

Draft Guidance on Fluorometholone

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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
Strength:	0.25%
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)³.
- 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:⁴
 - Comparative appearance, pH, specific gravity, osmolality, surface tension, buffer capacity, and viscosity
 - Comparative soluble fraction of fluorometholone in the final drug product
 - Comparative drug particle size distribution. The particle size distribution should be compared using 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 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 Please refer to the *Draft Guidance on Budesonide* inhalation suspension for additional information regarding PBE.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 ±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. 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 from the test and RS formulations⁵.
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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: 0.25%

Subjects: Patients undergoing indicated cataract surgery

Additional comments: Please refer to the *Draft Guidance on Loteprednol Etabonate* for 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

⁵ Please note that, if determined to be warranted, an in vitro release test (IVRT) method used as part of the quality control specifications may and/or can ultimately be different than the IVRT method developed to support bioequivalence determination and will be assessed at the time of review of the ANDA.