Contains Nonbinding Recommendations

Draft Guidance on Fluorometholone Acetate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Fluorometholone acetate

Dosage Form; Route: Suspension/drops; ophthalmic

Strength: 0.1%

Recommended Study: Two options: in vitro or in vivo study

I. In vitro option

To qualify for the in vitro option for this drug product all of the following criteria should 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, buffer capacity, and viscosity
- Comparable soluble fraction of fluorometholone acetate in the final drug product
- 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. 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 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
[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.

iii. Acceptable comparative in vitro drug release of fluorometholone acetate from the test and RS formulations.

II. In vivo option

Type of study: Bioequivalence study with pharmacokinetic (PK) endpoints
Design: Single-dose, crossover or parallel design, in vivo in aqueous humor
Subjects: Patients undergoing indicated cataract surgery
Additional Comments: Please refer to the *Guidance on Loteprednol Etabonate* ophthalmic suspension/drops for additional comments regarding the in vivo pharmacokinetic study design in aqueous humor

---

Analytes to measure (in appropriate biological fluid): Fluorometholone acetate in aqueous humor

Bioequivalence based on (90% CI): Fluorometholone acetate