

## Draft Guidance on Mupirocin Calcium

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

**Form/Route:** Cream/Topical

**Recommended studies:** 1 study

Type of study: Clinical Endpoint Bioequivalence (BE) Study

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

Strength: EQ 2% Base

Subjects: Healthy males and nonpregnant females with secondarily infected traumatic skin lesion.

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 clinical endpoint BE study:**

1. The Office of Generic Drugs (OGD) recommends conducting a clinical endpoint bioequivalence study in the treatment of secondarily infected traumatic skin lesions. Subjects are to be randomized to receive the generic mupirocin calcium topical cream, 2%, the reference listed drug (RLD) or placebo vehicle applied to the affected area three times daily for 10 days. The primary endpoint is the proportion of subjects with clinical cure at 7 days after the end of treatment (study Day 17).
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  $\geq 18$  months with a secondarily infected traumatic skin lesion(s) such as a laceration, sutured wound or abrasion. The laceration or sutured wound should not exceed 10 cm in length with surrounding erythema not more than 2 cm from the edge of the lesion. An abrasion should not exceed 100 cm<sup>2</sup> in total area with surrounding erythema not more than 2 cm from the edge of the abrasion.
  - b. Positive baseline culture for *Staphylococcus aureus* and/or *Streptococcus pyogenes* from a sample taken from the secondarily infected traumatic skin lesion.

- c. Positive Gram stain or Wright stain for confirmation of white blood cells in the pus/exudate from the secondarily infected traumatic skin lesion.
- d. Skin Infection Rating Scale (SIRS) total score for the secondarily infected traumatic skin lesion of at least 8 at baseline (per Table 1).

**Table 1. Sample Skin Infection Rating Scale**

<b>Sign/symptom</b>	<b>Score</b>	<b>Definition</b>
Exudate/pus	0=Absent 1=Mild 2=Moderate 3=Severe	No evidence of exudate or pus Small amount of fluid/pus coming from the skin lesion(s) Exudate/pus infected area is moderate Extensive area of skin lesion is infected and there is draining exudate
Crusting	0=Absent 1= Mild 2=Moderate 3=Severe	No evidence of crusting A few areas have some evidence of crusting lesions Crusting is present throughout the infected area Thick crusting appears over the entire infected area
Erythema/ inflammation	0=Absent 1=Mild 2=Moderate 3=Severe	Skin tone and color are normal; no signs of erythema or inflammation Skin is pink with minimal signs of inflammation Skin is red with definite signs of inflammation Skin is red and severe inflammation is present
Tissue edema	0=Absent 1=Mild 2=Moderate 3=Severe	No evidence of tissue edema Tissue has mild edema Tissue has moderate edema Tissue has severe edema
Tissue warmth	0=Absent 1=Mild 2=Moderate 3=Severe	No evidence of tissue warmth Tissue has mild warmth Tissue has moderate warmth Tissue has severe warmth
Itching	0=Absent 1=Mild 2=Moderate 3=Severe	No itching Some evidence of scratching or rubbing the area is evident and subject reports minor discomfort Evidence of scratching and subject reports bothersome itching Evidence of extensive scratching and subject reports itching interferes with daily activities or sleep.
Pain	0=Absent 1=Mild 2=Moderate 3=Severe	No pain Slight pain; not bothersome; no analgesics being taken Definite pain; subject reports bothersome pain, without loss of sleep, mild analgesic may be taken Intense pain that that interferes with daily activities or sleep; medication required to control pain

- 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 secondarily infected traumatic skin lesion(s), e.g., acute or chronic dermatitis involving affected area.

- c. Bacterial skin infection which, due to depth of severity, could not be appropriately treated by a topical antibiotic (e.g., severe cellulitis, abscess, ulcers, furunculosis).
  - d. Secondarily infected animal/human or insect bite or puncture wound.
  - e. Systemic sign and symptoms of infection (i.e., fever defined as an oral temperature greater than 101°F or 38.3°C).
  - f. Require surgical intervention for treatment of the infection prior to enrollment in the study.
  - g. Use within 1 week prior to baseline of systemic antibiotic or systemic corticosteroid.
  - h. Use within 48 hours prior to baseline of topical corticosteroid, topical antibiotic, or antifungal.
  - i. Primary or secondary immunodeficiency.
  - j. Diabetes.
  - k. Presence of any other medical condition that might adversely impact the safety of the study participants or confound the study results.
  - l. 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 subjects (i.e., on study Day 3) and provision for switching to an approved treatment (e.g., Bactroban or oral therapy) if the subject is not improving. These subjects 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.
    - b. Systemic (e.g., oral or injectable) antibiotics.
    - c. Systemic corticosteroids or immunosuppressive drugs.
  7. The recommended primary endpoint is the proportion of subjects in each treatment group with clinical cure (defined as a Skin Infection Rating Scale (SIRS) score of 0 for all signs and symptoms on a 4-point scale provided in Comment #3 above) at the Day 17 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 (+/- 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, 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 their secondarily infected traumatic skin lesion 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. 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.

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 type of skin lesion, size of treatment area and site of treatment area should be compared and tabulated for each treatment group.
25. 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 subjects in test treatment group

$n_R$  = sample size of reference treatment group

$c n_R$  = number of cured subjects 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:

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

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

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.

26. 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, lesion type, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.
  
27. 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. Type of secondarily infected traumatic skin lesion (e.g., laceration, abrasion, suture)
  - j. Size of Treatment Area (e.g., cm<sup>2</sup>)
  - k. Location of Treatment Area
  - l. Duration of Treatment (total exposure in days)
  - m. Completed the study (yes/no)
  - n. Reason for premature discontinuation of subject
  - o. Subject required additional treatment for their secondarily infected traumatic skin lesion due to unsatisfactory treatment response (yes/no)
  - p. Per Protocol (PP) population inclusion (yes/no)
  - q. Reason for exclusion from PP population
  - r. Modified Intent to Treat (mITT) population inclusion (yes/no)
  - s. Reason for exclusion from mITT population

- t. Safety population inclusion (yes/no)
- u. Reason for exclusion from Safety population
- v. Clinical outcome (cure/failure)
- w. Treatment compliance: number of missed doses per subject
- x. Concomitant medication (yes/no)
- y. 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	type_w	size	EXLOC	EXDUR	completd	disc_rs	add_trt	pp	pp_rs
101	1	01	21	YEARS	F	1	A	A	10	Face	14	Y		N	Y	
101	2	01	30	YEARS	F	1	B			Face	14	Y		N	Y	

mitt	mitt_rs	safety	safe_rs	clinout	complan	CM	AE
Y		Y		C	0	Y	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
- type: Type of secondarily infected traumatic skin lesion, e.g., L=laceration, A=abrasion, S=suture
- size: Size of Treatment Area (e.g., cm<sup>2</sup>)
- 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 infection 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

28. 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. Individual exudate/pus SIRS score
- j. Individual crusting SIRS score
- k. Individual erythema/inflammation SIRS score
- l. Individual tissue edema SIRS score
- m. Individual tissue warmth SIRS score
- n. Individual itching SIRS score
- o. Individual pain SIRS score
- p. Total SIRS score
- q. WBC identified on Gram stain or Wright stain (yes/no)
- r. Culture results
- s. Bacterial cure (yes/no)
- t. Clinical cure (yes/no)
- u. Concomitant medication reported during this visit (yes/no)
- v. Adverse event reported during this visit (yes/no)
- w. 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	exud_sco	crus_sco	ery_sco	edem_sco	warm_sco
101	1	A	F	1	2004-07-01	1		2	1	2	2	1

itch_sco	pain_sco	tota_sco	wbc	culture	bactcure	clincure	CMrpt	AErpt	LBtest
1	1	10	Y				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)
- ELTMBS: Elapsed Time since Baseline (days)
- EVAL: Evaluator: identity of the evaluator
- 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
- edem\_sco: Individual tissue edema SIRS score, e.g., 0, 1, 2, or 3
- warm\_sco: Individual tissue warmth SIRS score, e.g., 0, 1, 2, or 3
- itch\_sco: Individual itching SIRS score, e.g., 0, 1, 2, or 3
- pain\_sco: Individual pain SIRS score, e.g., 0, 1, 2, or 3
- tota\_sco: Total SIRS score, e.g., 0 to 15
- wbc: WBC, e.g., Y=Yes, N=No
- culture: Culture results
- bactcure: Bacterial cure, e.g., Y=Yes, N=No
- clincure: Clinical cure, 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

29. 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 calcium.