

*Contains Nonbinding Recommendations*  
*Draft - Not for Implementation*  
**Draft Guidance on Lithium Carbonate**  
**May 2023**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

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.

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**Active Ingredient:** Lithium carbonate

**Dosage Form; Route:** Capsule; Oral

**Recommended Studies:** Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting  
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo  
Strength: 600 mg  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: This drug product is classified as a narrow therapeutic index drug. See the Explanation section for further information.
2. Type of study: Fed  
Design: Single-dose, two-treatment, two-sequence, four-period, fully replicate crossover in vivo  
Strength: 600 mg  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: See comments above.

**Analyte to measure:** Lithium in plasma

**Bioequivalence based on (90% CI):** Lithium

**Waiver request of in vivo testing:** 150 mg and 300 mg strengths based on (i) acceptable bioequivalence studies on the 600 mg strength, (ii) acceptable in vitro dissolution testing of all the 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 evaluation of the abbreviated new drug application.

**Explanation:** FDA has concluded that lithium is a narrow therapeutic index drug based on the following evidence:

- The range between the effective lithium concentrations and the concentrations associated with serious toxicity is narrow.
- Sub-optimal lithium concentrations lead to severe therapeutic failure or toxicity.
- Lithium is subject to therapeutic drug monitoring based on pharmacokinetics measures.
- Lithium exhibits low-to-moderate within-subject variability.

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

- Scale bioequivalence limits to the variability of the reference product.
- Compare test and reference product within-subject variability.

For details about the method for statistical analysis using the reference-scaled average bioequivalence approach for narrow therapeutic index drugs, refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.<sup>a</sup>

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**Revision History:** Recommended July 2008; Revised November 2019, May 2023

**Unique Agency Identifier:** PSG\_017812

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<sup>a</sup> 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>.