*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

**Draft Guidance on Podofilox**

**October 2022**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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**Active Ingredient:** Podofilox

**Dosage Form; Route:** Gel; topical

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

## I. Option 1: One in vitro bioequivalence study and other characterization tests

To demonstrate bioequivalence for podofilox topical gel, 0.5% 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
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).
    - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
d. Characterization of pH
e. Characterization of drying rate
f. Characterization of specific gravity
g. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard should have equivalent rate of podofilox 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: 0.5%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Podofilox in receptor solution
    Equivalence based on: Podofilox (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 study should be included among those for which the Q3 attributes are characterized.

## 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: 0.5%
    Subjects: Male or female with external anogenital warts
    Additional comments: Specific recommendations are provided below.

**Additional comments regarding the bioequivalence study with clinical endpoint:**

1. FDA recommends a bioequivalence study with a clinical endpoint comparing the podofilox topical gel, 0.5% test product versus the reference standard and placebo control, with each subject applying the gel to the warts with the applicator tip or finger twice daily for 3 consecutive days, then discontinuing for 4 consecutive days. This one-week cycle of treatment is to be repeated until there is no visible wart tissue or for a maximum of four cycles (i.e., study product applied only on study Days 1, 2, 3, 8, 9, 10, 15, 16, 17, 22, 23, and 24). Application on the surrounding normal tissue should be minimized. Care should be taken to allow the gel to dry before allowing the return of opposing skin surfaces to their normal positions. Treatment should be limited to 10 $cm^2$ or less of wart tissue and to no more than 0.5 g of the gel per day.

2. The recommended primary endpoint of the study is the proportion of subjects in the per protocol (PP) population with "treatment success" defined as "total disappearance of all warts within all treated areas" at Week 4 (end of study). The "treatment success" is evaluated weekly and after four days (+5 days) of "rest" period after the last day of the last cycle of treatment. Five office visits are recommended: baseline (Day 0), Week 1 (Day 7), Week 2 (Day 14), Week 3 (Day 21) and Week 4 (Day 28). For determination of bioequivalence between products, statistical analysis of the primary endpoint should be conducted at Week 4 for all subjects.

3. Inclusion Criteria:
    a. Healthy male or female aged ≥ 18 years with a clinical diagnosis of external anogenital warts (i.e., perianal warts and/or external genital warts), two or more distinct external genital warts, and wart area to be treated that is equal to or less than 10 $cm^2$. Histological confirmation should be obtained if there is any doubt of the diagnosis.
    b. Females of childbearing potential may be enrolled if they were practicing a method of birth control with a reliability of at least 90%.
    c. Any female subject with childbearing potential has a negative urine pregnancy test on first day of dosing (study Day 1).
    d. Negative HIV test within 4 weeks before the first day of dosing (study Day 1).

4. Exclusion Criteria:
    a. Pregnant or lactating or planning to become pregnant during the study period.
    b. Known hypersensitivity or intolerance to podofilox or any component of the formulation.
    c. History of previous unsuccessful treatment with any formulation of podofilox.
    d. Mucous membrane wart, bowenoid papulosis, squamous cell carcinoma, or active herpes lesion within any treatment area.
    e. Primary or secondary immunodeficiency.
    f. Local irritation in any treatment area that would interfere with treatment.
    g. Use within 4 weeks prior to baseline of any: 1) treatment for anogenital warts, 2) systemic corticosteroid, or 3) systemic immunosuppressive drug.

5. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
    a. Any other topical products applied to the treatment area(s).
    b. Systemic corticosteroid or immunosuppressive drugs.
    c. Antipruritics, including antihistamines, within 24 hours of study visits.

6. Instruct subjects to wash their hands thoroughly before and after each application of study product and to avoid contact with the eyes. If contact with the eyes occurs, subjects should immediately flush the eyes with copious quantities of water and seek medical advice. Inform subjects that the study product in flammable and to keep it away from open flames.

7. Provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Site identifier: study center
    d. Age
    e. Age units (years)
    f. Sex
    g. Race
    h. Name of Actual Treatment (exposure): test product, reference product, placebo
    i. First Dose of Assigned Treatment Date
    j. First Dose of Assigned Treatment Time
    k. Last Dose of Assigned Treatment Date
    l. Last Dose of Assigned Treatment Time
    m. Duration of Treatment (total number of days from first to last application, inclusive)
    n. Per Protocol (PP) population inclusion (yes/no)
    o. Reason for exclusion from PP population
    p. Intent to Treat (ITT) population inclusion (yes/no)
    q. Reason for exclusion from ITT population
    r. Safety population inclusion (yes/no)
    s. Reason for exclusion from safety population
    t. Final designation as treatment success at Week 4 (yes/no)
    u. Treatment compliance: number of missed doses per subject
    v. Week 4 visit compliance (yes/no)
    w. Concomitant medication (yes/no)
    x. Adverse event(s) reported (yes/no)

8. Provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis time point, using the following headers, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Name of Actual Treatment (exposure): test product, reference product, placebo control

d. Visit number
e. Visit date
f. Number of days since baseline visit
g. Evaluator: identity of evaluator
h. Total number of anogenital warts within treatment area(s)
i. Total number of external genital warts
j. Total number of perianal warts
k. Skin reaction scores for each sign and symptom evaluated (e.g., erythema, dryness, burning/stinging, erosion, edema, pain, itching, bleeding, etc.)
l. Treatment success (yes/no)
m. Concomitant medication reported during this visit (yes/no)
n. Adverse event reported during this visit (yes/no)
o. Laboratory testing during this visit (yes/no)
p. Designation of treatment success at this visit (yes/no)

9. 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.

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

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**Revision History:** Recommended June 2012; Revised August 2021, October 2022

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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.