

## Draft Guidance on Clindamycin Phosphate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

<b>Active Ingredient:</b>	Clindamycin phosphate
<b>Dosage Form; Route:</b>	Gel; topical
<b>Recommended Studies:</b>	Two options: (1) in vitro approach, or (2) an in vivo study with clinical endpoints.

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**In Vitro Approach:** To demonstrate bioequivalence (BE) for this drug product using in vitro characterization based approaches, all of the following criteria should be met:

- A. The test and Reference Listed Drug (RLD) products should be qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry: *ANDA Submissions – Refuse-to-Receive Standards*, Revision 2 (December 2016)<sup>1</sup>, with allowance for the amount of a pH modifier utilized to match the pH of the RLD product.
- B. The test and RLD products should be physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three batches of the test and a minimum of three batches (as available) of the RLD product. The characterization of the test and RLD products should include the following comparisons of physical and structural attributes between the test and RLD products:
  - i. Assessment of appearance with representative microscopic images at multiple magnifications.
  - ii. 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. The comparative viscosity data at low, medium and high shear rates should be provided.
    - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
  - iii. Analysis of pH, specific gravity, and any other potentially relevant physical and structural similarity characterizations.

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<sup>1</sup> Guidance for Industry: *ANDA Submissions – Refuse-to-Receive Standards*, Revision 2 (December 2016)

- C. The test and RLD products should have an equivalent rate of clindamycin phosphate release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one batch each of the test and RLD products using an appropriately validated IVRT method. Refer to the *Guidance on Acyclovir* (for acyclovir topical cream, 5%)<sup>2</sup> for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test and RLD products evaluated in the IVRT study should be included among those for which the physical and structural similarity is characterized and compared.

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

**Bioequivalence based on (90% CI):** Refer to the *Guidance on Acyclovir* (for acyclovir topical cream, 5%)<sup>2</sup> for additional information regarding the analysis of in vitro studies.

**Waiver request of in vivo testing:** Not applicable

**Dissolution test method and sampling times:** Not applicable

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### **In Vivo Study with Clinical Endpoints**

Type of study: Bioequivalence (BE) Study with Clinical Endpoint  
Design: Randomized, double blind, parallel, placebo controlled in vivo  
Strength: EQ 1% Base  
Subjects: Males and nonpregnant females with acne vulgaris

Additional comments: Specific recommendations are provided below.

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

**Bioequivalence based on (90% CI):** Clinical Endpoint

**Waiver request of in vivo testing:** Not applicable

**Dissolution test method and sampling times:** Not applicable

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### **Additional comments regarding the BE study with clinical endpoint:**

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with a clinical endpoint in the treatment of acne vulgaris. Subjects are to be randomized to receive the test product, the reference listed drug (RLD), or placebo (vehicle). The study treatment is to be

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<sup>2</sup> Guidance on Acyclovir for acyclovir topical cream, 5% (recommended Dec 2014; revised Dec 2016).

administered twice daily, in the morning and evening, to the face as a thin film for 12 weeks. The two primary endpoints are: 1) mean percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts and 2) mean percent change from baseline to Week 12 in the non-inflammatory (open and closed comedones) lesion counts.

2. Inclusion Criteria (the sponsor may add additional criteria):
  - a. Male or non-pregnant, non-lactating female aged  $\geq 12$  and  $\leq 40$  years with a clinical diagnosis of acne vulgaris.
  - b. On the face,  $\geq 25$  non-inflammatory lesions (i.e., open and closed comedones) AND  $\geq 20$  inflammatory lesions (i.e., papules and pustules) AND  $\leq 2$  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<sup>3</sup>**

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 (other than study treatment) during the 12-week treatment period.
- e. Willing to maintain constant any estrogen or oral contraceptive therapy during the 12-week treatment period.
- f. 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):

<sup>3</sup> U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Acne Vulgaris: Developing Drugs for Treatment. Clinical/Medical. September 2005. Accessed at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071292.pdf>

- 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 clindamycin or lincomycin and/or any of the study medication ingredients.
  - e. History of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.
  - f. Use within 6 months prior to baseline of oral retinoids (e.g. Accutane<sup>®</sup>) 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 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. 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 the face.
  - b. Medicated soaps used on the face.
  - c. Neuromuscular blocking agents.
  - d. Spironolactone.
  - e. Oral retinoids, therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed) or other systemic treatment for acne vulgaris.
  - f. Systemic (e.g., oral or injectable) antibiotics.
  - g. Systemic steroids, systemic anti-inflammatory agents or immunosuppressive drugs.
  - h. Antipruritics, including antihistamines, within 24 hours of study visits.
  - i. 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.
  - j. Use of hormonal contraceptives should not be initiated or changed during the study.
  - k. Use of tanning booths, sunbathing, or excessive exposure to the sun.
5. The recommended 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 (study Day 84) 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.

6. 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 these expected application site reactions.
7. Please refer to the product-specific guidance on Adapalene; Benzoyl peroxide topical gel 0.3%; 2.5% (“Draft Guidance on Adapalene; Benzoyl Peroxide”) for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints:  
[\[https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM533014.pdf\]](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM533014.pdf)
8. Study data should be submitted in a standardized format. Please refer to the study data standards published at [www.fda.gov](http://www.fda.gov)<sup>4</sup>

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<sup>4</sup> Study Data Standards for Submission to CDER and CBER available at:  
<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>