

Draft Guidance on Loteprednol Etabonate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Loteprednol etabonate
Dosage Form; Route:	Suspension/drops; ophthalmic
Strength:	0.2%
Recommended Studies:	In vitro option

In vitro option:

To qualify for the in vitro option for this drug product, the following criteria should all be met:

- i. The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)¹ and quantitatively (Q2)² the same (Q1/Q2).³
- ii. 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:⁴
 - Comparable appearance, pH, specific gravity, osmolality, surface tension, and viscosity
 - Comparable soluble fraction of loteprednol etabonate in the final drug product
 - Comparable dose concentration (one or two drops per dose) of loteprednol etabonate from a minimum of ten units from three batches each of the test and RS products at beginning, middle, and end of the unit. The dose concentration should be compared using the population bioequivalence (PBE) statistical procedure (95% upper confidence bound). Please refer to the *Guidance on Budesonide inhalation suspension* for additional information regarding PBE.

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 $\pm 5\%$ of those used in the reference product.

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. *ANDA Submissions – Refuse-to-Receive Standards: Guidance for Industry*.

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

- Comparable drug particle size distribution. The particle size distribution should be compared using PBE (95% upper confidence bound) based on D_{50} and SPAN [i.e. $(D_{90}-D_{10})/D_{50}$]. 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.
- iii. Acceptable comparative in vitro drug release of loteprednol etabonate from the test and RS formulations. The methodology used for in vitro drug release testing should be able to discriminate the effect of process variability in the production of the test formulation.