Draft Guidance on Dapsone

Active Ingredient: Dapsone

Dosage Form; Route: Gel; topical

Recommended Studies: Two options: (1) a combination of in vitro and in vivo studies with pharmacokinetic (PK) endpoints, or (2) an in vivo study with clinical endpoints.

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

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

A. The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry: Abbreviated New Drug Application Submissions – Refuse-to-Receive Standards.

B. The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and a minimum of three lots (as available) of the RLD product. The influence of any differences in the container closure systems between the test and RLD 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 RLD products should include the following physicochemical characterizations for each lot of test and RLD products:

   a. Assessment of appearance.

   b. Analysis of the dapsone polymorphic form in the drug product.

   c. Analysis of particle size distribution and crystal habit with representative microscopic images at multiple magnifications.

   d. 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.

e. Analysis of specific gravity, pH and any other potentially relevant physical and structural similarity characterizations.

C. The test and RLD products have an equivalent rate of dapsone release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method. Refer to the Draft Guidance on Acyclovir Topical Cream for additional information regarding the development, validation, conduct and analysis of acceptable IVRT studies.

D. The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of dapsone permeation through excised human skin from a minimum of one lot each of the test and RLD 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 lots of test and RLD products evaluated in the IVPT study should be the same as those evaluated in the IVRT study, and that these lots should be included among those for which the physical and structural similarity is characterized and compared. Refer to the Draft Guidance on Acyclovir Topical Cream for additional information regarding the development, validation, conduct and analysis of acceptable IVPT studies.

E. The test and RLD products are bioequivalent based upon an acceptable in vivo PK study with one lot each of the test and RLD products.

Type of study: Fasting, in vivo PK study

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

Strength: 7.5%

Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments: The lots of test and RLD products evaluated in the in vivo PK 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 receptor solution (in vitro)

Bioequivalence based on (90% CI): Dapsone

Waiver request of in vivo testing: Not applicable (N/A)

Dissolution test method and sampling times: N/A

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2. Option 2: In vivo study with clinical endpoints

Type of study: BE study with clinical endpoints
Design: Randomized, double blind, parallel, placebo controlled, in vivo
Strength: 7.5%
Subjects: Males and non-pregnant, non-lactating females with acne vulgaris.
Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): N/A

Bioequivalence based on (90% CI): Clinical endpoints

Waiver request of in vivo testing: N/A

Dissolution test method and sampling times: N/A

Additional comments regarding the BE study with clinical endpoints:

1. The Office of Generic Drugs recommends conducting a BE study with clinical endpoint in the treatment of acne vulgaris. Subjects are to be randomized to receive the test product, reference listed drug (RLD), 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. A placebo (vehicle) control arm is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.

3. Inclusion Criteria (the sponsor may add additional criteria)
    a. Male or non-pregnant, non-lactating 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 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.

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.

4. 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.
    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).

[1] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Draft Guidance for Industry: Acne Vulgaris: Developing Drugs for Treatment. Clinical/Medical. September 2005. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071292.pdf

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.

5. 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.

6. 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.

7. 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.

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. Any other topical products applied to face.
    b. Medicated soaps used on face.
    c. Spironolactone.

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[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 patient 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.

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.

9. 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.

10. The dichotomized IGA severity scale should be treated as a secondary endpoint for supportive evidence. This secondary endpoint for bioequivalence should be evaluated as the proportion of subjects with a clinical response of "success" at week 12. Success should be defined as an IGA score that is at least 2 grades less than the baseline assessment. Failure should be defined as an IGA score that is the same, higher or one grade lower than the baseline assessment.

11. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations in the protocol.
    a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who meet the inclusion/exclusion criteria, apply a prespecified proportion of the scheduled applications (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 the evaluation 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 mITT and safety population include all randomized subjects who apply at least one dose of product.

12. Subjects who are discontinued prematurely from the study due to lack of treatment effect after completing 4 weeks of treatment should be included in the PP population using Last Observation Carried Forward (LOCF). Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of acne vulgaris during the study should be discontinued, included in the PP population analysis using LOCF, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF. Sponsors should provide a pre-specified definition of lack of treatment effect.

13. The start and stop date 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.

14. 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 if the incidence and severity of adverse reactions is different between the test product and RLD.

15. 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.

16. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the sponsor is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy and/or systemic or local availability of the drug. Inactive ingredients used should provide adequate margins of safety for the proposed clinical exposure in the target population.

17. The method of randomization should be described in the protocol and the randomization schedule should be provided. 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.

18. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.

19. Refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and 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 and Good Clinical Practices. 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.

20. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

21. To establish bioequivalence for a dichotomous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

    H_O: $\pi_T - \pi_R \leq \Delta_1$ or $\pi_T - \pi_R \geq \Delta_2$ versus H_A: $\Delta_1 < \pi_T - \pi_R < \Delta_2$

    where π_T = the success rate of the primary endpoint for the treatment group, and
    π_R = the success rate of the primary endpoint for the reference group.

    The null hypothesis, H_O, is rejected with a type I error (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the difference of the success rates between test and reference products ($\pi_T - \pi_R$) is contained within the interval $[\Delta_1, \Delta_2]$, where $\Delta_1 = -0.20$ and $\Delta_2 = 0.20$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

    To establish bioequivalence for a continuous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

    H_O: $\mu_T / \mu_R \leq \theta_1$ or $\mu_T / \mu_R \geq \theta_2$ versus HA : $\theta_1 < \mu_T / \mu_R < \theta_2$

    where μ_T = mean of the primary endpoint for the test group, and
    μ_R = mean of the primary endpoint of the reference group

    The null hypothesis, H_O, is rejected with a type I error (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the ratio of the means between test and reference products (μ_T / μ_R) is contained within the interval $[\theta_1, \theta_2]$, where $\theta_1 = 0.80$ and $\theta_2 = 1.25$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

22. To establish sensitivity within the study for either a dichotomous or continuous primary endpoint, the test and reference products should both be statistically superior to the placebo. Conduct an appropriate two-sided inferential test with a type I error (α) of 0.05, using the mITT population and the primary endpoint.

23. The study data should be submitted in standardized format. Refer to study data standards published at www.FDA.gov[6].

24. The protocol should include a full detailed statistical analysis plan.

25. Provide the Subject-Level Analysis Dataset, one record per subject, using the following headings, if applicable:

[6] Study Data Standards for Submission to CDER available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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. Completers population flag (yes/no)
r. Randomized population flag (yes/no)
s. Datetime of first exposure to treatment
t. Datetime of last exposure to treatment
u. End of study date
v. End of study status
w. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
x. Total number of inflammatory lesions on the face at baseline
y. Total number of non-inflammatory lesions on the face at baseline
z. Total number of nodules/cysts on the face at baseline
aa. IGA score at baseline
bb. Total number of inflammatory lesions on the face at week 12
cc. Total number of non-inflammatory lesions on the face at week 12
dd. Total number of nodules/cysts on the face at week 12
ee. IGA score at week 12
ff. Final designation for IGA (success/failure)
gg. Compliance rate (%)
hh. Subject missed the scheduled applications for more than XX consecutive days (yes/no)
ii. Adverse event reported (yes/no)
jj. Concomitant medication (yes/no)

26. Provide the basic data structure dataset with records per subject, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier
    b. Unique 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. Modified Intent-to-Treat (mITT) population flag (yes/no)
h. Per-Protocol (PP) population flag (yes/no)
i. Completers population flag (yes/no)
j. Analysis date
k. Analysis visit
l. Total number of Inflammatory lesions
m. Total number of noninflammatory lesions
n. Total number of Nodules/cyst lesions
o. IGA score
p. Study visit within the designated window (yes/no)
q. Additional treatment required during the visit (yes/no)
r. Adverse event reported during the visit (yes/no)
s. Concomitant medication during the visit (yes/no)