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Draft Guidance on Chloroprocaine Hydrochloride

August 2023

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Active Ingredient:	Chloroprocaine hydrochloride
Dosage Form:	Gel
Route:	Ophthalmic
Strength:	3%
Recommended Studies:	One in vitro bioequivalence study with supportive characterization studies

To be eligible for the bioequivalence studies recommended in this guidance, the test product should meet the following criteria:

1. The test and reference listed drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same.

[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.

2. Acceptable comparative physicochemical characterization of the test and the reference standard (RS) products. The comparative study should be performed on a minimum of three exhibit batches of the test product[3] and three batches of the RS product,[4] and it should include:
    a. Appearance
    b. pH
    c. Specific gravity
    d. Osmolality
    e. Rheological properties including yield stress and viscosity. The applicant should characterize viscosity over a range of shear rates.

One in vitro bioequivalence study with supportive characterization studies:

1. Type of study: In vitro drug release testing
   Design: Comparative in vitro drug release of chloroprocaine hydrochloride from test and RS products
   Additional comments:
    a. A properly developed and validated method that can detect potential formulation differences and capture the complete release profile of chloroprocaine hydrochloride should be provided. Equivalence in chloroprocaine hydrochloride release should be established using a proper statistical method from three batches of Test and RS products. One suggested approach is a model independent similarity (f2) factor. For more information on calculation of f2 factor, refer to the most recent version of the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.[a]
    b. For ophthalmic drug products, FDA has determined that, as a scientific matter, any Q1 or Q2 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 bioequivalence study or studies. Refer to the most recent version of the FDA guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*.[a]

Waiver request of in vivo testing: 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.

[3] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.
[4] If feasible, it is recommended to conduct comparative studies of the test product on or near release and at the end of the proposed shelf life, and the RS tested prior to expiry, after stored under conditions consistent with the label storage conditions.

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.

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*.[a]

Document History: Recommended August 2023

Unique Agency Identifier: PSG_216227

[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.