

Guidance for Industry

Bacterial Vaginosis — Developing Antimicrobial Drugs for Treatment

DRAFT GUIDANCE

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GUIDANCE FOR INDUSTRY¹

Bacterial Vaginosis — Developing Antimicrobial Drug Products for Treatment

I. INTRODUCTION

This is one in a series of guidance documents intended to assist the pharmaceutical industry in the development of antimicrobial drug products for the treatment of infections. The information presented here should help applicants plan clinical studies, design clinical protocol(s), implement and appropriately monitor the conduct of clinical studies, collect relevant data for analysis, and perform appropriate types and numbers of analyses of study data. Clinical trials planned and conducted as recommended in this guidance should yield the information necessary for the Agency to determine whether the antimicrobial under study is safe and effective in the treatment of the specific infection. For general information on related topics, the reader is referred to the guidance *Developing Antimicrobial Drugs — General Considerations for Clinical Trials (General Considerations)*.

This guidance for industry focuses on developing antimicrobial drugs for the treatment of bacterial vaginosis.

II. BACKGROUND

Over the years, the Agency has issued guidance to the pharmaceutical industry on how to design, carry out, and analyze the results of clinical trials for the development of antimicrobials for the treatment of infections in a variety of forms. Guidance has been provided verbally during various industry and FDA meetings, in letters written to sponsors, and in general guidance on related issues. This guidance is the result of efforts to collect all pertinent information and present it in

¹ This guidance has been prepared by Office of Drug Evaluation IV, representing the Division of Anti-Infective Drug Products, the Division of Special Pathogens and Immunological Drug Products, and the Division of Anti-Viral Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on developing antimicrobial drugs for the treatment of bacterial vaginosis. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

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one location. Where appropriate, this guidance contains relevant information from several sources, including *Clinical Evaluation of Anti-Infective Drugs (Systemic)* (1977); IDSA's "Guidelines for the Evaluation of Anti-Infective Drug Products" (1992) (IDSA guidance);² *Points to Consider: Clinical Development and Labeling of Anti-Infective Drug Products* (1992) (*Points to Consider*), an FDA guidance on issues related to evaluating new drug applications for anti-infective drug products; and *Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products* (February 1997), a draft guidance discussed at a March 1997 advisory committee meeting on anti-infective drug products, which will be superseded by this guidance once it is issued in final form.

III. BACTERIAL VAGINOSIS

A. Regulatory Synonyms

To date, this indication has encompassed several synonyms including non-specific vaginitis (1955, Gardner and Dukes), *Haemophilus vaginalis* or *Corynebacterium vaginalis* infection, vaginitis due to *Gardnerella vaginalis*, anaerobic vaginosis, and more recently, bacterial vaginosis (BV).

B. Study Considerations

1. Study Characteristics

Two statistically adequate and well-controlled multicenter trials establishing safety and effectiveness are recommended because there are no closely related indications and the microbiology for this infection is not well defined. In this infection, an evaluable patient should be expected to be clinically evaluable only. Rigorous entry criteria, including the presence of a homogeneous vaginal discharge that (a) has a pH greater than 4.5, (b) emits a "fishy" amine odor when mixed with a 10% KOH solution, and (c) contains clue cells on microscopic examination, should be employed in clinical trials. Gram's stain of vaginal discharge should be performed and results should be consistent with a diagnosis of bacterial vaginosis, including (a) markedly reduced or absent *Lactobacillus* morphology, (b) predominance of *Gardnerella* morphotype, and (c) absent or few white blood cells. Other pathogens commonly associated with vulvovaginitis (e.g., *Trichomonas vaginalis*, *Chlamydia trachomatis*, *N. gonorrhoeae*, *Candida albicans*, and *Herpes simplex virus*) should be ruled out. It should also be expected that the antimicrobial drug product exhibits acceptable in-vitro activity against the major pathogens associated with this clinical entity.

² This guidance appeared in IDSA's (Infectious Disease Society of America) supplement to *Clinical Infectious Diseases*, formerly *Reviews of Infectious Diseases*.

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a. Randomization

Patients should be randomized to a study arm after a screening history, vaginal exam, and office laboratory testing have been completed. All patients randomized should be followed throughout the study period (even if deemed noncompliant with the protocol), so that study withdrawals would be minimized and data collection would be maximized.

b. Blinding

Studies testing *intravaginal* drugs for both arms should be investigator-blinded and conducted without the use of a vehicle (the drug product minus the active ingredient). There is concern that the use of a vehicle as an intravaginal *placebo* may alter clinical outcomes in many ways (e.g., change the vaginal pH; cause local epithelial changes when applied to the vagina; dilute or displace the active drug product from the site of infection).

One recommendation is to use a comparator drug, which has the same route and preferably the same duration of administration as the test drug, to minimize bias and make investigator blinding easier.

The protocol should include a statement how investigator blinding will be ensured.

c. Pregnancy

Because of the association between BV and preterm delivery of low-birth-weight infants during the second and third trimester of pregnancy,³ the division encourages sponsors to include pregnant women in the studies, unless the drug is clearly contraindicated during pregnancy or the sponsor does not wish to pursue a pregnancy indication. If use during pregnancy is not studied, then the label would indicate that there are no data about efficacy and safety in pregnant women.

2. Historical Perspective and Disease Definitions

Bacterial vaginosis (BV) is the most common cause of vaginitis in women of childbearing age, causing 40-50% of all vaginal infections.⁴ The patients present with the following

³ Hillier, S. L., R. P. Nugent, D. A. Eschenbach, et al., and the Vaginal Infections and Prematurity Study Group, "Association between BV and Preterm Delivery of a Low-Birth-Weight Infant," *NEJM* 1995; 333:1737-42.

⁴ Sobel, J. D., Review article: "Vaginitis," *NEJM* 1997; 337:1896-1903.

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findings: an unpleasant, “fishy smelling” off-white, thin, and homogeneous discharge without an apparent inflammatory response. The disease represents a complex change in the vaginal flora with a reduction in the prevalence and concentration of lactobacilli (especially hydrogen peroxide producing forms), and a concomitant increase in *Gardnerella vaginalis*, *Mobiluncus* spp., anaerobic Gram-negative rods (of the genera *Bacteroides*, *Prevotella* and *Porphyromonas*), *Peptostreptococcus* spp. and *Mycoplasma hominis*. BV is implicated in recurrent urinary tract infections and preterm labor, and a variety of upper genital tract infections including postpartum endometritis, post-hysterectomy and post-abortion infection, and pelvic inflammatory disease.

Predisposing factors associated with BV are non-white ethnicity, prior pregnancy, use of an IUD, sexual activity, new sexual partners, and recent antibiotic use. It is also associated with concurrent trichomoniasis and/or the absence of hydrogen peroxide producing lactobacilli.

C. Inclusion Criteria

To be enrolled, postmenarchal females should have a clinical diagnosis of BV, defined as having all of the following findings:

1. Off-white (milky or gray), thin, homogeneous discharge with minimal or absent pruritus and inflammation of the vulva and vagina
2. The presence of “clue cells”⁵ \geq 20% of the total epithelial cells on microscopic examination of the saline “wet mount”
3. Vaginal secretion pH of >4.5
4. A fishy odor of the vaginal discharge with the addition of a drop of 10% KOH (i.e., a positive “whiff test”)

D. Exclusion Criteria

⁵ Diagnostic “clue cells” should have *Gardnerella* like organisms (small, non-motile, coccobacilli) covering not only the surface of the squamous epithelial cells, but also spreading out past the cell boundaries, obscuring the cytoplasmic margins and thus creating a “shaggy” appearance. The entire cell need not be covered with bacteria, but cells with organisms simply sticking to the surface without extending past the cytoplasmic margins should not be considered “clue cells.” Both the saline mount and the Gram's stain can easily and accurately be used to determine clue cells.

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1. Patients with other infectious causes of vulvovaginitis (e.g., candidiasis, *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Herpes simplex*, or human papilloma virus)
2. Patients with another vaginal or vulvar condition, which would confound the interpretation of clinical response
3. A Gram's stain slide Nugent score < 4
4. Patients who received antifungal or antimicrobial therapy (systemic or intravaginal) within 14 days of randomization (unless this therapy is completely unrelated to the vaginal findings, such as treatment for malaria or tuberculosis)
5. Women who will be under treatment during the study period for cervical intra-epithelial neoplasia (CIN) or cervical carcinoma
6. Women in the first trimester of pregnancy

E. Drug Compliance and Evaluability

The choice of control drug for the study should be consistent with one of the FDA-approved systemic and topical vaginal drug products for treating BV. These are available for treatment regimens of 3, 5, and 7 days.

All patients should accurately document in their diary the time and number of doses received and any reasons for non-compliance (see Attachment). Lot numbers and other identifiers should be provided for all study drugs. Evaluability depends on the treatment duration for the study arm and the clinical outcome (See section K below):

1. *One day*: 1 dose is considered evaluable
2. *Three days*: 3 doses are considered evaluable
3. *Five to seven days*: at least first 3 doses (3 consecutive days are considered evaluable)

F. Evaluation

Until recently, the reviewing division recommended three clinic visits during the course of a study. The division now believes that two study visits, a patient diary, and an interim telephone contact are sufficient to adequately characterize the safety and efficacy of a drug product intended to treat

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BV. The two visits include the entry visit and the test-of-cure visit (TOC). The TOC visit evaluability window is intended to be broad enough to accommodate for holidays, weekends, and menses. (See section G, below)

1. Entry Visit

Data entered onto the case report form (CRF) from tests performed at entry should include the visit date, past medical and obstetrical/gynecological history, recent contraceptive and sexual history, and the number of episodes of BV in the preceding 12 months and the treatments given. Signs and symptoms to be evaluated include: color, odor, and consistency of the vaginal discharge; vulvovaginal itching and irritation (subjective): absent, mild, moderate, or severe; and vulvovaginal inflammation (objective): absent, mild, moderate, or severe.

Specimens should be collected for the following tests:

- Papanicolaou (Pap) smear (Pap smear results from the previous 12 months are acceptable)
- Saline “wet mount”
- 10% KOH “whiff test”
- Gram's stain (the slide should be air-dried and heat-fixed and sent to a central reference lab)
- Pregnancy
- *Trichomonas vaginalis* culture (in patients with a negative wet mount for trichomonads)
- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- *Herpes simplex* (only if suspected)
- Complete blood count (CBC) and chemistry panel, if the study drug is administered systemically

Patients should refrain from the use of intravaginal products during the first 7 days of the study (e.g., douches, feminine deodorant sprays, spermicides, condoms, tampons, and

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diaphragms).

At the entry visit the patient should be instructed to properly record data in her diary, and to contact the investigator if her symptoms don't improve within 3 to 4 days. If clinically warranted at any time during the study period, she should be reassessed at an office visit. Similarly, if adverse events occur that concern the patient, she should contact the investigator.

2. Post-Treatment Telephone Contact

This post therapy contact should be initiated by the investigator and occur approximately 7 to 10 days after the beginning of therapy. The purpose of this telephone call is to ensure patient compliance with the protocol, to evaluate the patient's response to therapy, and to inquire about possible adverse events. If during the telephone interview the patient's clinical response is considered inadequate, the investigator should ask the patient to come to the office for a full evaluation. All information from this phone contact should be recorded on the CRF.

If the patient can't be contacted by telephone, she may still be considered evaluable (as long as all other evaluability criteria are fulfilled).

3. Test-of-Cure Visit

This clinic visit should occur 21 to 30 days after the first day of treatment. Data entered onto the CRF should include the visit date, the interim clinical history, and the patient diary. Signs and symptoms to be evaluated and recorded include: color, odor, and consistency of the vaginal discharge; vulvovaginal itching and irritation (subjective): absent, mild, moderate, or severe; and vulvovaginal inflammation (objective): absent, mild, moderate, or severe.

Specimens should be collected for the following tests:

- Saline "wet mount"
- 10% KOH "whiff test"
- Gram's stain (to be sent to the same central reference lab as the entry visit)
- *Trichomonas vaginalis* culture (in patients with a negative wet mount for trichomonads), if clinically indicated

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- *Chlamydia trachomatis*, if clinically indicated
- *Neisseria gonorrhoeae*, if clinically indicated
- *Herpes simplex*, if clinically indicated
- CBC and appropriate metabolic screens, if the study drug is administered systemically

The investigator should answer the following statement on the CRF: “*In your opinion, does the patient require additional treatment for bacterial vaginosis or any other infection at this time? (yes/no) If yes, please explain why.*”

G. Outcome

In most clinical studies in the past, there have been three categories of outcome: cure, improvement, and failure. The Agency now recommends that there should be only two categories: therapeutic cure and failure. The final therapeutic outcome is based on a combination of both the clinical outcome and the Gram's stain results (Nugent scoring system) in patients who are considered to be evaluable and also in the intent-to-treat population.

1. Clinically Evaluable

To be considered clinically evaluable, the patients should have

- a. Clinical assessment Gram's stain Nugent score result done between study days 21 to 30, relative to the first day of treatment
- b. No antimicrobial drug other than allowed per protocol during the study period, Days 1 to 30
- c. Started study medication within 48 hours of entry visit

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- d. Meet inclusion and exclusion criteria, comply with the treatment regimen, and have no protocol violations
- e. No additional intravaginal products during the first seven days of the study

Clinical Cure is defined as resolution of the clinical findings from the entry visit:

- The original discharge characteristic of bacterial vaginosis has returned to a normal physiological discharge which varies in appearance and consistency depending on the menstrual cycle.
- The whiff test is negative for any amine (“fishy”) odor
- The saline wet mount is negative for clue cells
- The pH is <4.7, using pH paper that measures from 4.0 to 6.0

Clinical Failure is defined as a patient who does not meet the definition of Clinical Cure or:

- In whom an antimicrobial drug not allowed per protocol is received during the study period, Days 1-30 or
- If the investigator answers, “Yes.” to the question, “In your opinion, does the patient require additional treatment for bacterial vaginosis infection at this time?”

Nonevaluable: *NOTE:* If patients use other vaginal products (e.g., douche, feminine deodorant spray, N-9 products, condoms, tampons) during the treatment phase of the study (e.g., Days 1-7), they will be considered non-evaluable. If this protocol violation occurs for the first time beyond the treatment phase (e.g., Days 8-30), the patients first should be analyzed separately before combining them with the per-protocol evaluable population.

2. Nugent Score Outcomes

The reviewing division recommends that the Nugent scoring system be used. This system uses a 0- to 4-point scale for the evaluation of the vaginal flora and is based on the weighted sum of the following 3 bacterial morphotypes scores calculated from slide exam under oil immersion (1000X):

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- a. *Lactobacillus*: large Gram-positive rods
- b. *Gardnerella/ Bacteroides* spp.: small Gram-variable coccobacilli/small Gram-negative rods
- c. *Mobiluncus* spp.: thin, curved, Gram-variable rods

The criterion for bacterial vaginosis according to Nugent’s criteria is a total score of 7 or more; a score of 4 to 6 is called *intermediate*, and a score of 0 to 3 is considered *normal*. A score of >3 is considered by the Agency to be *abnormal*, and a score of 0 to 3 is considered normal, or a *cure* at the TOC visit.

Nugent Scoring System for Gram's Stained Vaginal Smears			
SCORE*	Lactobacillus morphotypes	<i>Gardnerella/Bacteroides</i> spp. morphotypes	Curved Gram-variable rods
0	**4+	0	0
1	3+	1+	1+ or 2+
2	2+	2+	3+ or 4+
3	1+	3+	
4	0	4+	

* Morphotypes are scored as the average number seen per oil immersion field (minimum of 10-20 fields should be examined). Each morphotype is then given a score from the left hand column. The TOTAL SCORE is calculated by adding up the individual morphotype scores = Lactobacillus + Gardnerella/Bacteroides + Curved Gram-negative rods.

** QUANTIFICATION SCALE: 0 = no morphotypes seen; 1+ = <1 morphotype per field; 2+ = 1 to 4 morphotypes; 3+ = 5 to 30 morphotypes; 4+ = >30 morphotypes per field.

3. *Microbiological Outcomes*: This outcome is not applicable and is not included in the definition of cure or failure for bacterial vaginosis.

4. *Therapeutic Outcomes*: The overall therapeutic assessment of cure or failure is derived by taking into consideration both the clinical outcome and Nugent score (see table below).

- Therapeutic Cure: Patient who is considered both a clinical cure and Nugent score of 0-3 at the TOC visit.
- Therapeutic Failure: Patient who anytime during the study period (days 4-

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30) was considered by the investigator as a clinical failure or who had a Nugent criteria score of >3.

Determination of Therapeutic Response by TOC visit (summarized)		
If the clinical outcome is...	and the Nugent score result is...	then the overall therapeutic outcome is...
cure	0-3	cure
cure	>3	failure
failure	0-3	failure
failure	>3	failure
cure	NE	NE
NE	0-3	NE
NE	>3	NE

NE = non-evaluable

5. Safety

In general, when topically applied antimicrobials show minimal systemic absorption (based on pharmacokinetic studies), safety assessments can be limited to local descriptions of toxicity. However, where appreciable systemic absorption occurs, hematology, chemistry, and urine laboratory testing should be performed at both entry and TOC visits to assess organ toxicity.

H. Statistical and Analytical Considerations:

1. Analysis Plan

The reviewing division recommends analyses be performed on two populations and the results from both populations should be consistent.

- a. The per protocol analysis refers to that population that complied strictly with the protocol and is classified as clinically evaluable.
- b. The intent-to-treat analysis refers to the population of all patients randomized to the study. So that this analysis may be useful, the recommendation is made under randomization that all patients be followed throughout the course of the study. It is customary to consider patients who have missing data or otherwise violate the protocol as failures for the purposes of this analysis.

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2. Evaluations

- a. The primary efficacy variable proposed is the therapeutic cure rate, which includes both the clinical outcome and the Nugent score. In the past, clinical studies were analyzed using clinical criteria, and the Nugent score was examined to see if it was consistent with the clinical picture, but was not a component of the primary efficacy variable.
- b. The secondary efficacy variables are the
 - Clinical cure rate
 - Nugent score on Gram's stain
 - Time to resolution of symptoms (“abnormal” discharge and odor)

3. Statistical Considerations - Sample size

Each study should be adequately powered to demonstrate therapeutic equivalence using a 95% confidence interval around the difference in therapeutic cure rates of the test drug to the comparator for the per protocol evaluable population.

There should also be a adequate number of patients exposed to the investigational product (same formulation and duration of therapy) during all phases of clinical testing (e.g., 300) to provide for adequate evaluation of the safety of the drug.

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ATTACHMENT

Recommended Patient Diary:

To evaluate patient compliance and to gather information on the patient's response to treatment, it is customary in studies of vaginal drug products to ask patients to keep a diary and record information about drug administration, clinical response and adverse events. A sample diary is included

Please indicate on which date your symptoms were completely gone:_____.

If your symptoms returned, please indicate on which date:_____.

Please record the date you took each dose of study medicine below:

1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6 _____ 7 _____

Please circle one or more of the following products, if you used them during the first 7 days after starting the drug:

spermicide tampon douche condom diaphragm feminine deodorant product

Please circle one or more of the following products, if you used them between day 8 of the study and the TOC visit:

spermicide tampon douche condom diaphragm feminine deodorant product