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Draft Guidance on Loteprednol Etabonate

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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:	Suspension/drops; ophthalmic
Recommended Studies:	Two in vitro bioequivalence studies with supportive characterization studies

To qualify for the in vitro studies recommended in this guidance, all of the following criteria should be met:

1. The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)¹ and quantitatively (Q2)² the same (Q1/Q2).

¹ Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference 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 reference product

2. Acceptable comparative physicochemical characterization of the test and Reference Standard (RS) products. The comparative study should be performed on at least three batches of both the test and RS products and should include:³
 - Appearance, pH, specific gravity, osmolality, surface tension, and viscosity
 - Soluble fraction of loteprednol etabonate in the final drug product

In vitro bioequivalence study 1:

Drug particle and particle size distribution of loteprednol etabonate.

Additional Comments: The particle size distribution should be compared using the population bioequivalence (PBE) statistical analysis procedure (95% upper confidence bound) based on D₅₀ and SPAN [i.e. (D₉₀-D₁₀)/D₅₀]. The applicant should provide no fewer than ten data sets from three different batches of both the test and reference products for PBE analysis. Full profiles of the particle size distributions should also be submitted for all samples tested. Refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929)^a for additional information regarding PBE.

In vitro bioequivalence study 2:

Comparative in vitro drug release of loteprednol etabonate from the test and RS formulations.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

Additional information:

Device:

The reference listed drug (RLD) product is presented in a bottle fitted with a dropper tip. The bottle with dropper tip is the device constituent.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD device when designing the test device.

User Interface Assessment:

An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.^b

³ The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

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^a For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at <https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm>.

^b For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.