*Contains Nonbinding Recommendations*

# Draft Guidance on Imiquimod

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active ingredient:** Imiquimod

**Form/Route:** Cream/Topical

**Recommended studies:** 1 study

Type of study: Bioequivalence (BE) with Clinical Endpoint Study
Design: Randomized, double blind, parallel, placebo-controlled, in vivo.
Strength: 2.5%
Subjects: Immunocompetent males and nonpregnant females with clinically typical, visible or palpable actinic keratoses (AK) on the face or balding scalp.
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

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

1. The Office of Generic Drugs (OGD) recommends a BE study with clinical endpoint in the treatment of actinic keratoses (AK). Subjects are to be randomized to receive the generic imiquimod topical cream, 2.5%, the reference listed drug (RLD), or placebo. A placebo control arm is especially important when studying a disease such as AK, in which spontaneous resolution may occur. The study drug is to be applied once daily for two 2-week treatment cycles separated by a 2-week no-treatment period to the entire designated treatment area (either the entire face or balding scalp) just before normal sleeping hours, left on the skin for approximately 8 hours, and then removed by washing the area with mild soap and water. Hand washing before and after cream application is recommended. The primary endpoint is to be evaluated at study week 14 (8 weeks after completion of treatment).

2. Inclusion Criteria (the sponsor may add additional criteria):
   Immunocompetent male or nonpregnant female at least 18 years of age with at least five (5) and no more than twenty (20) clinically typical, visible or palpable AK lesions, each at least 4 mm in diameter, in an area that exceeds 25-$cm^2$ on either the face (excluding ear) or balding scalp, but not both.

3. Exclusion Criteria (the sponsor may add additional criteria):

a. Presence of atopic dermatitis, basal cell carcinoma, eczema, psoriasis, rosacea, squamous cell carcinoma, or other possible confounding skin conditions on face or balding scalp.
b. Use within six months prior to randomization on the face or balding scalp of 1) chemical peel, 2) dermabrasion, 3) laser abrasion, 4) PUVA (psoralen plus ultraviolet A) therapy, or 5) UVB therapy.
c. Use within one month prior to randomization on the face or scalp of 1) cryodestruction or chemodestruction, 2) curettage, 3) photodynamic therapy, 4) surgical excision, 5) topical 5-fluorouracil, 6) topical corticosteroids 7) topical diclofenac, 8) topical imiquimod, 9) topical retinoids, or 10) other treatments for actinic keratosis.
d. Use within one month prior to randomization of 1) immunomodulators or immunosuppressive therapies, 2) interferon, 3) oral corticosteroids or 4) cytotoxic drugs.
e. Known allergies to imiquimod or any excipients in the test product or RLD.

4. Subjects should not apply moisturizers, sun screen, make-up, creams, lotions, powders or any topical product other than the assigned treatment to the treatment area. Subjects should not use any type of bandage or occlusive dressing on the treatment area or apply the cream to open skin wounds, infections or exfoliative dermatitis. Subjects should avoid exposure to sunlight, the use of tanning booths, sunlamps, or nonprescription UV light sources, or contact of the study drug with the eyes, lips, or nostrils.

5. The protocol should include a list of the prescription and over-the-counter drug products and treatments that are prohibited during the study, such as:
   a. Any therapy for actinic keratosis, such as prescription topical retinoids, topical diclofenac, topical salicylic acid, bichloroacetic acid, trichloroacetic acid, cryodestruction, chemodestruction, surgical excision, $CO_2$ laser vaporization, electrocautery, photodynamic therapy, or curettage.
   b. Immunomodulators or immunosuppressive therapies, interferon, oral corticosteroids, cytotoxic drugs, systemic corticosteroids, or topical steroids anywhere on the head.

6. The recommended primary endpoint of the study is the proportion of subjects in the per protocol (PP) population with treatment success (100% clearance of all AK lesions within the treatment area) at study week 14 (8 weeks after completion of treatment). All actinic keratoses (i.e., baseline actinic keratoses and any new actinic keratoses) within the treatment area are to be treated and included in the efficacy lesion count for each visit.

7. The protocol should clearly define the PP, intent-to-treat (ITT) and safety populations.
   a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who met all inclusion/exclusion criteria, were compliant with the assigned study treatment, and completed the evaluation at week 14 (8 weeks after completion of treatment) within the designated visit window (+/- 4 days) with no protocol violations that would affect the treatment evaluation. The protocol should provide a definition of compliant subjects (e.g., used at least 75% and no more than 125% of study drug doses) and specify how compliance will be verified (e.g., by the use of subject diaries).
   b. The usual ITT population includes all randomized subjects who applied at least one dose of assigned product, and returned for at least one post-baseline evaluation visit.
   c. The safety population includes all randomized subjects who received study product.

8. Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of AK during the study should be discontinued, included in the PP population analysis as treatment failures, and provided with effective treatment. Subjects who are discontinued prematurely from the study due to lack of treatment effect should be included in the PP

population as treatment failures (i.e., non-responders). Subjects discontinued prematurely for other reasons should be excluded from the PP population, but included in the ITT population, using Last Observation Carried Forward (LOCF).

9. 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 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.

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 product with regard to the expected and unexpected application site reactions.

11. 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.

12. 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.

13. The method of randomization should be described in the protocol. 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 for each subject.

14. A detailed description of the blinding procedure is to be provided in the protocol. If the appearance of the test and reference products is markedly different, adequate blinding of the study would be a challenge. As much as possible, subjects should be blinded to the identity of their treatment. At a minimum, the placebo control should appear identical to the test product, and all study drugs should be provided in identical packaging.

15. Please 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 (GLP) and Good Clinical Practices (GCP). 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.

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

17. To establish bioequivalence, the 90% confidence interval of the difference in the proportion of subjects with treatment success between the test product and RLD treatment groups at week 14 (8

weeks after completion of treatment) must be within [-0.20, +0.20] for a dichotomous variable (success/failure), using the PP population.

18. As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to placebo control ($p<0.05$) with regard to the proportion of subjects with treatment success (100% clearance of all AK lesions within the treatment area) at week 14 (8 weeks after completion of treatment) using the ITT population and LOCF.

19. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (success/failure):

    Equivalence Analysis

    Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment must be contained within [-0.20, +0.20] in order to establish equivalence.

    The compound hypothesis to be tested is:

    $H_0$: $p_T - p_R < -0.20$ or $p_T - p_R > 0.20$

    versus

    $H_A$: $-0.20 \leq p_T - p_R \leq 0.20$

    where $p_T$ = success/cure rate of test treatment and $p_R$ = success/cure rate of reference treatment.

    Let

    $n_T$ = sample size of test treatment group

    c$n_T$ = number of success/cured patients in test treatment group

    $n_R$ = sample size of reference treatment group

    c$n_R$ = number of success/cured patients in reference treatment group

    $\hat{p}_T = \text{c}n_T / n_T$, $\hat{p}_R = \text{c}n_R / n_R$,

    and se = $(\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{½}$.

    The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

    $L = (\hat{p}_T - \hat{p}_R) - 1.645\ \text{se} - (1/n_T + 1/n_R)/2$

$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$

We reject $H_0$ if $L \geq -0.20$ and $U \leq 0.20$

Rejection of the null hypothesis $H_0$ supports the conclusion of equivalence of the two products.

20. Study data should be submitted to the OGD in electronic format.
    a. A list of file names, with a simple description of the content of each file, should be included. Such a list should include an explanation of the variables included in each of the data sets.
    b. Please provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
    c. SAS transport files, covering all variables collected in the Case Report Forms (CRFs) per subject, should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
    d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
    e. Please provide a separate dataset for variables such as demographics, lesion counts, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.
    f. The methods used to derive the variables should be included and explained.

21. Please provide a summary dataset containing a separate line listing for each subject (if data exist) 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, RLD, placebo control
    i. Location of Treatment Area
    j. Duration of Treatment (total exposure in days)
    k. Completed the study (yes/no)
    l. Reason for premature discontinuation of subject
    m. Subject required additional treatment for AK due to unsatisfactory treatment response (yes/no)
    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. Size of treatment area at baseline ($cm^2$)
    u. Size of all AK lesions within treatment area at baseline are at least 4 mm in diameter (yes/no)
    v. Total number of AK lesions in the treatment area at baseline
    w. Total number of AK lesions in the treatment area at week 6
    x. Total number of AK lesions in the treatment area at week 14

y. Total number of new AK lesions in the treatment area at week 6
z. Total number of new AK lesions in the treatment area at week 14.
aa. Final designation as treatment success (100% clearance of all AK lesions within the treatment area) or failure
bb. Treatment compliance: number of missed doses per subject
cc. Concomitant medication (yes/no)
dd. Adverse event(s) reported (yes/no)

Please refer to Table 1 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

**Table 1: Example of a summary dataset containing one line listing for each subject**

| STUDYID | SUBJID | SITEID | AGE | AGEU | SEX | RACE | EXTRT | EXLOC | EXDUR | completd | disc_rs | add_trt | pp | pp_rs | itt | itt_rs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 101 | 1 | 01 | 54 | YEARS | F | 1 | A | F | 28 | Y | | N | Y | | Y | |
| 101 | 2 | 01 | 58 | YEARS | F | 1 | B | F | 28 | Y | | N | Y | | Y | |

| safety | safetyrs | sizetrta | aksizeb | aknum_b | aknum6 | aknum14 | naknum6 | naknum14 | success | complian | CM | AE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Y | | 50 | Y | 4 | 2 | 0 | 0 | 0 | Y | 0 | Y | Y |
| Y | | 40 | Y | 8 | 4 | 2 | 1 | 0 | N | 0 | N | N |

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

| | |
|---|---|
| STUDYID: | Study Identifier |
| SUBJID: | Subject Identifier for the Study |
| SITEID: | Study Site Identifier |
| AGE: | Age |
| AGEU: | Age units (years) |
| SEX: | Sex, e.g., M=Male, F=Female, U=Unknown |
| RACE: | Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders |
| EXTRT: | Name of Actual Treatment (exposure), e.g., A=test product, B= RLD, C=placebo control |
| EXLOC: | Location of Treatment Area, e.g. F=face, BS=balding scalp |
| EXDUR: | Duration of Treatment (total exposure in days) |
| completd: | Subject completed the study, e.g., Y=Yes, N=No |
| disc_rs: | Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment |

| | |
|---|---|
| | unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event |
| add_trt: | Subject required additional treatment for AK due to unsatisfactory treatment response, e.g., Y=Yes, N=No |
| pp: | Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No |
| pp_rs: | Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc. |
| itt: | Intent to Treat (ITT) population inclusion, e.g., Y=Yes, N=No |
| itt_rs: | Reason for exclusion from ITT population, e.g., A=never treated, etc. |
| safety: | Safety population inclusion, e.g., Y=Yes, N=No |
| safetyrs: | Reason for exclusion from Safety population, e.g., A=never treated, etc. |
| sizetrta: | Size of treatment area at baseline ($cm^2$) |
| aksizeb: | Size of all AK lesions within treatment area at baseline are at least 4 mm in diameter, e.g., Y=Yes, N=No |
| aknum_b: | Total number of AK lesions in the treatment area at baseline |
| aknum6: | Total number of AK lesions in the treatment area at week 6 |
| aknum14: | Total number of AK lesions in the treatment area at week 14 |
| naknum6: | Total number of new AK lesions in the treatment area at week 6 |
| naknum14: | Total number of new AK lesions in the treatment area at week 14 |
| success: | Final designation, e.g., Y=Yes (100% clearance of all AK lesions within the treatment area), N=No (failure) |
| complian: | Treatment compliance, e.g., number of missed doses per subject |
| CM: | Concomitant medication, e.g., Y=Yes, N=No |
| AE: | Adverse event(s) reported, e.g., Y=Yes, N=No |

22. Please provide a dataset containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Name of Actual Treatment (exposure): test product, RLD, placebo control
    d. Location of Dose Administration: application site
    e. Visit number
    f. Visit date
    g. Number of days since baseline visit
    h. Evaluator: identity of evaluator
    i. Total number of AK lesions
    j. Total number of new AK lesions within treatment area
    k. Skin reaction scores for each sign and symptom evaluated (e.g., erythema, dryness, burning/stinging, erosion, edema, pain, itching, etc.)
    l. Concomitant medication reported during this visit (yes/no)
    m. Adverse event reported during this visit (yes/no)
    n. Laboratory testing during this visit (yes/no)

    Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

**Table 2: Example of dataset containing one line listing for each visit per subject**

| STUDYID | SUBJID | EXTRT | EXLOC | VISITNUM | SVSTDTC | ELTMBS | EVAL | aknum | naknum | erythema | dryness | burning | erosion | edema | pain | itching | CMrpt | AErpt | LBtest |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 101 | 1 | A | F | 1 | 2004-07-01 | 1 | JB | 7 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | Y | Y | N |

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

| | |
|---|---|
| STUDYID: | Study Identifier |
| SUBJID: | Subject Identifier for the Study |
| EXTRT: | Name of Actual Treatment (exposure), e.g. A=test product, B=RLD, C= placebo control |
| EXLOC: | Location of Treatment Area: specific anatomical site of application, e.g., e.g. F=face, BS=balding scalp |
| VISITNUM: | Visit Sequence Number |
| SVSTDTC: | Visit date: (SVSTDTC=Subject Visit Start Date Time-Character) |
| ELTMBL: | Elapsed Time since Baseline (days) |
| EVAL: | Evaluator: identity of the evaluator |
| aknum: | Total number of AK lesions within treatment area |
| naknum: | Total number of new AK lesions within treatment area |
| erythema: | Skin reaction erythema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense) |
| dryness: | Skin reaction dryness score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense) |
| burning: | Skin reaction burning score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3-severe (marked, intense) |
| erosion: | Skin reaction erosion score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense) |
| edema: | Skin reaction edema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense) |
| pain: | Skin reaction pain score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense) |
| itching: | Skin reaction itching score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense) |
| CMrpt: | Concomitant Medication reported during this visit, e.g., Y=Yes, N=No |
| AErpt: | Adverse Event reported during this visit, e.g., Y=Yes, N=No |
| LBtest: | Laboratory Testing performed during this visit, e.g., Y=Yes, N=No |

23. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of imiquimod.