

Draft Guidance on Mupirocin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Mupirocin

Form/Route: Ointment/Topical

Recommended studies: 1 study

Type of study: Clinical Endpoint Bioequivalence (BE) Study

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

Strength: 2%

Subjects: Healthy males and nonpregnant females with impetigo.

Additional comments: Specific recommendations are provided below.

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 clinical endpoint BE study:

1. The Office of Generic Drugs (OGD) recommends conducting a clinical endpoint bioequivalence study in the treatment of impetigo. Subjects are to be randomized to receive the generic mupirocin topical ointment, 2%, the reference listed drug (RLD) or placebo vehicle applied to the affected area three times daily for 7 days. The primary endpoint is the proportion of subjects with clinical cure at 7 days after the end of treatment (study Day 14).
2. A placebo 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. Healthy male or nonpregnant female aged ≥ 18 months with a clinical diagnosis of impetigo.
 - b. Positive baseline culture for *Staphylococcus aureus* and/or *Streptococcus pyogenes* from a sample taken from the target site.
 - c. Skin Infection Rating Scale (SIRS) total score for the target lesion of at least 4 with at least 3 of the five signs/symptom categories present at baseline (per Table 1).

Table 1. Sample Skin Infection Rating Scale

Sign/symptom	Score	Definition
Blistering	0=Absent	No evidence of blisters
	1=Mild	Few raised vesicles present on close evaluation
	2=Moderate	Fluid filled vesicles are obvious and are bothersome to the patient
	3=Severe	Extensive area covered with many vesicles which may include large bullous vesicles
Exudate/pus	0=Absent	No evidence of exudate or pus
	1=Mild	Small amounts of fluid/pus coming from the lesions
	2=Moderate	Exudate/pus infected area is moderate
	3=Severe	Extensive areas infected and there is draining exudate
Crusting	0=Absent	No evidence of crusting
	1=Mild	A few areas have some evidence of crusting lesions
	2=Moderate	Crusting is present throughout the infected area
	3=Severe	Thick crusting appears over the entire impetiginous area
Erythema/ inflammation	0=Absent	Skin tone and color are normal; no signs of erythema or inflammation
	1=Mild	Skin is pink with minimal signs of inflammation
	2=Moderate	Skin is red with definite signs of inflammation
	3=Severe	Skin is red and severe inflammation is present
Itching/pain	0=Absent	No signs of itching or indication of pain
	1=Mild	Some evidence of scratching or rubbing the area is evident and patient reports minor discomfort
	2=Moderate	Evidence of scratching and patient reports bothersome, painful lesions
	3=Severe	Evidence of extensive scratching and patient reports pain that interferes with daily activities or sleep.

4. Exclusion Criteria (the sponsor may add additional criteria)
 - a. Pregnant, breast feeding, or planning a pregnancy.
 - b. Any dermatological disorder that may interfere with the evaluation of the subject's impetigo, including presence of *staphylococcal* and/or *streptococcal* ecthyma, cellulitis, furunculosis, abscess, acute dermatitis, contact dermatitis, impetiginized eczema, or impetigo secondary to any human or animal bite.
 - c. Use of systemic antibiotic or systemic corticosteroid within 1 week prior to baseline.
 - d. Use of topical corticosteroid, topical antibiotic, or topical antifungal within 48 hours prior to baseline.
 - e. Subject whose disease is so widespread or severe that, in the opinion of the investigator, systemic treatment is needed.
 - f. Signs and symptoms of a concurrent infection requiring additional antibiotic therapy.
 - g. Primary or secondary immunodeficiency.
 - h. Diabetes.
 - i. Presence of any other medical condition that might adversely impact the safety of the study participants or confound the study results.
 - j. History of hypersensitivity or allergy to mupirocin and/or any of the study medication ingredients.

5. The study protocol should include early observation of the patients (as early as day 2 or 3 of therapy) and provision for switching to an approved treatment (e.g., Bactroban or oral therapy) if the patient is not improving. These patients should be discontinued and analyzed as treatment failures.
6. 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 (including antibacterial soaps) applied on or near the affected area of impetigo
 - b. Systemic (e.g., oral or injectable) antibiotics.
 - c. Systemic corticosteroids, systemic anti-inflammatory agents or immunosuppressive drugs.
7. The recommended primary endpoint is the proportion of subjects in each treatment group with clinical cure (defined as no additional antibiotic therapy required to treat impetigo and a Skin Infection Rating Scale (SIRS) score of 0 each for blistering, exudate/pus and crusting, and a SIRS score of ≤ 1 each for erythema/inflammation and itching/pain on a 4-point scale provided in Comment #3 above) at the Day 14 follow-up visit (7 days after the end of treatment).
8. The proportion of subjects with clinical cure at the end of treatment visit, bacteriological cure (defined as elimination of *Staphylococcus aureus* and *Streptococcus pyogenes* or response was such that no culture material was available and therefore evidence of pathogen eradication) at the end of treatment visit, and bacteriological cure at the follow-up visit should be treated as secondary endpoints for supportive evidence.
9. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations in the protocol.
10. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who met all inclusion/exclusion criteria, had a positive baseline bacteriological culture, applied a prespecified proportion of the scheduled applications (e.g., 75% to 125%) of the assigned product for the specified duration of the study, did not miss the scheduled applications for more than 3 consecutive days, and completed the evaluation within the designated visit window (\pm 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.
11. The mITT population includes all randomized subjects who met all inclusion/exclusion criteria, including a positive baseline bacteriological culture for *Staphylococcus aureus* and/or *Streptococcus pyogenes*, applied at least one dose of assigned product and returned for at least one post-baseline evaluation visit.
12. The safety population includes all randomized subjects who received study product.
13. Subjects who are discontinued early from the study due to lack of treatment effect after completing 3 days of treatment should be included in the PP population as treatment failures. Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of impetigo during the study should be discontinued, included in the PP population analysis, 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 Last Observation Carried Forward (LOCF).

14. Subjects with a negative culture at baseline should be discontinued from the study and excluded from the mITT and PP populations, but included in the ITT population for safety analysis.
15. 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.
16. 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.
17. 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.
18. 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 of each subject.
19. 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.
20. 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.
21. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
22. To establish bioequivalence, the 90% confidence interval of the difference between products for the primary endpoint (success proportion) must be contained within [-0.20, +0.20] for dichotomous variables (cure versus failure), using the PP study population.
23. As a parameter for determining adequate study sensitivity, the test product and RLD should be statistically superior to placebo ($p < 0.05$, two-sided) for the primary endpoint (cure versus failure) using the mITT study population and LOCF.

24. 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:

$$H_0: p_T - p_R < -0.20 \text{ or } p_T - p_R > 0.20$$

versus

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

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

Let

n_T = sample size of test treatment group

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

n_R = sample size of reference treatment group

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

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

$$\text{and se} = \left(\hat{p}_T (1 - \hat{p}_T) / n_T + \hat{p}_R (1 - \hat{p}_R) / n_R \right)^{1/2}.$$

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

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

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

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.

25. 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. All 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, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.
26. 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 impetigo due to unsatisfactory treatment response (yes/no)
 - n. Per Protocol (PP) population inclusion (yes/no)
 - o. Reason for exclusion from PP population
 - p. Modified Intent to Treat (mITT) population inclusion (yes/no)
 - q. Reason for exclusion from mITT population
 - r. Safety population inclusion (yes/no)
 - s. Reason for exclusion from Safety population
 - t. Clinical outcome (cure/failure)
 - u. Treatment compliance : number of missed doses per subject
 - v. Concomitant medication (yes/no)
 - w. 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	mitt	mitt_rs
101	1	01	21	YEARS	F	1	A	Face	14	Y		N	Y		Y	
101	2	01	30	YEARS	F	1	B	Face	14	Y		N	Y		Y	

safety	safe_rs	clinout	complan	CM	AE
Y		C	0	Y	Y
Y		F	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, etc.
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 impetigo 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.
mitt: Modified Intent to Treat (mITT) population inclusion, e.g., Y=Yes, N=No
mitt_rs: Reason for exclusion from mITT population, e.g., A=never treated, etc.
safety: Safety population inclusion, e.g., Y=Yes, N=No
safe_rs: Reason for exclusion from Safety population, e.g., A=never treated, etc.
clinout: Clinical outcome, e.g., C=cure; F=Failure
complan: 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

27. 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. Lesion count
 - j. Individual blistering SIRS score
 - k. Individual exudate/pus SIRS score
 - l. Individual crusting SIRS score
 - m. Individual erythema/inflammation SIRS score
 - n. Individual itching/pain SIRS score
 - o. Total SIRS score
 - p. Culture results (if applicable)
 - q. Bacterial cure (yes/no; if applicable)
 - r. Clinical cure (yes/no; if applicable)
 - s. Concomitant medication reported during this visit (yes/no)
 - t. Adverse event reported during this visit (yes/no)
 - u. 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	les_ct	blis_sco	exud_sco	crus_sco	ery_sco
101	1	A	F	1	2004-07-01	1			1	2	0	1

itch_sco	tota_sco	culture	bacture	clincure	CMrpt	AErpt	LBtest
1	4				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., F=face etc.
 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
 les_ct: Lesion count
 blis_sco: Individual blistering SIRS score, e.g., 0, 1, 2, or 3
 exud_sco: Individual exudate/pus SIRS score, e.g., 0, 1, 2, or 3
 crus_sco: Individual crusting SIRS score, e.g., 0, 1, 2, or 3
 ery_sco: Individual erythema/inflammation SIRS score, e.g., 0, 1, 2, or 3
 itch_sco: Individual itching/pain SIRS score, e.g., 0, 1, 2, or 3
 tota_sco: Total SIRS score, e.g., 0 to 15
 culture: Culture results (if applicable)
 bactcure: Bacterial cure (if applicable), e.g., Y=Yes, N=No
 clincure: Clinical cure (if applicable), e.g., Y=Yes, N=No
 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

28. 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 mupirocin.