*Contains Nonbinding Recommendations*

**Draft Guidance on Lanthanum Carbonate**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Active Ingredient:** Lanthanum carbonate

**Dosage Form; Route:** Powder; oral

**Recommended Studies:** Two options: In vitro or in vivo studies

## 1. In Vitro Option

FDA recommends the following in vitro dissolution, phosphate equilibrium binding, and phosphate kinetic binding studies to establish bioequivalence (BE) of the test and reference listed drug (RLD) powders at the 1000 mg strength.

### A. Dissolution Studies:

Dissolution should be conducted on 12 powder units each of the test and reference products. These data are to be submitted in addition to the method specified in the Dissolution Methods Database (see below), which is to be used for stability and quality control testing.

| | |
|---|---|
| Apparatus: | U.S. Pharmacopeia (USP) Apparatus 2 (paddle) |
| Rotation speed: | 50 rpm |
| Media: | 0.1 N HCl, pH 3.0 buffer, and pH 5.0 buffer[1] |
| 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 |

An f2 test should be performed using mean profiles to compare test (T) and reference (R) product drug release under a range of pH conditions. Note that it is not necessary to determine f2 when both T and R dissolve 85% or more in 30 minutes or less.

### B. Phosphate Binding Studies:

[1] The types of pH 3.0 and 5.0 buffers are not specified. It is the firm's responsibility to select the appropriate types of buffer. 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.

In addition to the dissolution data requested above and the dissolution data needed for stability and quality control, conduct in vitro equilibrium and kinetic phosphate binding studies to compare the extent and rate of phosphate binding between the test and reference powders. Any interference in phosphate binding from the inactive ingredients in the test or reference products should be documented. Studies should be conducted using 12 replicates for each condition. Submit individual data and summary statistics based on the following studies:

a) Equilibrium Binding Study:

Recommended steps:

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

The acid pretreatment step is included to expedite the powder 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 clearly demonstrated prior to selecting these eight phosphate concentrations for the study. The eight concentrations should approximately 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 maximum lanthanum-phosphate binding is achieved.

The Langmuir binding constants k1 and k2 for each pH should be determined in the equilibrium binding study. The T/R ratio should be calculated for k1. The 90% confidence interval should be calculated for k2.

b) Kinetic Binding Study:

For the kinetic study, the three following phosphate concentrations should be used to incubate lanthanum carbonate powder: the lowest and highest concentrations used in the corresponding equilibrium binding study, and the mid concentration (approximately 50%) of the highest concentration used. Furthermore, the study should be conducted in 250 mL at pH 1.2, 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 f2 test should be performed using mean profiles to compare lanthanum-phosphate binding kinetics of T and R powders under a range of phosphate concentrations and pH conditions.

Additional information about assay conditions was published by Yang et al. In Vitro Bioequivalence Approach for a Locally Acting Gastrointestinal Drug: Lanthanum Carbonate. Mol. Pharm. 2013 Feb 4;10(2):544-50. doi: 10.1021/mp300517p. Epub 2013 Jan 4.

**Waiver requests of in vitro studies in Option 1:** 750 mg based on (i) acceptable in vitro BE studies on the 1000 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution of all strengths.

## 2. In Vivo Option

In the case where BE will be demonstrated through the in vivo option, BE should be established by conducting a study using pharmacodynamic endpoints in healthy subjects. The most appropriate endpoint is change in urinary phosphate excretion.

A pilot study should first be conducted using the RLD to determine the most sensitive dose for the pivotal BE study. Submit a protocol to the Office of Bioequivalence, Office of Generic Drugs for review and concurrence prior to conducting the pivotal in vivo BE study.

**Waiver request of in vivo testing for Option 2:** Strength not used in the pharmacodynamic BE study based on (i) acceptable pharmacodynamic BE study on the powder strength used as identified in the pilot study, (ii) proportional similarity across all strengths, and (iii) acceptable in vitro dissolution comparison of all strengths.

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods Web site, 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).