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Draft Guidance on Phentolamine Mesylate

November 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Phentolamine mesylate
Dosage Form:	Solution
Route:	Ophthalmic
Strength:	EQ 0.75% Base
Recommended 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 phentolamine mesylate ophthalmic solution product must 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 that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent provided that 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

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 $\pm 5\%$ of those used in the RLD product.

³ Refer to 21 CFR 314.94(a)(9)(iv) for product for ophthalmic use. In addition, for ophthalmic route of administration, FDA has determined that, any qualitative or quantitative deviations from the RLD with regard to the inactive ingredients listed in 21 CFR 314.94(a)(9)(iv) would warrant scientific justification for the potential impact on safety and efficacy of the proposed test product to determine the potential need of an appropriate clinical study. A prospective applicant is recommended to submit a pre-abbreviated new drug application (pre-ANDA) development meeting request to discuss the justification.

Phentolamine mesylate ophthalmic solution products should have comparable physicochemical properties to the reference standard (RS) including but not limited to pH, specific gravity, osmolality, and viscosity, if applicable. Comparative analysis should be performed on three exhibit batches, if available, of both test and RS products.

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 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

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*.^a

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^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>.