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Draft Guidance on Orlistat

August 2021

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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 August 2010, FDA issued a draft product-specific guidance for industry on generic orlistat. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Orlistat

Dosage Form; Route: Capsule; oral

Recommended Study: One study

1. Type of study: Pharmacodynamic (PD) bioequivalence (BE) study
   Design: Multiple-dose, 3-way crossover in vivo, consisting of two doses of reference product and at least one dose of the test product
   Strength: 60 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments:
   - The product should be administered as per the reference product labeling.
   - The diet should be standardized and well-controlled throughout the study and should contain 30% of calories from fat as per the labeling.
   - Subjects should consume all the food that is provided.

- Begin the study with a run-in period of controlled diet and no drug for at least 5 days.
- Following this run-in period, subjects should be dosed as follows with

    (1) The reference product at 60 mg three times a day (tid);
    (2) The reference product at 2 x 60 mg or 120 mg tid; or
    (3) The test product at 60 mg tid and/or 2 x 60 mg tid.

- Each of the three treatment periods should proceed for at least nine (9) days.
- Each treatment period should be separated by a washout period of at least four (4) days.
- The collection and measurement of fecal samples should be accurate to ensure adequate data.

Analyte to measure: The percent of fecal fat excretion expressed as a ratio of the amount of fat excretion over a 24-hour period at steady-state relative to the amount of daily ingested fat

Bioequivalence based on (90% CI): Data from the in vivo PD BE study should be statistically analyzed using the dose-scale method incorporating the E_{max} model. The decision on whether and how to transform PD data should be specified and justified in the protocol. The 90% confidence interval for the relative bioavailability, F, should fall within 80.00-125.00% in order to establish bioequivalence.

Data from PD study on fecal fat excretion should be analyzed based on dose-scale analysis to estimate relative bioavailability. The FDA developed this method to overcome the complexities of curvilinear responses associated with PD endpoints. Based on this method, the assessment of BE is made in terms of relative bioavailability of the test and reference formulations at the site(s) of action. The relative bioavailability, F, is the ratio of the doses of test and reference formulations that produce an equivalent PD response. The F is estimated by fitting an E_{max} model that describes the within-study dose response relationship. Among available statistical methods for E_{max} model fitting, nonlinear mixed effect (NLME) modeling is recommended, because the NLME modeling is capable of characterizing between-subject variability and residual unexplained variability, and less sensitive to aberrant observation and missing value.

PD BE study designs using only single doses of the test product are acceptable. However, multiple doses of both test and reference products may enrich the study data and enhance precision of the estimated values. The PD study should be conducted as a randomized crossover design with at least 2 doses of the RLD and 1 dose of the test product. Additional doses of the test and reference products may be considered to improve precision of parameters in the dose scale analysis. For both types of studies, relative bioavailability of the test product can be determined by simultaneously fitting the within-study pooled individual dose response data of both the test and reference products to the following model:

$$y = E_0 + \frac{E_{\max} * Dose * F^i}{ED_{50} + Dose * F^i}$$

Where y = Response, Dose = Administered dose, E_0 = Baseline response in the absence of the drug, E_{max} = Fitted maximum drug effect, ED_{50} = Dose required to produce 50% the fitted maximum effect, and i = Treatment indicator (0 = Ref, 1 = Test), with the understanding that $F^0 = 1$ and that F^1 is the relative potency used to evaluate bioequivalence.

This model is based on assumption that both E_0 and E_{max} are the same for the test and reference products. ED_{50} for the reference product is ED_{50} itself, while ED_{50} for the test product is ED_{50}/F^1. When applying NLME modeling, the fixed effects are E_0, E_{max}, ED_{50} and F, the between-subject random effects should be specified for parameters such as E_0 and E_{max}, and the residual error random effect should be included. Appropriate justification may be submitted to support the final selected model.

Calculation of Confidence Intervals for F:

To determine BE, 90% confidence interval for F can be estimated by a bootstrap procedure. Each bootstrap estimation includes the calculation of F by fitting the above Emax model to a "sample dose-response data set", which is generated by resampling with replacement. In order to maintain the correlation of observations within subject, resampling by subject (remaining observations from all T and R treatment arms) is recommended rather than resampling by observations. Efron's bias corrected and accelerated (BCa) method[1] is recommended to compute a 90% confidence interval for F. Alternatively, 90% confidence interval for F can be estimated without a bootstrap procedure, directly from the point estimate of F and its standard error calculated using NLME modeling.

Waiver request of in vivo testing: 120 mg based on (i) acceptable BE studies on the 60 mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths

Note that orlistat capsules, 60 mg and 120 mg, are the subject of two separate reference products. Two separate applications must be submitted referencing the appropriate new drug applications (NDAs) for the respective test products. A request for a waiver of in vivo BE testing requirements may be submitted for the 120 mg strength provided that it (i) submits an abbreviated new drug application (ANDA) containing an acceptable in vivo PD BE on the 60 mg strength; (ii) cross-references the ANDA for the 120 mg strength; and (iii) meets the criteria of 21 CFR § 320.22(d) (2). Refer to the Guidance for Industry, *Variations in Drug Products that May Be Included in a Single ANDA*. If a single ANDA is submitted for the 120 mg strength, the in vivo PD BE study described above should be conducted using the 120 mg strength.

[1] Efron, B., & Tibshirani, R. J. (1994). *An introduction to the bootstrap*. CRC press.

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 each of all strengths of the test and reference products. Specifications will be determined upon review of the ANDA.

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