Draft Guidance on Orlistat

Active ingredient: Orlistat

Form/Route: Capsule/Oral

Recommended studies: 1 study

> Type of study: In vivo bioequivalence (BE) study with pharmacodynamic (PD) endpoints
> Design: Multiple-dose, 3-way crossover consisting of two doses of reference product and at least one dose of the test product. The product should be administered as per the reference product labeling.
> Strength: 60 mg
> Subjects: Healthy males and nonpregnant females, general population.
> Additional comments:
> - 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 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 must be accurate to ensure adequate data.
> - Firms are encouraged to submit a protocol to the FDA for evaluation prior to initiating the pivotal bioequivalence studies.

PD Endpoint: 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.

Metric for Establishing BE: Data from the in vivo PD BE study should be statistically analyzed using the Dose-Scale Method incorporating the E_{max} model. The 90% confidence

interval for the relative bioavailability, F, must fall within 80-125% in order to establish bioequivalence.

Data from PD study on fecal fat excretion should be analyzed based on a two–step **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. Its calculation takes into consideration the within-study dose response.

Analysis for studies using one dose of the test product
The relationship between the dose (D_R) and the observed response (E_R) of the reference product is assumed to follow an E_{max} model:

$$E_R = \phi_R(D_R) = E_{0R} + \frac{E_{maxR} * D_R}{ED_{50R} + D_R}$$

Where:
- E_R = Response
- D_R = Administered dose
- E_{0R} = Baseline response in the absence of the drug
- E_{maxR} = Fitted maximum drug effect
- ED_{50R} = Dose required to produce 50% the fitted maximum effect.

For application of the Dose-Scale method to determination of relative bioavailability, ϕ_R in the above equation can be fitted to the mean, or pooled, dose response data for multiple (0 mg (baseline), 60 mg tid , 120 mg tid, …) doses of the reference product. Baseline response should be determined from the run-in period. Mean responses may be computed as geometric mean or arithmetic mean depending on the distribution of the PD response data. If the data are normally distributed, arithmetic mean may be used, whereas geometric mean may be more appropriate for log-normally distributed data. The results of the fitting are values for the three model parameters: E_{0R}, E_{maxR}, and ED_{50R}

The relative bioavailability F of a dose of the test product relative to that of the reference product can be calculated by applying the inverse of ϕ_R to the mean of response data of the test product, E_T, as follows (using the fitted values for the three model parameters):

$$\phi_R^{-1}(E_T) = \frac{(E_T - E_{0R}) * ED_{50R}}{E_{max\,R} - (E_T - E_{0R})}$$

$$F = \frac{\phi_R^{-1}(E_T)}{D_T}$$

Where E_T = Mean of, or the pooled, observed response of the test product to the dose (D_T) of the test product.

Analysis for studies using multiple doses of the test product
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. If you wish, you may include additional doses of the test and reference products to improve precision of parameters in the Dose-Scale Analysis. For such studies, relative bioavailability F of the test product can be determined by simultaneously fitting the within-study dose response data of both the test and reference products to the following modification of the above model:

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

Where y = Response, 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 modified model is based on assumption that both E_0 and E_{max} are the same for the test and reference products. ED_{50R} (for the Reference product) is ED_{50} itself, while ED_{50T} (for the Test product) is ED_{50}/F^1.

Calculation of Confidence Intervals for F
Determination of BE based on the Dose-Scale method is a two-step procedure. First, using either of the procedures described above, a within-study dose response relationship is mathematically described by fitting the relevant version of the E_{max} model to the mean dose-response data and an estimate for F is obtained. Second, a 90% confidence interval for F is estimated by a bootstrap procedure. Each bootstrap estimation includes the calculation of F by fitting one of the above models to a "sample dose-response data set", which is generated by repetitive sampling with replacement. The Agency has used Efron's bias corrected and accelerated (BCA) method to compute a 90% confidence interval for F.

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

Please 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 NDAs for the respective test products. A request for a waiver of in vivo bioequivalence testing requirements may be submitted for the 120 mg strength provided that it (i) submits an 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). Please refer to the Guidance for Industry, *Variations in Drug Products that May Be Included in a Single ANDA*, located at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. Additionally, if a single ANDA application is submitted for the 120 mg strength, the in vivo PD BE study described above should be conducted using the 120 mg strength.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please 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 data submitted in the application.