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Draft Guidance on Tazarotene

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Active Ingredient: Tazarotene

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 tazarotene topical cream, 0.1% 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 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 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 should have an equivalent rate of tazarotene 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: 0.1%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Tazarotene in receptor solution
    Equivalence based on: Tazarotene (IVRT endpoint: drug release rate)
    Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test (IVRT) 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 should have an equivalent rate and extent of tazarotene 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: 0.1%
   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: Tazarotene and tazarotenic acid in receptor solution
   Equivalence based on: Tazarotene (IVPT endpoints: total cumulative amount (AMT) and maximum flux (Jmax))
   Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Permeation Test (IVPT) Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVPT 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.

Waiver request for 0.05% strength: The 0.05% strength of the cream product containing sufficient data may be approved based on (i) acceptable demonstration of bioequivalence of the 0.1% strength using the bioequivalence approach outlined within Option 1, (ii) the formulations of the lower and higher strengths of the test product are exactly the same, except for the amount of tazarotene and the corresponding change in the amount of the diluent, and have the same manufacturing process, (iii) acceptable comparative Q3 characterization tests using a minimum of three batches of the lower strength of the test product and three batches of the higher strength of the test product; the relationship of the Q3 attributes of the two strengths of the test product should be compared to the relationship of the Q3 attributes of the two strengths of the reference standard, and (iv) an acceptable IVRT study comparing a minimum of one batch of the lower and higher strengths of the test product using an appropriately validated IVRT method. The relationship of the release rate of tazarotene from the two strengths of the test product should be proportional to the relationship of the release rates between the two strengths of the reference standard.

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: 0.1%
   Subjects: Males and non-pregnant, non-lactating females with acne vulgaris
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends conducting a single bioequivalence study with clinical endpoint in the treatment of acne vulgaris comparing the tazarotene topical cream, 0.1% test product versus the reference standard and placebo control, each applied once daily in the evening for 12 weeks. The two co-primary endpoints, percent change from baseline in the inflammatory (papules and pustules) and non-inflammatory (comedones) lesion counts, are to be evaluated at the end of treatment (Study Day 84; Week 12).

2. Inclusion Criteria (the sponsor may add additional criteria):
    a. Male or non-pregnant female aged ≥ 12 and ≤ 40 years with a clinical diagnosis of acne vulgaris.
    b. On the face, ≥ 25 non-inflammatory lesions (i.e., open and closed comedones) AND ≥ 20 inflammatory lesions (i.e., papules and pustules) AND ≤ 2 nodulocystic lesions (i.e., nodules and cysts).
    c. Investigator's Global Assessment (IGA) of acne severity Grade 2, 3, or 4 (per Table 1).
    d. Willing to refrain from use of all other topical acne medications or antibiotics during the 12-week treatment period.
    e. If female of childbearing potential, the subject must have a negative result for a pregnancy test having sensitivity down to at least 50 mIU/mL for hCG within 2 weeks prior to starting treatment, begin treatment during a normal menstrual period, and be willing to use an acceptable form of birth control throughout the study.

3. Exclusion Criteria (the sponsor may add additional criteria):
    a. Females who are pregnant, breast feeding, planning a pregnancy or do not agree to use an acceptable form of birth control throughout the study.
    b. Presence of any skin condition that would interfere with the diagnosis or assessment of acne vulgaris (e.g., on the face: rosacea, dermatitis, psoriasis, squamous cell carcinoma, eczema, acneform eruptions caused by medications, steroid acne, steroid folliculitis, or bacterial folliculitis).
    c. Facial sunburn.
    d. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of acne vulgaris.
    e. History of hypersensitivity or allergy to tazarotene, retinoids and/or any component of the test product or reference standard.
    f. Use within 6 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).
    g. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study.
    h. Use on the face within 1 month prior to baseline or during the study of 1) cryodestruction or chemodestruction, 2) dermabrasion, 3) photodynamic therapy, 4) acne surgery, 5) intralesional steroids, or 6) x-ray therapy.

i. Use within 1 month prior to baseline of 1) spironolactone, 2) systemic steroids, 3) systemic antibiotics, 4) systemic treatment for acne vulgaris (other than oral retinoids, which require a 6-month washout), or 5) systemic anti-inflammatory agents.
j. Use within 2 weeks prior to baseline of 1) topical steroids, 2) topical retinoids, 3) topical acne treatments including over-the-counter preparations, 4) topical anti-inflammatory agents, or 5) topical antibiotics.

4. Scale to be used for evaluation of baseline disease severity and treatment effect:

Table 1. Sample IGA Scale for Acne Vulgaris[1]

Grade	Description
0	Clear skin with no inflammatory or noninflammatory lesions
1	Almost clear; rare noninflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than Grade 2; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4*	Severe; greater than Grade 3; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions

* The Case Report Forms for acne studies can allow for reporting by investigators of lesion worsening beyond Grade 4 with treatment. It is recommended that enrollment of acne vulgaris subjects not include subjects with nodulocystic acne. Subjects who worsen beyond Grade 4 are to be described in the safety evaluation.

5. Tazarotene cream is contraindicated during pregnancy. Therefore, in a bioequivalence study with clinical endpoint, all females of childbearing potential should be maintained on an appropriate method of contraception throughout the study. The informed consent form must clearly discuss the potential risk of teratogenicity.

[1] Guidance for industry *Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment*. 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.

6. It is recommended to repeat the urine pregnancy test (with sensitivity down to at least 50 mIU/mL hCG) for all females of childbearing potential during the study visits at Study Day 28 (Week 4), Study Day 56 (Week 8) and end of treatment (Study Day 84; Week 12). If a female of childbearing potential discontinues prematurely, the pregnancy test should be performed at the exit visit.

7. Subjects should gently clean and dry the face and then apply the product onto the affected areas of the face once daily, in the evening, avoiding contact with the eyes, eyelids and mouth.

8. 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. Medicated soaps used on face.
    b. Topical product other than the assigned treatment (including moisturizers, new brands of make-up, creams, ointments, lotions, and powders) applied on or near the treatment area.
    c. Photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides).
    d. Application of study treatment to unaffected skin.
    e. More than 10,000 IU/day of Vitamin A supplements.
    f. Spironolactone.
    g. Oral retinoids, therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed) or other systemic treatment for acne vulgaris.
    h. Systemic (e.g., oral or injectable) antibiotics.
    i. Systemic steroids, systemic anti-inflammatory agents or immunosuppressive drugs.
    j. Antipruritics, including antihistamines, within 24 hours of study visits.
    k. Use on the face of 1) cryodestruction or chemodestruction, 2) dermabrasion, 3) photodynamic therapy, 4) acne surgery, 5) intralesional steroids, or 6) x-ray therapy.
    l. The treated areas should not be bandaged, covered or wrapped as to be occlusive.
    m. Tanning booths, sun lamps, or nonprescription UV light sources.
    n. Phototherapy.
    o. Subjects should be instructed to minimize exposure to natural sunlight. to use sunscreens of at least SPF 15 and wear protective clothing during the day, to not allow the cream to come in contact with the eyes, eyelids, or mouth, to not use study treatment on skin that has eczema, and to always wash hands thoroughly after application of study medication.

9. The recommended two co-primary endpoints of the study are percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts and in the noninflammatory (open and closed comedones) lesion counts. The protocol should clearly define papules, pustules, open comedones, closed comedones, nodules and cysts. When counting facial acne lesions, it is important that all lesions be counted, including those present on the nose. Counts of nodules and cysts should be reported separately and not included in the inflammatory or non-inflammatory lesion counts.

10. Application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain and itching are to be recorded at each visit to allow a comparison between treatment groups. A descriptive analysis comparing the application site reactions for each treatment group is recommended. It is important to ensure that the test product is not worse than the reference standard with regard to the expected and unexpected application site reactions.

11. If the tazarotene topical cream, 0.1% test product demonstrates bioequivalence for the acne vulgaris indication, it is not necessary to conduct an additional bioequivalence study with clinical endpoint for the psoriasis indication. If a sponsor requests approval of their tazarotene topical cream, 0.1% test product for both reference listed drugs, submits the appropriate labeling for both, and their test product demonstrates bioequivalence in the acne vulgaris indication, it is not necessary to conduct an additional bioequivalence study with clinical endpoint for the indication "as an adjunctive agent for use in the mitigation (palliation) of facial fine wrinkling, facial mottled hyper- and hypopigmentation, and benign facial lentigines in patients who use comprehensive skin care and sunlight avoidance programs."

12. 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.

13. 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.