

Draft Guidance on Metronidazole

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Gel/Vaginal

Recommended studies: 2 studies

1. Type of study: Bioequivalence (BE) Study with Pharmacokinetic (PK) Endpoints
Design: Single-dose, two-way crossover, in vivo
Strength: 0.75% [dose: one applicator full (5 grams containing approximately 37.5 mg of metronidazole in the to-be-marketed or currently marketed applicator provided with product), administered intravaginally]
Subjects: Healthy females, general population
Additional comments: Subjects should not be pregnant or lactating, and if applicable, should use appropriate contraception during the study. No sexual intercourse or use of spermicides, tampons, douches, diaphragms, or condoms or insertion into the vagina of any drug or non-drug product are permitted within 48 hours of dosing. Exclude subjects with any vulvar or vaginal condition that may affect drug absorption (e.g., vulvovaginitis). Measure applicator weight after filling and after dosing to calculate weight of dose. Subjects should remain supine for at least 4 hours after dosing.

2. Type of study: BE Study with Clinical Endpoint
Design: Randomized, double blind, parallel, placebo-controlled in vivo
Strength: 0.75%
Subjects: Healthy females with bacterial vaginosis
Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Metronidazole in plasma

Bioequivalence based on (90% CI): Metronidazole in plasma (PK Study #1); Clinical Endpoint (Clinical Endpoint Study #2)

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times: Not Applicable

Additional comments regarding the BE study with clinical endpoint:

1. The Office of Generic Drugs (OGD) recommends a bioequivalence study with a clinical endpoint in the treatment of non-pregnant female subjects with a confirmed clinical diagnosis of bacterial vaginosis (BV). Subjects are to be randomized to receive the generic metronidazole vaginal gel, 0.75%, the reference listed drug (RLD), or placebo as one applicator full (approximately 5 grams

containing approximately 37.5 mg of metronidazole in the to-be-marketed or currently marketed applicator provided with the product) administered intravaginally once daily at bedtime for 5 days. The primary endpoint is therapeutic cure rate, which includes both clinical cure (resolution of clinical signs and symptoms) AND bacteriological cure (Nugent Score <4), evaluated at the Test of Cure visit (study Day 22-30).

2. Inclusion Criteria (the sponsor may add additional criteria):
 - a. Healthy nonpregnant female aged ≥ 18 years.
 - b. Diagnosis of bacterial vaginosis, defined as the presence of all of the following:
 - i. Clinical diagnosis of bacterial vaginosis (e.g., thin, homogenous vaginal discharge associated with minimal or absent pruritus inflammation AND
 - ii. Saline wet mount of vaginal discharge demonstrating the proportion of clue cell to be $\geq 20\%$ of the total epithelial cells AND
 - iii. Vaginal pH > 4.5 , using pH paper that measures from 4.0-6.0 AND
 - iv. Positive "whiff test" after addition of a drop of 10% KOH to vaginal discharge) AND
 - v. Gram stain Nugent score ≥ 4 on first day of dosing (study Day 1)
 - c. Any subject with childbearing potential has a negative urine pregnancy test on first day of dosing (study Day 1).
 - d. Willing to refrain from using any intra-vaginal product (e.g., spermicide, tampon, douche, diaphragm, or condom or insertion into the vagina of any drug or non-drug product during treatment), other than study product, on study Days 1-5, for 48 hours prior to the first dose of study product, and for 48 hours prior to Test of Cure visit.
 - e. Willing to refrain from sexual intercourse on study Days 1-5 (i.e., during treatment).
 - f. Willing to refrain from alcohol ingestion on study Days 1-6 (i.e., during treatment and on first post-treatment day).
3. Exclusion Criteria (the sponsor may add additional criteria):
 - a. Pregnant or lactating or planning to become pregnant during the study period.
 - b. Menstruating when diagnosis of BV is determined at Baseline visit.
 - c. Primary or secondary immunodeficiency.
 - d. Severe liver disease.
 - e. Central nervous system disease.
 - f. Evidence of any vulvovaginitis other than bacterial vaginosis. (e.g., candidiasis, *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Herpes simplex*, or human papilloma virus)
 - g. Subject with another vaginal or vulvar condition, which would confound the interpretation of clinical response.
 - h. Subject will be under treatment during the study period for cervical intraepithelial neoplasia (CIN) or cervical carcinoma.
 - i. History of hypersensitivity or allergy to metronidazole, parabens, other nitroimidazole derivatives or other ingredients of the formulation.
 - j. Use within 2 weeks prior to baseline of 1) disulfiram, 2) lithium, 3) topical or systemic antibiotics or 4) topical or systemic antifungal.
 - k. Use of spermicides, tampons, douches, diaphragms, condoms or other intra-vaginal product within 48 hours prior to dosing on study Day 1.
 - l. Current use of anticoagulation therapy or cimetidine.
4. At the Baseline visit, a medical history should be obtained and should include information on contraception, past episodes of bacterial vaginosis, and sexual history.

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 anticoagulation therapy.
 - b. Systemic corticosteroid or immunosuppressive drugs.
 - c. Systemic or topical antibiotics, other than study product.
 - d. Cimetidine.
 - e. Lithium.
 - f. Any product inserted into the vagina during treatment (e.g., on study Days 1-5) and for 48 hours prior to Test of Cure visit.
 - g. Subjects should be instructed not to engage in vaginal intercourse during treatment (e.g., on study Days 1-5). Subjects should be cautioned about drinking alcohol during treatment
6. The primary endpoint of the study is the therapeutic cure rate, defined as both a clinical cure (resolution of clinical signs and symptoms, e.g., normal physiological vaginal discharge, whiff test is negative for any amine “fishy” odor, saline wet mount is negative for clue cells, and vaginal pH is < 4.7, using pH paper that measures pH from 4.0-6.0) AND a bacteriological cure (Nugent score <4), evaluated at the Test of Cure visit (study Day 22-30). Subjects who used any bacterial vaginosis therapy, other than study product, during the study or had a Nugent score >3 at the Test of Cure visit should be considered therapeutic failures.
7. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
 - a. The PP population includes all randomized subjects who met all inclusion/exclusion criteria, were compliant with the assigned study treatment, returned to the study site for the primary endpoint visit within the specified window (on study Days 22-30) OR discontinued from the study as a treatment failure, and did not have any protocol violations. The PP population should be used for the bioequivalence evaluation of test vs. reference. The protocol should provide a definition of compliant subjects (e.g., used at least 75% and no more than 125% of study treatment doses) and specify how compliance will be verified (e.g., by the use of subject diaries).
 - b. The mITT population includes all randomized subjects who met all inclusion/exclusion criteria, received study treatment, and returned for at least one post-baseline visit. The mITT population should be used to compare both test and reference products to placebo.
 - c. The safety population includes all randomized subjects who received study treatment.
8. Subjects who discontinued early from the study due to lack of treatment effect after completing at least three days of treatment should be included in the mITT and PP population as treatment failures. Subjects discontinued early for other reasons, as well as those subjects who had a non-evaluable clinical outcome at the Test of Cure visit, should be excluded from the PP population, but included in the mITT 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, 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.
10. 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.

11. 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.
12. 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.
13. 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.
14. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
15. To establish bioequivalence, the 90% confidence interval for the primary endpoint (test-reference difference in cure rate) must be within [-0.20, +0.20] for dichotomous variables, using the PP population.
16. As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to placebo ($p < 0.05$, two-sided) for the primary endpoint, using the mITT study population and LOCF.
17. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (success/failure):

Equivalence Analysis for a Dichotomous Variable

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 should 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

cn_T = number of cured subjects in test treatment group

n_R = sample size of reference treatment group

cn_R = number of cured subjects in reference treatment group

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

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

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.

18. 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.
 - 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 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, baseline admission criteria, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.
19. 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
- i. Duration of Treatment (total exposure in days)
- j. Per Protocol (PP) population inclusion (yes/no)
- k. Reason for exclusion from PP population
- l. Modified Intent to Treat (mITT) population inclusion (yes/no)
- m. Reason for exclusion from mITT population
- n. Safety population inclusion (yes/no)
- o. Reason for exclusion from safety population
- p. Clinical cure(yes/no)
- q. Bacteriological cure (yes/no)
- r. Treatment success (therapeutic cure) (yes/no)
- s. Treatment compliance: number of missed doses per subject
- t. Concomitant medication (yes/no)
- u. 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 | EXDUR | pp | pp_rs | mitt | mitt_rs | safety | safe_rs | cure_cl | cure_ba | success | complan | CM | AE |
|---------|--------|--------|-----|-------|-----|------|-------|-------|----|-------|------|---------|--------|---------|---------|---------|---------|---------|----|----|
| 101 | 1 | 01 | 22 | YEARS | F | 1 | A | 28 | Y | | Y | | Y | | Y | Y | Y | 0 | Y | Y |
| 101 | 2 | 01 | 30 | YEARS | F | 1 | B | 28 | Y | | Y | | Y | | Y | N | 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., F=Female
- 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
- EXDUR: Duration of Treatment (total exposure in days)
- 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, B=negative baseline culture, 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.
- cure_cl: Clinical cure, e.g., Y=Yes, N=No
- cure_ba: Bacteriological cure, e.g., Y=Yes, N=No
- success: Treatment success (therapeutic cure), e.g., Y=Yes, N=No
- 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

20. 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. Visit number
 - e. Visit date
 - f. Number of days since baseline visit
 - g. Evaluator: identity of evaluator
 - h. Abnormal vaginal discharge (yes/no)
 - i. Clinical cure(yes/no)
 - j. Bacteriological cure (yes/no)
 - k. Treatment success (therapeutic cure) (yes/no)
 - l. Concomitant medication reported during this visit (yes/no)
 - m. Use of any vaginal products other than study product (yes/no)
 - n. Compliant with protocol (yes/no)
 - o. Adverse event reported during this visit (yes/no)
 - p. Laboratory testing during this visit (yes/no)
 - q. Clue cells on wet mount ($\geq 20\%$, $< 20\%$, or none)
 - r. Vaginal pH
 - s. KOH “whiff test” (positive/negative)
 - t. Nugent score (0, 1, 2, 3, or 4)
 - u. Chlamydia trachomatis (positive/negative)
 - v. Neisseria gonorrhoeae test, (positive/negative)
 - w. Urine pregnancy test ((positive/negative)

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 | VISITNUM | SVSTDTC | ELTMBS | EVAL | abn_vagd | cure_cl | cure_ba | success | CMrpt | CMvag | compla | AErpt | LBtest | clue_c | ph_vag | koh | nugent | chlamydia | n_gonorr | preg_ur |
|---------|--------|-------|----------|------------|--------|------|----------|---------|---------|---------|-------|-------|--------|-------|--------|--------|--------|-----|--------|-----------|----------|---------|
| 101 | 1 | A | 1 | 2004-07-01 | 0 | JB | N | Y | Y | Y | Y | N | Y | N | Y | | | | | | | |

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
 VISITNUM: Visit Sequence Number
 SVSTDTC: Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
 ELTMBL: Elapsed Time since Baseline (days)
 abn_vagd: Abnormal vaginal discharge, e.g., Y=Yes, N=No
 cure_cl: Clinical cure, e.g., Y=Yes, N=No
 cure_ba: Bacteriological cure, e.g., Y=Yes, N=No
 success: Treatment success (therapeutic cure), e.g., Y=Yes, N=No
 CMrpt: Concomitant Medication reported during this visit, e.g., Y=Yes, N=No
 CMvag: Use of any vaginal products other than study product, e.g., Y=Yes, N=No
 complia: Compliant with protocol, 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
 clue_c: Clue cells on wet mount, e.g., A= $\geq 20\%$, B= $< 20\%$, C=none)
 ph_vag: Vaginal pH
 koh: KOH “whiff test”, e.g., P=Positive; N=Negative
 nugent: Nugent score, e.g., 0, 1, 2, 3, or 4
 chlamydia: Chlamydia trachomatis test e.g., P=Positive; N=Negative
 n_gonorr: Neisseria gonorrhoeae test, e.g., P=Positive; N=Negative
 preg_ur: Urine pregnancy test, e.g., P=Positive; N=Negative

21. 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 metronidazole.