Contains Nonbinding Recommendations

Draft Guidance on Fluorometholone

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Suspension/drops; ophthalmic

Recommended Studies: 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).

ii. Acceptable comparative physicochemical characterizations of the test and Reference Standard (RS) products. The comparative study should be performed on at least three exhibit batches of both the test and RS products and should include:[3]

- Comparative appearance, pH, specific gravity, osmolality, surface tension, buffer capacity, and viscosity
- Comparative soluble fraction of fluorometholone in the final drug product
- Comparative dose concentration (one drop per dose) of fluorometholone from a minimum of ten units from three batches each of the test and reference 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.
- Comparative 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.

[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.
[3] 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 from the test and RS formulations. The methodology used for in vitro drug release testing should be able to discriminate the effect of process and variability in the product of the test formulation.

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
Strength: 0.1%
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 in aqueous humor

Bioequivalence based on (90% CI): Fluorometholone

In vitro dissolution test method: Please develop an in vitro drug release testing method for this drug product for stability and quality controls. Specification will be determined upon review of the Abbreviated New Drug Application (ANDA).