

Draft Guidance on Vancomycin Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Capsules/Oral

Recommended studies: **2 Options: *In Vitro* or *In Vivo* Studies**

1. **In Vitro Option:**

If the test product formulations are qualitatively (Q_1) (i.e., contain all of the same inactive ingredients) and quantitatively (Q_2) the same as the reference listed drug (RLD) with respect to inactive ingredients, bioequivalence (BE) of all capsule strengths may be established based on comparative dissolution.

For test product formulations that are Q_1 and Q_2 the same as the RLD, dissolution data in each specified medium should be provided for 12 capsules each of test and reference products, as follows:

Apparatus:	USP Apparatus 1 (basket)
Rotation speed:	100 rpm
Medium:	0.1N HCl (or 0.1N HCl with NaCl at pH 1.2), pH 4.5 Acetate buffer, and pH 6.8 Phosphate buffer
Volume:	900 mL
Temperature:	37°C
Sample times:	5, 10, 20, 30, and 45 minutes or as needed for profile comparison

An f_2 test¹ should be performed using mean profiles to ensure comparable test (T) and reference (R) product drug release under a range of pH conditions. The f_2 test comparing T vs. R in each medium should be between 50 and 100.

2. **In Vivo Option**

If the test product formulations are not Q_1 and Q_2 the same as the RLD with respect to inactive ingredients, BE should be established by conducting an in vivo study with clinical endpoints in patients with *Clostridium difficile* Associated Diarrhea (CDAD). We recommend that any sponsor choosing this option submit their protocol to the OGD clinical review team for review and concurrence prior to initiating the study.

¹Dissolution profiles may be compared using the following equation that defines a similarity factor (f_2):

$$f_2 = 50 \text{ LOG } \{ [1 + 1/n \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} \times 100 \}$$

where R_t and T_t are the percent dissolved at each time point. An f_2 value between 50 and 100 suggests the two dissolution profiles are similar. See Guidance for Industry *Immediate Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995), at 23.

Dissolution testing for stability and quality control:

USP Method

Scientific Rationale for In Vitro and In Vivo BE Recommendations

1. Vancomycin HCl Capsules are administered orally for treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains) and antibiotic-associated pseudomembranous colitis caused by *C. difficile*. Vancomycin HCl is poorly absorbed after oral administration. During multiple dosing of 250 mg every 8 hours for 7 doses, no blood concentrations were detected and urinary recovery did not exceed 0.76%. Orally administered vancomycin does not usually enter the systemic circulation even when inflammatory lesions are present.²
2. Vancomycin acts locally in the lower gastrointestinal (GI) tract. After oral administration, a vancomycin capsule releases the drug in the stomach and upper GI tract, the released drug is completely solubilized in GI fluids, and is transported along with GI fluids to its site of action in the lower GI tract. The BE of two capsule formulations of oral vancomycin HCl is determined by the following factors:
 - Equivalent release of vancomycin from the two capsule formulations,
 - The high solubility of vancomycin drug substance,
 - The effect of inactive ingredients on the transport of vancomycin drug through the GI tract and/or the effectiveness of drug at the site of action

FDA's BE recommendation includes evaluation of all of these factors and is supported by FDA laboratory investigations.

3. The FDA laboratory conducted solubility studies at physiologically relevant pH ranges (attached). The results demonstrate that vancomycin HCl is highly soluble over the physiologically relevant pH range of 1.0 to 7.5. Vancomycin HCl at pH 1, 3, 4, 5 and 7.5 would require 1.78, 1.27, 83.8, 26.3 and 14.2 ml of aqueous media, respectively, to dissolve the highest dose strength of 250 mg of vancomycin HCl.
4. The FDA laboratory conducted dissolution studies in physiologically relevant dissolution media at pH 1.0, 4.5, and 6.8 buffers (attached). The data show that the reference vancomycin HCl capsules (Vancocin) will generally dissolve more than 85% in 30 minutes at pH 1.0, in 45 minutes at pH 4.5, and in 60 minutes at pH 6.8. Given that vancomycin is highly soluble at pH conditions encountered in the GI tract³ and the dosage form is expected to be in contact with a relatively large fluid volume,⁴ vancomycin is expected to be in solution long (e.g., hours) before it reaches the site of action in the lower GI tract.⁵ FDA's BE recommendation recognizes that the patient population may have variability in GI pH or transit times and thus requests that the test and reference products demonstrate similar ($f_2 > 50$) dissolution profiles over a range of relevant

² Approved label for Vancocin® HCl Capsules, USP, © 2005, ViroPharma Inc., Exton, PA, 19431.

³ The pH range in the GI tract under fasted conditions is 1.5 to 2.5 in the stomach, 5.0 to 6.0 in the duodenum, 6.0 to 7.0 in the jejunum, and 7.5 in the ileum. See Willmann S, Schmitt W, Keldenich J, et al. *J Med Chem.* **47**: 4022-4031, (2004).

⁴ The physiological fluid volume of the small intestine varies from 500 mL (fasting conditions) to approximately 1000 mL or more (fed conditions). See Dressman J and Reppas C. *Eur J Pharm Sci.* **11**: S73-S80 (2000)

⁵ The average transit time in the small intestine is 3 to 4 hours. See Davis S, Hardy J, and Fara J. *Gut.* **27**: 886-892, (1986).

pH conditions. Similar dissolution profiles ensure that test and reference products will be equivalent even in patients with relatively short GI transit times.

5. Inactive ingredients in oral formulations may affect the transport of drug through the GI tract and/or the effectiveness of drug at the site of action. To ensure that differences in inactive ingredients will not affect the safety and effectiveness of generic vancomycin HCl oral capsules, we recommend a BE study with clinical endpoints for test products that are not Q₁ and Q₂ the same relative to the RLD with respect to inactive ingredients unless the ANDA sponsor provides evidence that the differences in excipients will not affect the safety or efficacy of the proposed generic drug product.

BE Recommendation History

As set forth in the Clinical Pharmacology section of the approved product labeling for Vancocin Oral Capsules, the RLD to which generic vancomycin HCl must be demonstrated to be BE, vancomycin is poorly absorbed after oral administration and does not usually enter the systemic circulation. Thus, plasma and urine concentrations of vancomycin are generally undetectable following oral administration, and traditional BE studies with pharmacokinetic (PK) measurements are of limited utility. Accordingly, in 1996, FDA recommended an in vivo BE study with clinical endpoints in patients to demonstrate BE of generic vancomycin HCl oral capsules.

In October 2004, FDA asked its Advisory Committee for Pharmaceutical Science to consider when dissolution testing could be used to establish BE for locally acting GI drugs. The Committee concluded that dissolution testing along with PK studies should be acceptable to establish BE for such products. In light of the Committee's conclusions, after obtaining data showing that vancomycin HCl is highly soluble at pH conditions encountered in the GI tract and expected to be in solution long before it reaches the site of action in the lower GI tract, FDA revised its recommendation in early 2006 to include in vitro dissolution studies to demonstrate BE of generic vancomycin HCl oral capsules. This approach would provide OGD with information about drug availability at the site of action and would be more sensitive than clinical trials in detecting differences in product performance. FDA provided its 2006 revised BE recommendation to those parties that had requests pending with FDA for this information. In March 2006, Viropharma, Inc., the manufacturer of the RLD Vancocin, filed a petition for stay of action (PSA), challenging FDA's revised recommendation (Docket No. FDA-2006-P-0007).⁶

In this draft recommendation, FDA further clarifies its recommendations on the design of studies for demonstrating BE of vancomycin HCl capsules. Because, as set forth above, generic applicants may use different inactive ingredients, which may affect the transport, absorption, and/or effectiveness of the drug, FDA is currently recommending in vitro dissolution studies only for test formulations that are Q₁ and Q₂ the same as the RLD. For test formulations that are not Q₁ and Q₂ the same as the RLD with respect to inactive ingredients, FDA is recommending in vivo BE studies with clinical endpoints.

We note that the proposed recommendations for the BE evaluation of vancomycin capsules are consistent with the 2004 Advisory Committee's conclusion. PK studies are not appropriate in this case, however, because as stated above, vancomycin levels are generally not detectable in the plasma or urine due to very limited absorption.

FDA invites comments on this draft recommendation and will carefully consider such comments before responding to Viropharma's PSAs and finalizing this recommendation.

⁶ This PSA was originally assigned docket number 2006P-0124. The number was changed to FDA-2006-P-0007 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008. This docket also includes a second PSA and numerous supplements filed by ViroPharma.