Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Brimonidine Tartrate

October 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Brimonidine tartrate
Dosage Form:	Solution/drops
Route:	Ophthalmic
Strength:	0.1%
Recommended Studies:	Two options: (1) request for waiver of in vivo bioequivalence study requirements, or (2) one in vivo comparative clinical endpoint bioequivalence study

I. Option 1: 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 brimonidine tartrate ophthalmic solution product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

[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.

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 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] Brimonidine tartrate ophthalmic solution 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, if available, of both test product and RS.

II. Option 2: One comparative clinical endpoint bioequivalence study

1. Type of study: Comparative clinical endpoint bioequivalence study
   Design: Randomized, double-masked, parallel, two-arm, in vivo
   Strength: 0.1%
   Subjects: Males and nonpregnant females with chronic open angle glaucoma or ocular hypertension in both eyes
   Additional comments: Specific recommendations are provided below.

Additional comments:

1. The Agency recommends conducting a bioequivalence study with a clinical endpoint in the treatment of open angle glaucoma and ocular hypertension comparing the test product to the RS, each applied as one drop in both eyes three times daily at approximately 8:00 a.m., 4:00 p.m., and 10:00 p.m. for 42 days (6 weeks). Administration times are recommended to be consistent for each subject.

2. Inclusion criteria (the sponsor may add additional criteria):
   a. Males and nonpregnant females aged at least 18 years with chronic open angle glaucoma or ocular hypertension in both eyes
   b. Subject requires treatment of both eyes and is able to discontinue use of all ocular hypotensive medication(s) or switch ocular hypotensive medications and undergo appropriate washout period
   c. Adequate wash-out period prior to baseline of any ocular hypotensive medication (see Table 1). To minimize potential risk to patients due to intraocular pressure (IOP) elevations during the washout period, the investigator may choose to substitute a parasympathomimetic or carbonic anhydrase inhibitor in place of a sympathomimetic, alpha-agonist, beta-adrenergic blocking agent, or prostaglandin; however, all patients must have discontinued all ocular hypotensive medication for the minimum washout period provided in Table 1

[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 (ANDA) development meeting request to discuss the justification.

d. Baseline (Day 0/hour 0) IOP ≥ 22 mm Hg and ≤ 34 mm Hg in each eye and any asymmetry of IOP between the eyes no greater than 5 mm Hg
e. Baseline best corrected visual acuity equivalent to 20/200 or better in each eye

Table 1: Washout Periods for Ocular Hypotensive Medications

Medications	**Minimum Washout Period**
Parasympathomimetics [e.g., pilocarpine (Isopto® Carpine), carbachol (Isopto® Carbachol)]	4 days
Carbonic anhydrase inhibitors (systemic or topical) [e.g., acetazolamide (Diamox®), dorzolamide hydrochloride (Trusopt®), brinzolamide (Azopt®)]	4 days
Sympathomimetics [e.g., dipivefrin (Propine®), epinephrine (Epifrin®)]	2 weeks
Alpha-agonists [e.g., apraclonidine (Iopidine®), brimonidine tartrate (Alphagan®, Alphagan® P), brimonidine tartrate and brinzolamide (Simbrinza®)]	2 weeks
Beta-adrenergic blocking agents [e.g., timolol (Timoptic®, Betimol®, Timoptic XE®, Istatol®), timolol maleate and dorzolamide hydrochloride (Cosopt®), timolol maleate and brimonidine tartrate (Combigan®), levobunolol (Akbeta®, Betagan®), betaxolol (Betoptic®, Betopic-S®), metipranolol (Opti-Pranolol®), carteolol (Ocupress®)]	4 weeks
Prostaglandin analogs (e.g., latanoprost (Xalatan®), travoprost (Travatan®), bimatoprost (Lumigan®), tafluprost (Zioptan™)]	4 weeks

3. Exclusion criteria (the sponsor may add additional criteria):
    a. Females who are pregnant, breast feeding, or planning a pregnancy
    b. Females of childbearing potential who do not agree to utilize an adequate form of contraception
    c. Current or past history of severe hepatic or renal impairment
    d. Current or history within two months prior to baseline of significant ocular disease, e.g., corneal edema, uveitis, ocular infection, or ocular trauma in either eye
    e. Current corneal abnormalities that would prevent accurate IOP readings with the Goldmann applanation tonometer
    f. Functionally significant visual field loss
    g. Contraindication to brimonidine tartrate therapy or known hypersensitivity to any component of brimonidine tartrate therapy
    h. Use at any time prior to baseline of an intraocular corticosteroid implant
    i. Use within one week prior to baseline of contact lens
    j. Use within two weeks prior to baseline of: (1) topical ophthalmic corticosteroid, or (2) topical corticosteroid
    k. Use within one month prior to baseline of: (1) systemic corticosteroid, (2) monoamine oxidase (MAO) inhibitor therapy, (3) any antidepressant which

affects noradrenergic transmission (e.g., tricylic antidepressants, mianserin) or (4) adrenergic-augmenting psychotropic drug (e.g., desipramine, amitriptyline)

l. Use within six months prior to baseline of intravitreal or subtenon injection of ophthalmic corticosteroid
m. Underwent within six months prior to baseline any other intraocular surgery (e.g., cataract surgery)
n. Underwent within twelve months prior to baseline refractive surgery, filtering surgery, or laser surgery for IOP reduction

4. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
    a. Ocular hypotensive drug product other than a study treatment, e.g., acetazolamide (Diamox®), betaxolol solution (Betoptic®), betaxolol and pilocarpine (Betoptic® Pilo), bimatoprost (Lumigan®), brimonidine tartrate (Alphagan®, Alphagan® P), brimonidine tartrate and brinzolamide (Simbrinza®), brimonidine tartrate and timolol maleate (Combigan®), brinzolamide (Azopt®), carbachol (Miostat®), carteolol (Ocupress®), dorzolamide hydrochloride (Trusopt®), dorzolamide hydrochloride and timolol maleate (Cosopt®), epinephrine (Epifrin®), latanoprost (Xalatan®), levobetaxolol (Betaxon®), levobunolol (Akbeta®, Betagan®), mannitol (Osmitrol®), metipranolol (OptiPranolol®), pilocarpine (Isopto® Carpine, Pilopine HS®), tafluprost (Zioptan™), timolol (Betimol®, Istalol®, Timoptic®, Timoptic XE®), travoprost (Travatan®, Travatan Z®)
    b. Ophthalmic over-the-counter or prescription product, other than study treatment and the occasional use of artificial tears
    c. Monoamine oxidase (MAO) inhibitor
    d. Tricyclic antidepressant or any other antidepressant which affects noradrenergic transmission
    e. Adrenergic-augmenting psychotropic drug (e.g., desipramine, amitriptyline)
    f. Topical or systemic corticosteroid
    g. Topical ophthalmic corticosteroid
    h. Intraocular corticosteroid implant
    i. Intravitreal or subtenon injection of ophthalmic corticosteroid
    j. Change in concurrent treatment or initiation of treatment with agents potentially affecting IOP
    k. Contact lenses
    l. Ocular surgery

5. The recommended primary endpoint is the change in IOP measure from baseline evaluated at four time points, i.e., 8:00 a.m. (Hour 0; before the morning drop) and 10:00 a.m. (Hour 2) at Day 14 (Week 2) and at Day 42 (Week 6) visits. For each subject at each timepoint, the primary IOP measure should be based on the average of the IOP of both eyes.

6. The study should enroll subjects with both light- and dark-colored irides, if feasible, and each arm (Test vs. Reference) should have a comparable distribution of light- and dark-eyed participants.

7. The protocol should clearly define the per-protocol (PP) and safety populations.
    a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, instill a pre-specified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned product for the specified duration of the study, do not miss the scheduled applications for more than 3 consecutive days, and complete evaluations at Day 14 (week 2) and Day 42 (week 6) within the designated visit window (+/- 4 days) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries.
    b. The safety population includes all randomized subjects who receive study product.

8. Subjects whose condition worsens (e.g., IOP $\geq$ 36 mm Hg in either eye) and require alternate or supplemental therapy for the treatment of their chronic open angle glaucoma or ocular hypertension during the study should be discontinued, excluded from the PP population analysis, and provided with effective treatment.

9. The start and stop dates of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.

10. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome, and date of resolution. This information is needed to determine whether the incidence and severity of adverse reactions is different between the test product and RS.

11. Generally, a drug product intended for ophthalmic use shall contain the same inactive ingredients and in the same concentration as the RLD. For an ophthalmic drug product that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent [as permitted by the chemistry, manufacturing, and controls (CMC) regulations for ANDAs, 21 CFR 314.94(a)(9)(iv)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

12. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

13. A detailed description of the masking procedure is to be provided in the protocol. The packaging of the test and reference products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate masking of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. If the two treatments differ in appearance, evaluators should not be in the room whenever the treatment is taken out of the external packaging or the subject is dosed with a study treatment.

14. Refer to 21 CFR 320.38, 320.63 and the most recent version of the FDA guidance for industry on *Handling and Retention of BA and BE Testing Samples*[a] regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of BE testing. In addition, the investigators should follow the procedures of ICH E6 *Good Clinical Practice: Consolidated Guideline* for retention of study records and data in order to conduct their studies in compliance with good laboratory practices (GLPs) and good clinical practices (GCPs). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

15. It is the applicant's responsibility to enroll sufficient subjects for the study to demonstrate BE between the products.

16. To establish bioequivalence, the limits of each two-sided 95% confidence interval of difference (test minus reference) in the mean change from baseline in IOP must be within ± 1.5 mm Hg at all four timepoints, and within ± 1.0 mm Hg for majority (i.e., three) of the four time points. The primary analysis should be based on the PP population.

    To assess bioequivalence, the null and the alternative hypotheses to be tested are as followed:

$$H_0 \ : \ \mu_T - \mu_R \leq -\theta \ or \ \mu_T - \mu_R \geq \theta$$
$$H_a \ : \ -\theta < \mu_T - \mu_R < \theta$$

    Where:

    μ_T= mean of the primary endpoint for the test group,
    μ_R = mean of the primary endpoint for the reference group,
    $\theta = 1 \ or \ 1.5$

17. The protocol should include a section with fully detailed statistical analysis plan.

18. Refer to the Study Data Standards Resources website https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources.

19. Provide Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Study site identifier (if applicable)
    d. Age
    e. Sex
    f. Race
    g. Iris color of each eye
    h. Name of planned treatment
    i. Name of actual treatment
    j. Safety population flag (yes/no)
    k. Reason for exclusion from safety population
    l. Intent-to-Treat (ITT) population flag (yes/no)
    m. Per Protocol (PP) population flag (yes/no)
    n. Reason for exclusion from PP population
    o. Completers population flag (yes/no)
    p. Randomized population flag (yes/no)
    q. Datetime of first exposure to treatment
    r. Datetime of last exposure to treatment
    s. End of study date
    t. End of study status
    u. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
    v. Intraocular pressure (IOP) of each eye at baseline (Day0/hour0)
    w. Best corrected visual acuity of each eye at baseline, 20/200 or better (yes/no)
    x. Compliance rate (%)
    y. Subject missed the scheduled application for more than 3 consecutive days (yes/no)
    z. Adverse event(s) reported (yes/no)
    aa. Concomitant medication (yes/no)

20. Provide the basic data structure (BDS) dataset with records per subject, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Study site identifier (if applicable)
    d. Name of planned treatment
    e. Name of actual treatment
    f. Safety population flag (yes/no)
    g. Intent-to-Treat (ITT) population flag (yes/no)
    h. Per-Protocol (PP) population flag (yes/no)
    i. Completers population flag (yes/no)
    j. Analysis date and time
    k. Analysis visit
    l. Study visit within the designated window (yes/no)

m. Analysis timepoint (e.g., hour 0, hour 2)
n. Intraocular pressure (IOP) of each eye
o. Additional treatment required during the visit (yes/no)
p. Adverse event reported during the visit (yes/no)
q. Concomitant medication during the visit (yes/no)

21. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of brimonidine tartrate.

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.

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]

Document History: Recommended September 2008; Revised February 2014, December 2014, March 2015, October 2017, October 2025

Unique Agency Identifier: PSG_021770

[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.