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Draft Guidance on Lithium Carbonate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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

Active Ingredient: Lithium carbonate

Dosage Form; Route: Tablet, extended release; 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: 450 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: 450 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

Additional strength: Not applicable

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

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.

Lithium carbonate extended release tablets are scored. To ensure the performance of the split tablet, perform manual as well as mechanical splitting and conduct dissolution testing of split tablet portions versus the whole tablet for both test and reference products.

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*.[a]

Revision History: Recommended February 2010; Revised May 2023

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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.