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Draft Guidance on Oxymetazoline Hydrochloride

October 2022

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Active Ingredient: Oxymetazoline hydrochloride

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: (1) two in vitro bioequivalence studies and other characterization tests or (2) one in vivo bioequivalence study with clinical endpoint

I. Option 1: Two in vitro bioequivalence studies and other characterization tests

To demonstrate bioequivalence for oxymetazoline hydrochloride topical cream, 1% using in vitro studies, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard in the same packaging configuration (tube or pump) that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and reference standard are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the FDA guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*[a], and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.

2. The test product and reference standard in the same packaging configuration (tube or pump) should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization tests with a minimum of three batches of the test product and three batches (as available) of the reference standard. The test product and reference standard batches should ideally represent the product at different ages throughout its shelf life. Refer to the most recent version of the FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug*

Products Submitted in ANDAs[a] for additional information regarding comparative Q3 characterization tests. The comparison of the test product and reference standard should include characterizations of the following Q3 attributes:

a. Characterization of visual appearance and texture
b. Characterization of phase states and structural organization of matter
    - Microscopic examination with representative high-resolution microscopic images at multiple magnifications
    - Analysis of globule size distribution
c. Characterization of rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:
    - A characterization of shear stress vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
    - A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
    - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
    - The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported. Any non-linear viscosity behavior over a range of shear rates should also be investigated, measured and reported.
d. Characterization of pH
e. Characterization of specific gravity
f. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard in the same packaging configuration (tube or pump) should have an equivalent rate of oxymetazoline hydrochloride release based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVRT method.

    Type of study: Bioequivalence study with IVRT endpoint
    Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro
    Strength: 1%
    Test system: A synthetic membrane in a diffusion cell system
    Analytes to measure: Oxymetazoline in receptor solution
    Equivalence based on: Oxymetazoline (IVRT endpoint: drug release rate)
    Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test product and reference standard evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

4. The test product and reference standard in the same packaging configuration (tube or pump) should have an equivalent rate and extent of oxymetazoline permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVPT method.

   Type of study: Bioequivalence study with IVPT endpoints
   Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an unoccluded finite dose, in vitro
   Strength: 1%
   Test system: Barrier-competent human skin from male and/or female donors of at least 18 years of age in a diffusion cell system
   Analytes to measure: Oxymetazoline in receptor solution
   Equivalence based on: Oxymetazoline (IVPT endpoints: total cumulative amount (AMT) and maximum flux (J_{max}))
   Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVPT bioequivalence methods/studies. The batches of test product and reference standard evaluated in the IVPT bioequivalence study should be the same as those evaluated in the IVRT bioequivalence study.

II. Option 2: One in vivo bioequivalence study with clinical endpoint

1. Type of study: Bioequivalence study with clinical endpoint
   Design: Randomized, double blind, parallel, placebo controlled, in vivo
   Strength: 1%
   Subjects: Males and non-pregnant, non-lactating females with moderate to severe persistent facial erythema of rosacea
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends conducting a bioequivalence study with clinical endpoint in the treatment of moderate-to-severe persistent facial erythema of rosacea. The study should compare the test product versus the reference standard and placebo (vehicle) control, each administered by applying a pea-size amount of the assigned study treatment to each of the five areas of the face (forehead, chin, nose, each cheek)—avoiding the eyes and lips—once daily for 15 days.

2. Inclusion Criteria (the sponsor may add additional criteria):
    a. Males or non-pregnant, non-lactating females aged at least 18 years
    b. A clinical diagnosis of facial rosacea
    c. Moderate to severe persistent facial erythema associated rosacea at baseline, as determined by both:
        - A Clinician Erythema Assessment (CEA) score of ≥ 3 at screening and on baseline/Day 1 prior to study drug application (per Table 1)
        - A Patient's Self-Assessment (PSA) score of ≥ 3 at screening and on baseline/ Day 1 prior to study drug application (per Table 2)

Table 1: Sample CEA Scale for Rosacea

Grade	Description
0	Clear skin with no signs of erythema
1	Almost clear; slight redness
2	Mild erythema; definite redness
3	Moderate erythema; marked redness
4	Severe erythema; fiery redness

Table 2: Sample PSA Scale for Rosacea

Grade	Description
0	No redness
1	Very mild redness
2	Mild redness
3	Moderate redness
4	Severe redness

    d. Subject's willingness to minimize external factors that might trigger rosacea flare-ups (e.g., spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds, alcoholic beverages)

4. 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. Particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other concomitant facial dermatoses that are similar to rosacea such as peri-oral dermatitis, demodicidosis, facial keratosis pilaris, seborrheic dermatitis, acute lupus erythematosus, or actinic telangiectasia
    d. Presence of ≥ 3 facial inflammatory lesions of rosacea
    e. Subjects with Raynaud's syndrome, thromboangiitis obliterans, orthostatic hypotension, severe cardiovascular disease, cerebral or coronary insufficiency, renal or hepatic impairment, scleroderma, Sjögren's syndrome, or depression

f. Presence of any skin condition on the face that would interfere with the diagnosis or assessment of rosacea
g. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with the study treatments or study assessments
h. Dermatologic or surgical procedure on the face within four weeks prior to baseline
i. Known hypersensitivity reaction to any component of oxymetazoline therapy
j. Current use of monoamine oxidase (MAO) inhibitors, barbiturates, opiates, sedatives, systemic anesthetics, alpha-agonists, cardiac glycosides, beta blockers, other antihypertensive agents, or brimonidine tartrate ophthalmic solution
k. Use within six months prior to baseline of oral retinoids (e.g., Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed)
l. Use within 12 weeks prior to baseline of systemic immunomodulators
m. Use within four weeks prior to baseline of 1) topical immunomodulators, 2) systemic antibiotics, 3) systemic corticosteroids, 4) systemic anti-inflammatory agents, 5) systemic treatment for rosacea, or 6) systemic treatment for acne (other than oral retinoids, which require a 6-month washout)
n. Use within two weeks prior to baseline of 1) topical corticosteroids, 2) topical retinoids, 3) topical antibiotics, 4) topical anti-inflammatory, 5) topical treatment for rosacea, or 6) topical treatment for acne
o. Use within 1 week prior to baseline of niacin ≥ 500 mg per day

5. 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. Any other topical products applied to face.
    b. Medicated soaps used on face.
    c. Dermatologic or surgical procedure on face.
    d. MAO inhibitors, barbiturates, opiates, sedatives, systemic anesthetics, alpha-agonists, cardiac glycosides, beta blockers, other antihypertensive agents, or brimonidine tartrate ophthalmic solution.
    e. Systemic treatment for rosacea.
    f. Systemic corticosteroids, systemic antibiotics, systemic immunomodulators, systemic anti-inflammatory agents, oral retinoids, or other systemic treatment for acne vulgaris.
    g. Use of tanning booths, sunbathing, or excessive exposure to the sun.
    h. Subjects should be instructed to wash their hands with soap and water before and after applying treatment and to avoid contact of the study product with the eye or lips.

6. The CEA should be performed at the screening visit, the baseline/Day 1 visit, and the End of Study/Day 15 visit. The screening visit and the Day 1 visit should be on separate days. During the screening visit, the CEA and PSA should be performed once. During the Day 1 and Day 15 visits, the CEA should be performed five times: prior to dosing and at 3, 6, 9, and 12 hours post-application.

7. The recommended primary endpoint is the proportion of subjects with treatment success at Hour 3, 6, 9, and 12 post-application on Day 15, where treatment success is defined as a 2-grade improvement from pre-dose on Day 1 on CEA only. During the assessment of Day 15, investigators should evaluate CEA in comparison to baseline assessment of the subjects' erythema (e.g., CEA scores, photographs).

8. Provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier for the study
    d. Study site identifier (if applicable)
    e. Age
    f. Age units (years)
    g. Sex
    h. Race
    i. Name of planned treatment
    j. Name of actual treatment
    k. Safety population flag (yes/no)
    l. Reason for exclusion from safety population
    m. Modified Intent-to-Treat (mITT) population flag (yes/no)
    n. Reason for exclusion from mITT population
    o. Per-Protocol (PP) population flag (yes/no)
    p. Reason for exclusion from PP population
    q. Randomized population flag (yes/no)
    r. Date/time of first exposure to treatment
    s. Date/time of last exposure to treatment
    t. End of study date
    u. End of study status
    v. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
    w. CEA score at screening visit
    x. PSA score a screening visit
    y. CEA score at Day 1 visit at pre-dose
    z. PSA score at Day 1 visit at pre-dose
    aa. CEA score at Day 1 visit at 3 hours post-application
    bb. CEA score at Day 1 visit at 6 hours post-application
    cc. CEA score at Day 1 visit at 9 hours post-application
    dd. CEA score at Day 1 visit at 12 hours post-application
    ee. CEA score at Day 15 visit at pre-dose
    ff. CEA score at Day 15 visit at 3 hours post-application
    gg. CEA score at Day 15 visit at 9 hours post-application
    hh. CEA score at Day 15 visit at 12 hours post-application
    ii. Compliance rate (%)
    jj. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)

kk. Adverse event reported (yes/no)
ll. Concomitant medication (yes/no)

9. Provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier for the study
    d. Study site identifier (if applicable)
    e. Name of planned treatment
    f. Name of actual treatment
    g. Safety population flag (yes/no)
    h. Modified ITT population flag (yes/no)
    i. Per-Protocol (PP) population flag (yes/no)
    j. Analysis date
    k. Analysis visit
    l. Study visit within the designated window (yes/no)
    m. Analysis timepoint (e.g., hour 0, hour 3, 6, 9, and 12 hours post-application)
    n. CEA score
    o. PSA Score
    p. Additional treatment required during the visit (yes/no)
    q. Adverse event reported during the visit (yes/no)
    r. Concomitant medication during the visit (yes/no)

10. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[b] for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoint.

11. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

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[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[b] For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.