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Draft Guidance on Fluorometholone

February 2024

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Active Ingredient:	Fluorometholone
Dosage Form:	Suspension/drops
Route:	Ophthalmic
Strength:	0.1%
Recommended Studies:	Two options: (1) two in vitro bioequivalence studies with supportive comparative characterization studies, or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

I. Option 1: Two in vitro bioequivalence studies with supportive comparative characterization studies

To demonstrate bioequivalence by this option, the test product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).[3]

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

Two in vitro bioequivalence studies:

1. Type of study: Drug particle size and particle size distribution of fluorometholone
   Design: In vitro bioequivalence study on three batches of both test and reference standard (RS) products
   Strength: 0.1%
   Additional comments: The sample preparation method and selected particle sizing methodology should be adequately optimized and validated to demonstrate the adequacy of the selected method in accurately and reliably identifying and measuring the size of the drug particles. Prospective applicant should perform size characterization at different dilution conditions as part of method development to demonstrate the impact of dilution. Full particle size distribution profiles representative of all test product and RS product batches tested should be submitted as supporting information.

   Parameters to measure: D_{50} and SPAN $[(D_{90}-D_{10})/D_{50}]$

   Bioequivalence based on (95% upper confidence bound): Population bioequivalence (PBE) analysis of the D_{50} and SPAN. Prospective applicants should provide no less than 10 datasets from three batches each of the test and RS products to be used in the PBE analysis. For additional information on PBE statistical analysis, refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929).[a]

2. Type of study: Comparative in vitro release testing (IVRT) of fluorometholone
   Design: Should be performed on three batches of both test and RS products using at least 12 units from each batch
   Strengths: 0.1%
   Additional comments: The IVRT method study should include information on the method development and validation to detect potential formulation differences and capture the complete release profile of fluorometholone.

   Bioequivalence based on: Comparative analysis of release profiles should be established using an appropriate statistical method (e.g., model independent approach using similarity factor (f_2)). For more information on calculation of f_2 factor, refer to the most recent version of the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.[b]

Comparative characterization studies:

Comparative physicochemical characterization of the test product and RS product. The comparative study should be performed on at least three batches of both the test product[4] and RS product and should include:

a. Appearance
b. pH
c. Specific gravity
d. Osmolality
e. Surface tension
f. Buffer capacity
g. Viscosity
h. Soluble fraction of fluorometholone in the finished drug product

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, crossover or parallel design in vivo in aqueous humor
   Strength: 0.1%
   Subjects: Patients undergoing cataract surgery
   Additional comments: Refer to most recent version of the FDA product-specific guidance on *Loteprednol Etabonate Ophthalmic Suspension/Drops* (NDA 020583)[a] for additional comments regarding the in vivo pharmacokinetic study design in aqueous humor.

Analyte to measure: Fluorometholone in aqueous humor

Bioequivalence based on (90% CI): Fluorometholone

Additional information:

Device:
The RLD is presented in a bottle with a dropper tip. The bottle with dropper tip is the device constituent part.

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

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

User interface assessment:
An abbreviated new drug application 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]

Quality assessment:
For quality-related recommendations for supporting drug product development, refer to the most recent version of the FDA guidance for industry on *Quality Considerations for Topical Ophthalmic Drug Products*.[b]

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[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[b] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.