

*Contains Nonbinding Recommendations*

*Draft - Not for Implementation*

## **Draft Guidance on Lanthanum Carbonate**

**August 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 May 2017, FDA issued a draft product-specific guidance for industry on generic lanthanum carbonate. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

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**Active Ingredient:** Lanthanum carbonate

**Dosage Form; Route:** Tablet, chewable; oral

**Recommended Studies:** Two options: (1) two in vitro bioequivalence studies (comparative dissolution and phosphate binding) or (2) one in vivo bioequivalence study with pharmacodynamic endpoints

**I. Option 1: Two in vitro bioequivalence studies (comparative dissolution and phosphate binding)**

The following in vitro dissolution, phosphate equilibrium binding and phosphate kinetic binding studies are recommended to establish bioequivalence of the test and reference products at the EQ 1000 mg Base strength.

1. Comparative dissolution studies:

Dissolution should be conducted on 12 whole and 12 crushed tablets for each of test and reference products. Crushed tablets should be prepared by gently crushing each tablet to a fine powder. These data should be submitted in addition to the method specified in the Dissolution Methods Database (see below), which is for stability and quality control testing.

Apparatus:	U.S. Pharmacopeia Apparatus 2 (paddle)
Rotational speed:	50 rpm
Media:	0.1 N HCl, pH 3.0 buffer and pH 5.0 buffer <sup>1</sup>
Volume:	900 mL
Temperature:	37°C
Sample times:	At least 8 time points up to 24 hours or until 85% or more of the drug dissolves

For crushed tablets, an f2 test should be performed using mean profiles to compare test and reference product drug release under a range of pH conditions. Note that it is not necessary to determine f2 when both test and reference products dissolve 85% or more in 30 minutes or less.

Submit the f2 data for whole tablets as supporting evidence. The dissolution profiles of the whole tablet for the test product should be similar to that of the reference product or their dissolution profiles should be within the acceptable range of dissolution profiles of whole and crushed tablets of the reference product.

2. Phosphate binding studies:

In addition to the dissolution studies, conduct in vitro equilibrium and kinetic phosphate binding studies to compare the extent and rate of phosphate binding between the test and reference products. Any interference in phosphate binding from the inactive ingredients should be documented. Studies should be conducted using 12 replicates for each study condition. Each study should be conducted based on one EQ 1000 mg Base lanthanum carbonate chewable tablet using the entire tablet. Submit individual data and summary statistics based on the following studies.

a. Equilibrium binding study:

The equilibrium binding study may be conducted on a crushed tablet. The recommended steps for the equilibrium study are as follows:

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<sup>1</sup> The types of pH 3.0 and 5.0 buffers are not specified. It is the applicant's responsibility to select the appropriate types of buffers. For example, a phosphate buffer should not be selected because it interferes with the binding studies. If the anions of the buffer system react with lanthanum cation and form an insoluble salt, the buffer system should not be selected.

1. Incubate the crushed tablet in the 0.1 N HCl (pH 1.2) medium until it completely dissolves.
2. Adjust the pH to the target pH (3.0 or 5.0).
3. Wait for at least one hour.
4. Add phosphate solutions to the various final concentrations and monitor and adjust the pH as required. The final reaction system should be 250 mL.
5. The solution should be incubated at 37°C until the maximum lanthanum-phosphate binding is achieved.

Inclusion of the acid pretreatment step is to expedite the tablet dissolution and facilitate the equilibrium binding study. Binding conditions should contain at least eight different phosphate concentrations in 250 mL. The maximum phosphate binding region (attainment of plateau) should be demonstrated prior to selecting these eight phosphate concentrations for the study. The eight concentrations should range from the plateau downward to about one-tenth of that concentration and should characterize the rapidly rising portion of the binding curve. Each concentration should also be conducted at pH 3.0 and 5.0. For each set of conditions, the solution should be incubated at 37°C until the maximum lanthanum-phosphate binding is achieved.

The Langmuir binding constants  $k_1$  and  $k_2$  for each pH should be determined in the equilibrium binding study. The test/reference ratio should be calculated for  $k_1$ . The 90% confidence interval should be calculated for  $k_2$ .

b. Kinetic binding study:

For the kinetic study, the three following phosphate concentrations should be used to incubate crushed lanthanum carbonate tablets: the lowest and highest concentrations used in the corresponding equilibrium binding study, and the mid concentration of approximately 50% of the highest concentration used. The study should be conducted in 250 mL medium at pH 3.0 and 5.0. Lanthanum-phosphate binding should be monitored as a function of time. At least 8 time points should be chosen up to 24 hours that adequately address binding under each condition. All incubations should be conducted at 37°C under constant gentle shaking.

An  $f_2$  test should be performed using mean profiles to compare lanthanum-phosphate binding kinetics of test and reference tablets under a range of phosphate concentrations and pH conditions.<sup>2</sup>

## II. Option 2: One in vivo bioequivalence study with pharmacodynamic endpoints

Bioequivalence should be established by conducting an in vivo bioequivalence study with pharmacodynamic endpoint(s) in healthy subjects. The most appropriate endpoint is change in urinary phosphate excretion.

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<sup>2</sup>Additional information about assay conditions is published by Yang et al. Mol. Pharm. 2013 Feb 4;10(2):544-50. doi: 10.1021/mp300517p.

**Additional comments:** A pilot study should be conducted using the reference product to determine the most sensitive dose for the pivotal bioequivalence study. Tablets should be chewed then swallowed with water.

**Waiver request of in vitro testing in Option 1:** EQ 500 mg Base and EQ 750 mg Base strengths based on (i) acceptable in vitro bioequivalence study on EQ 1000 mg Base strength, (ii) acceptable in vitro dissolution testing of all the strengths, and (iii) proportional similarity of the formulations across all strengths

**Waiver request of in vivo testing in Option 2:** Strengths not used in the bioequivalence study with pharmacodynamic endpoint(s) based on (i) acceptable in vivo bioequivalence study with pharmacodynamic endpoint(s) on the tablet strength used as identified in the pilot study, (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 ANDA.

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