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Draft Guidance on Loteprednol Etabonate

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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This is a new draft product-specific guidance for industry on generic loteprednol etabonate.

Active Ingredient:	Loteprednol etabonate
Dosage Form; Route:	Gel; ophthalmic
Strength:	0.38%
Recommended Studies:	Two options: in vitro or in vivo study

I. In vitro option:

The proposed test drug product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same[3] as the Reference Listed Drug (RLD). Bioequivalence may be established based on comparative

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD product.

in vitro testing of three exhibit batches of the test product and three batches of the designated Reference Standard (RS) product and should include:[4]

- Appearance, pH, specific gravity, and osmolality.
- Soluble fraction of loteprednol etabonate in the final drug product.
- Rheological properties including yield stress and viscosity. The applicant should characterize viscosity over a range of shear rates.
- Drug particle size distribution. The particle size distribution should be compared using population bioequivalence (PBE) (95% upper confidence bound) based on D50 and SPAN [i.e. (D90-D10)/D50)]. The applicant should provide no fewer than ten data sets each batch from three different batches of both the test and RS products for PBE analysis. Full profiles of the particle size distribution should also be submitted for all samples tested. Please refer to the Guidance on Budesonide inhalation suspension for additional information regarding PBE.
- In vitro drug release tests of loteprednol etabonate from the test and RS products. Detailed information on development and validation of a proposed in vitro drug release testing method should be provided.

II. In vivo option:

1. Type of study: Bioequivalence study with pharmacokinetic (PK) endpoints
   Design: Single-dose, crossover or parallel design, in vivo in aqueous humor
   Strength: 0.38%
   Subjects: Patients undergoing indicated cataract surgery and scheduled to receive ophthalmic corticosteroids just prior to their eye surgery
   Additional Comments: Specific recommendations are provided below.

Analyte to measure: Loteprednol etabonate in aqueous humor

Bioequivalence based on (90% CI): Loteprednol etabonate

Additional Comments Regarding the In Vivo Pharmacokinetic Study in Aqueous Humor:

1. The study is conducted in patients undergoing indicated cataract surgery and scheduled to receive ophthalmic corticosteroids just prior to their eye surgery. A single dose of the test or reference product is instilled into the inferior cul de sac of the eye prior to cataract extraction. Only one single sample of aqueous humor is collected from one eye from each patient, at one assigned sampling time point.

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[3] For ophthalmic drug products, FDA has determined that, as a scientific matter, any qualitative or quantitative deviations from the RLD, even in inactive ingredients listed in 21 CFR 314.94(a)(9)(iv), should be accompanied by an appropriate in vivo BE study or studies. Guidance for industry: *ANDA Submissions –Refuse-to-Receive Standards*.

[4] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches

Applicant may consider a parallel design for the bioequivalence study. If using a parallel study design, please note that each patient should receive only one treatment, test or reference, but not both. Alternatively, a crossover study design may be used in patients undergoing indicated cataract surgery for both eyes. When crossover study design is used, each patient should receive both test and reference treatments. The wash-out period for the crossover study should not exceed 35 days.

2. In order to demonstrate bioequivalence, an adequate estimation of the rate (C_{max}) and extent (AUC) of loteprednol etabonate absorption is needed.

   The following statistical model is recommended:

   The mean AUC_t for each product and time point *t* of measurement is calculated by using the mean concentrations ($\overline{C_t}$) at each time point t to derive the mean profile for each product. On the basis of the trapezoid rule, mean AUC_t is computed as the weighted linear combination of these mean concentrations at each time point through time *t*. The AUC_t is the area under the concentration - time curve from zero to the time *t*. Generally, we have j concentration measurements at times $t_1 < t_2 < t_3 ..., < t_j$ ($t_1 > 0$).

   AUC_{t_j} is calculated for time from 0 to t_j as:

$$AUC_{t_j} = t_1 \times \overline{C_{t_1}} / 2 + \sum_{i=1}^{j-1} \left(\overline{C_{t_i}} + \overline{C_{t_{i+1}}} \right) \times \left(t_{i+1} - t_i \right) / 2$$

   The ratio (Rt) of AUC_t from the test product to AUC_t from the reference product is used to assess bioequivalence for AUC_{0-t}. Estimation of the standard deviation(s) and confidence interval of Rt may be done by bootstrap techniques or a parametric method.

   Bioequivalence is supported if the 90% confidence interval for R_t ($R_t \pm 1.645\ s_t$) lies within (0.8, 1.25). The bootstrapping technique or a parametric method can be used to determine C_{max} and T_{max} and assess bioequivalence for C_{max}.

Unique Agency Identifier: PSG_208219