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Draft Guidance on Phenylephrine Hydrochloride; Tropicamide

February 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 Ingredients:	Phenylephrine hydrochloride; Tropicamide
Dosage Form:	Spray, metered
Route:	Ophthalmic
Strength:	1%; 2.5%
Recommended Studies:	Request for waiver of in vivo bioequivalence study requirements, two in vitro bioequivalence studies, and two comparative spray characterization studies

Request for waiver of in vivo bioequivalence study requirements:

To qualify for a waiver from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b)(1), a generic phenylephrine hydrochloride; tropicamide ophthalmic spray product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

An applicant may seek approval of a drug product intended for ophthalmic use that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent provided that

[1] Q1 (Qualitative sameness) means that the test 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 test products are within ±5% of those used in the RLD.

the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.[3]

Phenylephrine hydrochloride; tropicamide ophthalmic spray products should have comparable physicochemical properties to the reference standard (RS) including but not limited to pH, specific gravity, osmolality, buffer capacity, and viscosity, if applicable. Comparative analysis should be performed on three exhibit batches of both test product and RS, if available.[4]

Two in vitro bioequivalence studies:

FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies on samples from each of three batches of the test product and three batches of the RS, with no fewer than 10 units from each batch. The test product should consist of the final device constituent part and final drug constituent formulation intended to be marketed. The following in vitro bioequivalence tests are recommended:

1. Single actuation content (SAC)
2. Droplet size distribution

Additional comments: Refer to the most recent version of the FDA product-specific guidance on *Fluticasone Propionate Nasal Metered Spray* (NDA 020121)[a] for recommendations on design and equivalence criteria for the aforementioned in vitro bioequivalence studies, and general recommendations on the conduct of the in vitro bioequivalence studies and data submission.[5]

Two comparative spray characterization studies:

The following comparative in vitro studies are recommended to be conducted on at least 10 units from three batches of both test product and RS, if available:[6]

1. Spray Pattern
2. Plume geometry

[3] FDA has determined that any qualitative or quantitative deviations from the RLD regarding the inactive ingredients specified in 21 CFR 314.94(a)(9)(iv) necessitate scientific justification. This justification should address the potential impact on bioequivalence of the proposed test product and inform the determination of whether appropriate in vivo bioequivalence studies are required. Prospective applicants are advised to submit a pre-Abbreviated New Drug Application (ANDA) development meeting request to discuss the justification for any such deviations and the intended approach to demonstrate bioequivalence.

[4] Evaluating fewer than three lots of the RS may be acceptable if the prospective applicant provides sufficient justification and supporting evidence demonstrating that additional RS lots are unavailable. However, data from a minimum of three batches of the test product must be included in the ANDA.

[5] Specific recommendations for in vitro bioequivalence testing at various lifestages are not relevant for this product given it is a single-use configuration.

[6] Id. 4

Additional information:

Device:
The RLD is presented in an ophthalmic metered spray dispenser consisting of a cartridge and base. The dispenser 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 including:

- Multi-dose disposable dispenser cartridge
- Reusable dispenser base
- Eye alignment feature

User interface assessment:
An ANDA 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 guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

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

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