

Draft Guidance on Dapsone

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

Active Ingredient:	Dapsone
Dosage Form; Route:	Gel; topical
Recommended Studies:	Two options: (1) a combination of in vitro and in vivo studies with pharmacokinetic endpoints, or (2) an in vivo study with clinical endpoints.

1. Option 1: In vitro and in vivo studies with pharmacokinetic endpoints

To demonstrate bioequivalence for this drug product using studies with pharmacokinetic endpoints, including one in vitro study evaluating local (cutaneous) pharmacokinetics and one in vivo study evaluating systemic (plasma) pharmacokinetics, all of the following criteria should be met:

- A. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference product in the same packaging configuration that may significantly affect the local or systemic availability of the active ingredient. For example, if the test and reference products are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the guidance for industry *ANDA Submissions – Refuse-to-Receive Standards* and the criteria below are also satisfied, the bioequivalence of the test product with respect to the reference product may be established using a characterization based bioequivalence approach.
- B. The test and reference products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three batches of the test and three batches (as available) of the reference product. The influence of any differences in the container closure systems between the test and reference products, which may influence the physicochemical properties of the gel when dispensed, should be considered in the design of the physical and structural characterization studies and discussed in the associated reports. Comparison of physical and structural similarity for the test and reference products should include the following physicochemical characterizations for each batch of test and reference products:
 - i. Assessment of appearance.
 - ii. Analysis of the dapsone polymorphic form in the drug product.

- iii. Analysis of particle size distribution and crystal habit with representative microscopic images at multiple magnifications.
 - iv. Analysis of the 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 complete flow curve of shear stress (or viscosity) vs. shear rate should consist of multiple data points 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.
 - v. Analysis of specific gravity, pH and any other potentially relevant physical and structural similarity characterizations.
- C. The test and reference products have an equivalent rate of dapson release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one batch each of the test and reference products using an appropriately validated IVRT method. Refer to the *Guidance on Acyclovir* (for acyclovir topical cream, 5%) for additional information regarding the development, validation, conduct and analysis of acceptable IVRT studies.
- D. The test and reference products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of dapson permeation through excised human skin from a minimum of one batch each of the test and reference products using an appropriately validated IVPT method.

Type of study: IVPT study

Design: Parallel, single-dose, multiple-replicate per treatment group study design

Strength: 7.5%

Skin: Barrier-competent skin from male and/or female donors of at least 18 years of age, general population

Additional comments: The batches of test and reference products evaluated in the IVPT study should be the same as those evaluated in the IVRT study, and that these batches should be included among those for which the physical and structural similarity is characterized and compared. Refer to the *Guidance on Acyclovir* (for acyclovir topical cream, 5%) for additional information regarding the development, validation, conduct and analysis of acceptable IVPT studies.

- E. The test and reference products are bioequivalent based upon an acceptable in vivo pharmacokinetic study with one batch each of the test and reference products.

Type of study: Fasting, in vivo pharmacokinetic study

Design: Single-application, two-way crossover study design

Strength: 7.5%

Subjects: Males and nonpregnant, nonlactating females, general population

Additional comments: The batch of test and reference products evaluated in the in vivo pharmacokinetic study should be the same as those evaluated in the IVPT study.

Analytes to measure (in appropriate biological fluid): Dapsone in plasma (in vivo) or in IVPT receptor solution (in vitro)

Bioequivalence based on (90% CI): Dapsone

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

2. Option 2: In vivo study with clinical endpoints

Type of study: Bioequivalence study with clinical endpoints

Design: Randomized, double blind, parallel, placebo controlled, in vivo

Strength: 7.5%

Subjects: Males and nonpregnant, nonlactating females with acne vulgaris.

Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Not applicable

Bioequivalence based on (90% CI): Clinical endpoints

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

Additional comments regarding the bioequivalence study with clinical endpoints:

1. The Office of Generic Drugs recommends conducting a bioequivalence study with clinical endpoint in the treatment of acne vulgaris. Subjects are to be randomized to receive the test product, reference product, or placebo (vehicle). The study treatment is to be administered once daily for 12 weeks. The two primary endpoints are to be evaluated at the end of treatment (Study Week 12).
2. Inclusion Criteria (the sponsor may add additional criteria):
 - a. Male or nonpregnant, nonlactating 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)

Table 1. Sample IGA Scale for Acne Vulgaris¹

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.

- 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, willing to use an acceptable form of birth control during the study
3. Exclusion Criteria (the sponsor may add additional criteria):
- a. Pregnant, breast feeding or planning a pregnancy.
 - 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. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of acne vulgaris.
 - d. History of hypersensitivity or allergy to dapsone or any of the study medication ingredients.

¹ Guidance for industry *Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment*. Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acne-vulgaris-establishing-effectiveness-drugs-intended-treatment>

- e. 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).
 - f. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study.
 - g. Use on the face within 1 month prior to baseline of 1) cryodestruction or chemodestruction, 2) dermabrasion, 3) photodynamic therapy, 4) acne surgery, 5) intralesional steroids, or 6) x-ray therapy.
 - h. 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.
 - i. 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.
 - j. Case reports^{2,3} have described cases of methemoglobinemia following topical dapsone, 5% application. Consider excluding subjects with known G6PD deficiency, or congenital or idiopathic methemoglobinemia. All enrolled subjects should be monitored for adverse effects consistent with hemolysis or methemoglobinemia.
4. One scientific publication has reported greater efficacy in females (compared to males) with facial acne vulgaris treated with dapsone topical gel, 5%,⁴ and similar results were observed in a study of subjects using the 7.5% gel;⁵ thus, consider randomizing approximately equal numbers of male and female subjects to each of the three arms in the study.
 5. Once daily, subjects should wash their face with a mild or soapless, non-medicated cleanser, gently pat skin dry with a clean towel, and then apply a thin layer of study medication, approximately a pea-sized amount, to cover the entire affected skin areas of the face. The subject should be instructed to avoid contact of the study product with the mouth, eyes and open wounds, and to wash their hands after application.
 6. Subjects should not apply moisturizers, new brands of make-up, creams, lotions, powders or any topical product other than the assigned treatment to the treatment area. Subjects should minimize exposure to sunlight, including sunlamps, while using the product. Use of sunscreen products and protective clothing over treated areas is recommended when sun exposure cannot be avoided.

² Graff DM, Bosse GM, Sullivan J. Case report of methemoglobinemia in a toddler secondary to topical dapsone exposure. *Pediatrics*. 2016;138(2):e20153186.

³ Swartzentruber GS, Yanta JH, Pizon AF. Methemoglobinemia as a complication of topical dapsone. *N Engl J Med*. 2015;372(5):491–2.

⁴ Tanghetti E et al. The efficacy and tolerability of dapsone 5% gel in female vs. male patients with facial acne vulgaris: gender as a clinically relevant outcome variable. *J Drugs Dermatol*. 2012 Dec; 11 (12): 1417-21.

⁵ Draelos ZD, Rodriguez DA, Kempers SE, et al. Age and gender as predictors of treatment outcomes with once-daily dapsone 7.5% topical gel for acne vulgaris [abstract no. 3244 plus poster]. *J Am Acad Dermatol*. 2016;74(5 Suppl 1):AB2.

7. 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. Spironolactone
 - d. Oral retinoids, therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed) or other systemic treatment for acne vulgaris
 - e. Systemic (e.g., oral or injectable) antibiotics
 - f. Systemic steroids, systemic anti-inflammatory agents or immunosuppressive drugs
 - g. Antipruritics, including antihistamines, within 24 hours of study visits
 - h. 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
 - i. Use of hormonal contraceptives should not be initiated or changed during the study
 - j. Use of tanning booths, sunbathing, or excessive exposure to the sun
8. The two primary endpoints of the study are: 1) mean percent change from baseline to Week 12 (Study Day 84) in the inflammatory (papules and pustules) lesion count and 2) mean percent change from baseline to Week 12 in the non-inflammatory (open and closed comedones) lesion count. 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.
9. 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 product with regard to the expected and unexpected application site reactions.
10. Please refer to the product-specific guidance on adapalene; benzoyl peroxide topical gel, 0.3%; 2.5% entitled *Guidance on Adapalene; Benzoyl Peroxide* for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.
11. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov⁶.

⁶ Study Data Standards for Submission to CDER and CBER available at:
<https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

