Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Clobetasol Propionate

May 2025

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Clobetasol propionate
Dosage Form:	Suspension/drops
Route:	Ophthalmic
Strength:	0.05%
Recommended Studies:	Two in vitro bioequivalence studies with supportive comparative characterization studies

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

Two in vitro bioequivalence studies:

1. Type of study: Drug particle and particle size distribution of clobetasol propionate
   Design: In vitro bioequivalence study on three batches of both T product[3] and reference standard (RS)
   Strength: 0.05%
   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

[1] Q1 (Qualitative sameness) means that the T product uses the same inactive ingredient(s) as the RLD.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T product are within ±5% of those used in the RLD.
[3] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

drug particles. As part of method development/validation, prospective applicants should provide data to demonstrate the impact of dilution on particle size measurement. Full particle size distribution profiles representative of all T product and RS 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 ten datasets from three batches each of the T product and RS to be used in the PBE analysis. Refer to the section of "Recommendation Related to the PBE Statistical Analysis Procedure" in the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929)[a] for additional information regarding PBE computation.[4]

2. Type of study: Comparative in vitro drug release testing (IVRT) of clobetasol propionate
Design: Should be performed on three batches of both T product and the RS using at least 12 units from each batch
Strength(s): 0.05%
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 clobetasol propionate.

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:

Acceptable comparative physicochemical characterization of the T product and the RS. The comparative study should be performed on at least three batches of both the T product and the RS, and should include:

a. Appearance
b. Solid state of clobetasol propionate
c. Specific gravity
d. pH
e. Buffer capacity
f. Osmolality
g. Surface tension
h. Viscosity
i. Zeta potential

[4] The recommendation on collecting data on different life stages is NOT applicable.

Additional information:

Device:
The RLD is presented in a vial with a dropper tip. The vial 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 T device.

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]

Document History: Recommended May 2025

Unique Agency Identifier: PSG_218158

[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.