



DEPARTMENT OF HEALTH & HUMAN SERVICES

Docket No. FDA-2006-P-0007

Food and Drug Administration
Rockville MD 20857

APR 9 2012

- Thomas F. Doyle
ViroPharma, Inc.
730 Stockton Drive
Exton, PA 19341

Re: Docket No. FDA-2006-P-0007¹

Dear Mr. Doyle:

This letter responds to your citizen petition for a stay of action dated March 17, 2006, and amended March 30, 2006 (petition), concerning how abbreviated new drug application (ANDA) applicants, or applicants submitting applications under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for vancomycin hydrochloride (HCl) (vancomycin) oral capsule drug products, may establish bioequivalence to Vancocin HCl Capsules (new drug application (NDA) 050606), the reference listed drug (RLD) product. In summary, you have petitioned the U.S. Food and Drug Administration (FDA or the Agency): (1) to stay approval of any ANDA or 505(b)(2) application for vancomycin capsules;² (2) to rescind the 2008 draft guidance for Vancomycin Hydrochloride (Draft Vancomycin BE Guidance)³ that recommends a methodology for establishing the bioequivalence of vancomycin capsules to the innovator drug product, Vancocin, using in vitro dissolution data; and (3) to require any applicant seeking to demonstrate bioequivalence to Vancocin to use in vivo data from clinical endpoint studies. You have raised scientific, legal, and procedural challenges to FDA's bioequivalence recommendation. In addition, in a recent submission, you claim that changes to Vancocin's labeling approved on December 14, 2011, are based on new clinical safety and efficacy data to which ViroPharma holds exclusive rights, and that generic vancomycin capsule products that omit this information should not be approved for 3 years from the December approval date.

¹ This citizen petition was originally assigned docket number 2006P-0124/PSA1 and PSA2. 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.

² ViroPharma seeks a stay of approval of any application filed under section 505(j) or 505(b)(2) of the FD&C Act that references Vancocin. For simplicity's sake, this petition response addresses FDA's recommended bioequivalence methodologies for vancomycin capsules in the context of ANDAs submitted under section 505(j). We note here that the Agency's discussion of, and conclusions with respect to, demonstrating bioequivalence to Vancocin set forth in this petition response also are applicable to applications submitted under section 505(b)(2) of the FD&C Act that seek to submit bioequivalence data to bridge to the finding of safety and effectiveness for Vancocin. We note, however, that in contrast to section 505(j), section 505(b)(2) of the FD&C Act does not require an applicant to demonstrate bioequivalence.

³ Draft Guidance for Vancomycin Hydrochloride (Dec. 2008).

In addition to your original submission and the amendment thereto, you have filed 20 supplements to the petition and 16 submissions to the related FDA Docket No. 2008-D-0626 that concerns the Draft Vancomycin BE Guidance.⁴ You have presented materials to an FDA advisory committee considering vancomycin bioequivalence methodologies, you have met directly with Agency representatives to discuss your position, and numerous congressional inquiries have been submitted on your behalf.⁵

FDA has carefully considered the issues that you have raised, other submitters' comments to the citizen petition docket and the Draft Vancomycin BE Guidance docket that concern the issues in your petition and supplements, the relevant scientific and legal authorities, and additional relevant material, including an FDA advisory committee's unanimous endorsement of FDA's 2008 bioequivalence recommendation for vancomycin. Upon review, FDA has determined that the recommendation in the Draft Vancomycin BE Guidance is scientifically sound, that FDA has clear legal authority to recommend in vitro dissolution data to demonstrate the bioequivalence of generic vancomycin, and that the process by which the Agency developed the current recommendation involved a robust, public consideration of the issues raised in your petition, in accordance with the relevant legal authorities. Finally, the Agency has concluded that under the limitation provision in section 505(v) of the FD&C Act, Vancocin is not eligible for 3 years of exclusivity for the recently approved changes to the Vancocin label. Your petition is granted in part to the extent that you request and have been provided notice of and an opportunity to comment on FDA's recommended bioequivalence methodology for generic vancomycin capsules, and FDA has provided data underlying the scientific bases for that recommendation directly to you in response to your Freedom of Information Act (FOIA) requests. Your petition otherwise is denied, as explained in detail below.⁶

I. BACKGROUND

A. Vancocin Capsules

FDA approved a new drug application (NDA) for Vancocin Capsules in 1986 for the treatment of enterocolitis in the gastrointestinal (GI) tract caused by *Staphylococcus aureus* (including methicillin-resistant strains) (SAE) and diarrhea associated with *Clostridium difficile* (CDAD).⁷ Vancocin is only one of two FDA-approved therapies

⁴ Some of your submissions were cross-filed in both the citizen petition and draft guidance dockets. For the sake of efficiency, your individual supplements to this citizen petition will be referred to in the following form: "VP [insert date] Supp." Any submissions made by others or by you to other agency dockets or matters will be identified accordingly.

⁵ See, e.g., Letter fr. Hon. A. Specter to A. von Eschenbach, M.D. (Dec. 29, 2006) (letter inquiry into appropriate bioequivalence methodology for ViroPharma's Vancocin product).

⁶ Concurrent with this response, FDA is approving three ANDAs for generic vancomycin capsules. A final guidance for vancomycin hydrochloride bioequivalence consistent with this citizen petition response is forthcoming.

⁷ Vancocin HCl Capsules Package Insert (Vancocin PI), at 2, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/050606s028lbl.pdf. FDA originally approved Vancocin Capsules under then-section 507 of the FD&C Act, the statutory provision under which antibiotic

indicated for treatment of CDAD.⁸ The active ingredient in Vancocin Capsules is vancomycin hydrochloride, a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*). Vancomycin acts locally in the GI tract by inhibiting cell wall biosynthesis in gram-positive bacteria, and is poorly absorbed after oral administration, meaning it does not enter the body systemically.⁹ The labeling also lists as ingredients F-D & C Blue No. 2, gelatin, iron oxide, polyethylene glycol, titanium dioxide, and other inactive ingredients.¹⁰

B. Applicable Statutory and Regulatory Framework

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the FD&C Act, which established the ANDA approval process for generic drugs.¹¹ To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant relies on FDA's previous finding that the RLD is safe and effective.¹² The ANDA applicant must identify the listed drug on which it seeks to rely and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the listed drug it references.¹³

The ANDA applicant also must demonstrate that its proposed generic drug is bioequivalent to the RLD it references.¹⁴ The statute, regulations and case law give FDA

products were approved prior to 1997. As discussed in detail below in section II.C.9.b., Congress incorporated antibiotic approval into section 505 of the FD&C Act in 1997.

⁸ On May 27, 2011, FDA approved NDA No. 201699 submitted by Optimus Pharmaceutical Inc. for Dificid (fidaxomicin) tablets for the treatment of *Clostridium difficile*-associated diarrhea in adults.

⁹ Vancocin PI, at 9. See also id. at 3 ("[t]his preparation for the treatment of colitis is for oral use and is not systemically absorbed"). During multiple dosing of 250 mg every 8 hours for 7 doses, fecal concentrations of vancomycin in volunteers exceeded 100 mg/kg in the majority of samples. No blood concentrations were detected and urinary recovery did not exceed 0.76%. In anephric subjects with no inflammatory bowel disease who received vancomycin oral solution 2 g for 16 days, blood concentrations of vancomycin were less than or equal to 0.66 µg/mL in 2 of 5 subjects. No measurable blood concentrations were attained in the other 3 subjects. Following doses of 2 g daily, concentrations of drug were >3100 mg/kg in the feces and <1 µg/mL in the serum of subjects with normal renal function who had *C. difficile*-associated diarrhea. Id. at 9. As noted on the label, there is a possibility of systemic absorption for patients who have taken multiple oral doses of Vancocin for active *C. difficile*-associated diarrhea, and patients with inflammatory disorders of the intestinal mucosa. Id. at 3.

¹⁰ Id. at 8.

¹¹ *Drug Price Competition and Patent Term Restoration Act of 1984*, Pub. L. No. 98-417, 98 Stat. 1585.

¹² A reference listed drug or RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, generally known as "the Orange Book."

¹³ Sections 505(j)(2)(A) and (j)(4) of the FD&C Act. See also 21 CFR 314.94(a).

¹⁴ See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (requiring "information to show that the new drug is bioequivalent to the listed drug"); 21 CFR 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the reference listed drug); 21 CFR 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the RLD referred to in the ANDA).

considerable flexibility in determining how this requirement is met. Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is bioequivalent to the listed drug if:

the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . .¹⁵

Section 505(j)(8)(C) of the FD&C Act provides that different approaches to demonstrating bioequivalence may apply to locally acting, nonsystemically absorbed drug products:

For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.¹⁶

Such methods include using *in vivo* data (data from a study on human subjects), or *in vitro* data (data from laboratory studies). FDA's wide discretion to determine appropriate bioequivalence standards is reflected in Congress's requirement that FDA publish in the Orange Book "whether *in vitro* or *in vivo* bioequivalence, or both such studies, are required for applications filed under [section 505(j)] which will refer to the drug published."¹⁷

FDA's regulations likewise reflect the flexibility that FDA has in choosing the appropriate methods to establish bioequivalence for particular drug products. Under the bioequivalence regulations in 21 CFR part 320, the bioequivalence requirement is defined as "a requirement imposed by the Food and Drug Administration for *in vitro* and/or *in vivo* testing of specified drug products which must be satisfied as a condition of marketing."¹⁸ Section 320.24, which sets out the types of evidence that may be used to establish bioequivalence, provides that:

FDA may require *in vivo* or *in vitro* testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug

¹⁵ See also 21 CFR 320.1(e) and 320.23(b).

¹⁶ Congress enacted this provision as part of the *Medicare Prescription Drug, Improvement, and Modernization Act of 2003* (MMA), Pub. L. 108-173, 117 Stat. 2066 (Dec. 8, 2003). Congress made clear that subsection 505(j)(8)(C) codified the Agency's long-standing authority to make bioequivalence determinations. See id. at section 1103(b) ("[t]he amendment made by subsection (a) does not alter the standards for approval of drugs under ... 21 U.S.C. 355(j)").

¹⁷ Section 505(j)(7)(A)(i)(III) of the FD&C Act; see also *Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995) (noting that this provision "vests the FDA with the discretion to determine whether *in vivo* or *in vitro* bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated approval process").

¹⁸ 21 CFR 320.1(f).

products The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.¹⁹

(Emphasis added.)

Section 320.24(b) of FDA's regulations describes preferred bioequivalence methods in what, for systemically absorbed products, is the descending order of accuracy, sensitivity, and reproducibility.²⁰ They include: (1) in vivo pharmacokinetic studies, (2) in vivo pharmacodynamic effect studies, (3) clinical endpoint studies, and (4) in vitro studies.²¹ In addition, consistent with section 505(j)(8)(C) of the FD&C Act, section 320.24(b)(6) of the regulation states that FDA has the authority to use “[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence.”²² For some drug products, adequate methods for demonstrating bioequivalence have not yet been developed. In such cases, FDA will not approve an ANDA.

If FDA determines that in vivo data is the appropriate means of demonstrating bioequivalence for a product or product class, 21 CFR 320.21(f) provides that applicants may apply for a waiver of the in vivo requirement consistent with section 320.22.²³ Section 320.22 in turn directs that FDA “must” waive that in vivo requirement upon a subsequent showing that the individual applicant’s product meets certain additional criteria.²⁴ For example, if FDA requires in vivo data for a parenteral solution intended solely for administration by injection, or for an ophthalmic or otic solution, FDA must waive that requirement if the ANDA applicant demonstrates that its individual product from that product class contains the same active and inactive ingredients in the same concentration as the RLD.²⁵ Even in instances in which such additional criteria are met, however, FDA may require in vivo data if the Agency determines that any differences between the drug product and the RLD may affect the bioequivalence of the drug product.²⁶ Section 320.22 also provides that FDA “may” waive any Agency-imposed in vivo bioequivalence data requirement for a particular product “for good cause . . . if waiver is compatible with the protection of the public health,” underscoring FDA’s

¹⁹ 21 CFR 320.24(a).

²⁰ As discussed in detail in section I.C. below, this descending order of methodologies is not applicable to many locally acting drug products due to characteristics of those products that differ from most systemically acting drug products.

²¹ 21 CFR 320.24(b).

²² Id. See also *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 20 (D.D.C. 2009) (quoting 21 CFR 320.24(b) in upholding FDA sameness determination of generic drug product).

²³ 21 CFR 320.21(f) (“Information to permit FDA to waive the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence shall meet the criteria set forth in 320.22”).

²⁴ 21 CFR 320.22(a).

²⁵ 21 CFR 320.22(b)(1). See, generally, 21 CFR 320.22(b)-(d) (additional categories of products for which waivers of an in vivo data requirement may be sought).

²⁶ 21 CFR 320.22(f).

discretion to determine the most appropriate bioequivalence methodology for each product.²⁷

The Agency's authority to make bioequivalence determinations on a case-by-case basis using in vivo, in vitro, or both types of data enables FDA to effectuate several long-recognized policies that protect the public health: (1) refraining from unnecessary human research when other methods of demonstrating bioequivalence meet the statutory and regulatory standards;²⁸ (2) permitting the Agency to utilize the latest scientific advances in approving drug products;²⁹ (3) protecting the public by ensuring only safe and effective generic drugs are approved for marketing;³⁰ and (4) making more safe and effective generic drugs available.³¹

C. General Scientific Principles of Bioequivalence

For systemically acting drug products, the rate and extent of systemic absorption of the drug is usually the most sensitive, accurate, and reliable indicator of the rate and extent to which the active ingredient becomes available at the site of drug action. The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption generally rests on a comparison of drug and/or metabolite concentrations in an accessible biologic fluid, such as blood or urine, after administration of a single dose or multiple doses of each drug product to healthy volunteers.³²

²⁷ 21 CFR 320.22(e). FDA also has the general discretion to waive any requirement set forth in subpart C of part 314, which sets forth the approval scheme for ANDAs. 21 CFR 314.99(b) ("An applicant may ask FDA to waive under this section any requirement that applies to the applicant under 314.92 through 314.99. The applicant shall comply with the requirements for a waiver under 314.90"). As FDA noted with respect to the analogous section 314.90, such waivers are intended "to give applicants the flexibility to seek alternative ways of complying with the regulatory requirements for drug approval." *New Drug and Antibiotic Regulations*, 50 FR 7452, 7490 (Feb. 22, 1985).

²⁸ 21 CFR 320.25(a) ("guiding principle" that "that no unnecessary human research should be done" expressed in regulation addressing conduct of an in vivo bioavailability study); *Abbreviated New Drug Application Regulations, Proposed Rule*, 54 FR 28872, 28883 (July 10, 1989) (in discussing section 320.22, states "the agency does not believe that Congress intended that unnecessary human research be conducted ... if the agency concludes that bioequivalence can be demonstrated by in vitro tests").

²⁹ *Bioavailability and Bioequivalence Requirements: Procedures for Establishing a Bioequivalence Requirement*, 42 FR 1624, 1629 (Jan. 7, 1977) (in promulgating final bioequivalence regulations, FDA noted that "[a]s with all new regulations relating to an evolving science, the Commissioner reserves the right to consider other factors that may indicate the need to establish a bioequivalence requirement").

³⁰ *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 650 (D.D.C. 1992), (citing as one underlying policy of the Hatch-Waxman Amendments, to "ensure the safety of these drugs before they are substituted for their name-brand counterparts").

³¹ Id. (Purposes of Hatch-Waxman Amendments are "to make more inexpensive generic drugs available" and "to ensure the safety of these drugs"); *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 866-67 (D.D.C. 1994) (bioequivalence waiver provision "comports with the structure and broader policy objectives of the Hatch-Waxman Act" including making safe and affordable generic drugs available).

³² Section 505(j)(8)(B) of the FD&C Act; guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products -- General Considerations*, at 6 (Mar. 2003) (BA/BE Guidance).

By contrast, a traditional in vivo bioequivalence study comparing rate and extent of absorption of the active ingredient into the bloodstream is of limited utility for locally acting, nonsystemically absorbed drug products such as vancomycin capsules. Rather, for locally acting, nonsystemically absorbed drug products, a showing that the active or therapeutic ingredient in the proposed generic drug reaches the site of action at a rate and extent that is not significantly different from that of the RLD, along with satisfaction of other requirements for an ANDA, generally will permit FDA to conclude that the proposed generic drug can be expected to behave the same way in the body as the RLD.³³

The choice of appropriate bioequivalence study design is based on the ability of the study to compare the drug delivered by the two products at the particular site of action of the drug, and Congress assigned this decision to FDA. Congress intended to grant FDA wide discretion to establish bioequivalence standards on a drug-by-drug basis when it enacted the Hatch-Waxman Amendments,³⁴ and courts that have considered FDA's bioequivalence determinations consistently have upheld FDA's scientific discretion to determine how the bioequivalence requirement should be met for a given product or class of products.³⁵

D. Development of FDA's Current Bioequivalence Recommendations for Generic Vancomycin

1. Original Approval of Vancomycin Capsules

Vancomycin in some form has been used for the systemic treatment of *resistant staphylococcal infections* since the 1950s.³⁶ In 1958, FDA approved an NDA submitted by Lilly Research Laboratories (Lilly) for Vancocin Injection.³⁷ The Agency approved

³³ Section 505(j)(8)(C) of the FD&C Act.

³⁴ *Bristol-Myers Squibb v. Shalala*, 923 F. Supp. 212, 217 (D.D.C. 1996) ("the expressed desire of Congress, through the 1984 amendments, was that FDA retain its historically wide discretion in defining showings of bioequivalence") (internal citation and quotation omitted); *Schering Corp. v. FDA*, 51 F.3d at 399 ("there is no evidence that Congress intended to limit the discretion of the FDA in determining when drugs were bioequivalent for the purposes of ANDA approval").

³⁵ *Schering Corp. v. FDA*, 51 F.3d at 397-400 (3rd Cir. 1995); *Schering Corp. v. Sullivan*, 782 F. Supp. at 651 (deference afforded Agency's determination so long as it is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion"); *Fisons Corp v. Shalala*, 860 F. Supp. at 866-67 (D.D.C. 1994) ("[T]he factual determination of how bioequivalence is determined properly rests within the FDA's discretion."); *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d at 19 (the "high degree of deference" given to FDA's scientific determinations "has been applied to the FDA's determinations regarding which methodologies it determines are needed to test the bioequivalency of a given generic").

³⁶ Lucas, R.A., Bowtle, W.J., Ryden, R. "Disposition of Vancomycin in Healthy Volunteers From Oral Solution and Semi-Solid Matrix Capsules." *J. Clin. Pharm. Ther.* 1987; 12:27-31.

³⁷ National Academy of Sciences-National Research Council Drug Efficacy Study, Log No. 1828 (Vancocin HCl Vancomycin Hydrochloride Ampules USP) (original approval Oct. 23, 1958); see also Vancomycin HCl Injection, NDA 60-180. Drugs@FDA, available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>.

an amendment to the NDA for the marketing of Vancocin Solution for oral use in 1972,³⁸ and a new indication for this solution product for the treatment of *pseudomembranous colitis* produced by CDAD in 1983.³⁹

Lilly filed a new NDA for Vancocin Capsules⁴⁰ in 1985 for the treatment of SAE and CDAD.⁴¹ NDA applicants must demonstrate the in vivo bioavailability of the drug, or an appropriate basis for waiver of that requirement.⁴² Bioavailability is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.⁴³ On review of Lilly's application, FDA concluded that it could not assess systemic bioavailability of vancomycin HCl capsules from the in vivo bioavailability data Lilly had submitted because of low absorption of the capsule product. The Agency therefore permitted waiver of the in vivo bioavailability data requirement under 21 CFR 320.22(b)(3), which at that time permitted waiver of the bioavailability requirement for oral dosage forms not intended to be absorbed systemically.⁴⁴ In the course of its review, the Agency also concluded that the drug dissolved adequately to reach the targeted microorganisms in the GI tract.⁴⁵ FDA approved the capsule NDA in 1986.⁴⁶ ViroPharma licensed Vancocin Capsules from Lilly in 2004. The Vancocin oral solution product was withdrawn from the market in 2004, leaving the oral capsule product the only finished product for oral administration.⁴⁷

The Vancocin oral capsule is the only RLD for vancomycin capsules. Therefore, any ANDA for generic vancomycin HCl oral capsules must establish bioequivalence to Vancocin to gain approval.

³⁸ Summary Basis of Approval, NDA 61-667, Vancocin for Intravenous Injection, Food and Drug Administration, Division of Freedom of Information (HFI-35), Office of Shared Services, Office of Public Information and Library Services, 5600 Fishers Lane, Rockville, MD 20857.

³⁹ Vancocin Oral Solution ANDA 61667. Drugs@FDA, available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>.

⁴⁰ In the original capsule application, the Vancocin capsules were described as "pulvules." Summary Basis of Approval for NDA 50606, Vancomycin HCl Pulvules. Food and Drug Administration, Division of Freedom of Information (HFI-35), Office of Shared Services, Office of Public Information and Library Services, 5600 Fishers Lane, Rockville, MD 20857.

⁴¹ Id.

⁴² 21 CFR 320.21.

⁴³ 21 CFR 320.1(a).

⁴⁴ *Bioavailability and Bioequivalence Requirements*, 42 FR at 1648.

⁴⁵ Summary Basis of Approval for NDA 50-606, FDA Medical Officer Review for Pulvules Vancocin HCL, at 1 (July 10, 1985) (in review of dosage form and route of administration, concluding "[d]issolution tests show that vancomycin hydrochloride is released quickly from the formulation"); FDA Pharmacokinetic Evaluation Division Review for Pulvules Vancocin HCL, at 2 (June 1, 1985) ("[t]he firm's dissolution specification for the capsule formulation is acceptable to the Division of Biopharmaceutics").

⁴⁶ Vancocin HCl Capsules, NDA 050606, Drug Details, Drugs@FDA, available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory.

⁴⁷ Drugs@FDA, Vancomycin Hydrochloride Oral Solution (indicating discontinued status) (ANDA No. 061667), available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>.

2. FDA's Initial Recommendation of In Vivo Studies with Clinical Endpoints to Establish Bioequivalence for Vancomycin Capsules

FDA's initial recommendation for sponsors to establish bioequivalence to vancomycin capsules was to conduct in vivo studies with clinical endpoints. After oral administration, a vancomycin capsule releases the drug in the stomach and upper GI tract. The released drug completely dissolves in GI fluids, and then is transported along with GI fluids to its site of action in the lower GI tract.⁴⁸ The Clinical Pharmacology section of the approved product labeling for Vancocin describes vancomycin as poorly absorbed after oral administration.⁴⁹ Thus, plasma and urine concentrations of vancomycin are generally undetectable following oral administration, and traditional bioequivalence studies with pharmacokinetic (PK) measurements of such concentrations are of limited utility.⁵⁰ Until 2006, FDA recommended that generic applicants for vancomycin capsules submit an in vivo bioequivalence clinical endpoint study in lieu of in vivo PK measurements to demonstrate bioequivalence of generic vancomycin. In accordance with Agency practice at that time, FDA provided this in vivo clinical study bioequivalence recommendation in letters to members of the public upon request.⁵¹

3. FDA's 2006 Amendment of the Vancomycin Recommendation to Accept In Vitro Data to Establish Bioequivalence

In 2006, the Agency changed its bioequivalence recommendation for vancomycin capsules, permitting applicants to establish bioequivalence with certain in vitro dissolution studies in lieu of in vivo data. This change resulted from the Agency's evaluation of evolving scientific knowledge regarding the circumstances under which bioequivalence for certain classes of drug products may be established using in vitro dissolution data.

In August 2000, FDA had issued guidance setting forth a biopharmaceutics classification system for the waiver of in vivo data otherwise required by the Agency to demonstrate bioequivalence for immediate release (IR) solid oral dosage forms (the BCS Guidance).⁵² For such dosage forms, differences in the bioavailability of two products (i.e., differences in the rate and extent of absorption of a drug from two solid dosage products of those products in vivo) are caused by differences in dissolution.⁵³ Bioavailability at the site of action also can be affected by the drug product's solubility (extent to which the drug substance can be dissolved in a set amount of liquid) and permeability (proportional to the rate at which a drug substance is absorbed across the intestinal membrane). In its

⁴⁸ Draft Vancomycin BE Guidance at 2.

⁴⁹ Vancocin PI at 9.

⁵⁰ Draft Vancomycin BE Guidance at 3.

⁵¹ See, e.g., Letter fr. R. Patnaik, Ph.D., Acting Dir. OGD BE Div. (Dec. 17, 1996) (in response to letter inquiry, setting forth in vivo study requirement to demonstrate bioequivalence for vancomycin capsules).

⁵² Guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (Aug. 2000).

⁵³ Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R. "A Theoretical Basis for a Biopharmaceutical Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability." *Pharm. Res* 1995, 12:413-20.

scientific judgment, FDA concluded that if an RLD is a rapidly dissolving,⁵⁴ highly soluble⁵⁵ and highly permeable⁵⁶ IR dosage form, demonstration of rapid in vitro dissolution of a proposed generic IR solid dosage form under appropriate dissolution criteria should provide sufficient assurance of rapid in vivo dissolution, thereby ensuring the same bioavailability as (and thus bioequivalence to) the RLD.⁵⁷ Such products were described as “Class I” products in the guidance.⁵⁸ Based on these principles, the BCS Guidance explained how a Class I product could qualify for a waiver of a requirement for in vivo data, under section 320.22(e) of FDA’s regulations. The guidance did not expressly address locally acting oral drug products like vancomycin, nor did the guidance set forth the exclusive pathway to demonstrating bioequivalence through in vitro data. Rather, it outlined certain baseline scenarios in which the Agency concluded that in vitro data could be sufficient to establish bioequivalence and that a waiver of in vivo data that FDA otherwise required would be appropriate.

Shortly after publishing the BCS Guidance, FDA issued a draft guidance entitled *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products -- General Considerations* in response to a growing number of ANDA submissions and requests for bioequivalence recommendations for specific products.⁵⁹ In that guidance, FDA discussed 21 CFR 320.24(b), which, as detailed above, sets out the hierarchy of generally preferred methodologies for demonstrating bioequivalence for most drug products. The Agency noted that comparative clinical studies generally are disfavored for orally administered drugs. Such trials “[are] generally considered insensitive and [should] be avoided where possible (21 CFR 320.24).”⁶⁰ Although the guidance primarily concerned systemically acting oral drug products, it noted that bioequivalence for orally administered drugs intended for local action in the GI tract “can be achieved using bioequivalence studies with clinical efficacy and safety endpoints and/or suitably designed and validated in vitro studies, if the latter studies are either reflective of important clinical effects or are more sensitive to changes in product performance compared to a clinical study.”⁶¹

⁵⁴ The BCS Guidance provides that an IR drug product is considered rapidly dissolving “when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using *U.S. Pharmacopeia* (USP) Apparatus at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less” in three different media (BCS Guidance at 2-3).

⁵⁵ An IR drug product is considered highly soluble under the BCS Guidance “when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5.” Id. at 2.

⁵⁶ An IR drug product is considered highly permeable under the BCS Guidance “when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.” Id. at 2.

⁵⁷ The BCS Guidance was premised on the well-established pharmacology principle that for a drug to become available at the site of action, it must first dissolve into solution. Id. at 2.

⁵⁸ Id. at 1.

⁵⁹ Draft guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products -- General Considerations* (Oct. 2000). The guidance was finalized in 2003 (the *BA/BE Guidance* (see n. 29)).

⁶⁰ Id. at 9-10.

⁶¹ Id. at 20.

During this time period, FDA's expert advisory committees were also considering in vitro methodologies for establishing bioequivalence. At a March 2003 meeting, FDA's Advisory Committee for Pharmaceutical Science (ACPS) considered the issue of bioequivalence for locally acting drug products applied topically to treat diseases or conditions of the skin. At that meeting, Dr. Dena Hixon, then Associate Director for Medical Affairs in FDA's Office of Generic Drugs (OGD), noted that at that time most locally acting drugs required clinical endpoint studies to demonstrate bioequivalence.⁶² Dr. Hixon then outlined challenges that the Agency faced with clinical endpoint studies, including increased variability compared to pharmacokinetic endpoints, longer study duration, endpoint study cost, safety concerns related to the patient population, and lack of consistency between studies.⁶³ In October 2004, FDA asked the ACPS specifically to consider when dissolution testing could be used to establish bioequivalence for locally acting GI drugs. The Committee considered a range of products, and discussed whether dissolution testing, along with PK studies for some drug products that demonstrated certain levels of permeability, could be acceptable to establish bioequivalence for locally acting GI products, but the Committee did not vote on any recommendations.⁶⁴

After the 2004 ACPS meeting, a generic applicant for vancomycin capsules submitted in vitro data that purported to show that vancomycin is "rapidly dissolving" under the BCS Guidance definition thereby justifying waiver of the in vivo clinical data requirement in place at that time.⁶⁵ FDA conducted a separate analysis to confirm that vancomycin is highly soluble, but did not independently assess the ANDA applicant's dissolution data.⁶⁶ On consideration of the ACPS's discussions regarding scientific developments on in vitro dissolution data,⁶⁷ developments in the greater scientific community regarding in vitro

⁶² Tr. of Mar. 13, 2003, Meeting of FDA Advisory Committee for Pharm. Sci. (2003 ACPS Tr.), at 189.

⁶³ Id. at 189-93.

⁶⁴ See, e.g., Tr. of Oct. 20, 2004, Meeting of FDA Advisory Committee for Pharm. Sci. (2004 ACPS Tr.), at 289, 295, 336-37. You claim that the Committee's Final Report of the meeting, which states that "[i]n conclusion, the Committee agreed it was difficult to reach a consensus, but that in order to provide bioequivalence in vitro dissolution along with pharmacokinetics should be acceptable" (Summary Minutes of ACPS October 19-20, 2004, Meeting, at 6 (Nov. 16, 2004)) is not accurate because the Advisory Committee did not formally vote to endorse in vitro testing for any particular local GI drug or class of GI drugs at the 2004 meeting. VP May 17, 2007 Supp., at 7; VP Dec. 30, 2007, Supp. at 7; VP Mar. 18, 2009, Comments to Draft Guidance Docket No. 2008-D-0626 (VP Draft Guidance Resp.) at 21. You are correct that the Committee did not formally "agree" because it did not vote on the appropriate methodology, but you have not demonstrated that this summary of the proceedings (or an FDA employee's subsequent reference to this summary, VP Draft Guidance Resp. at 24) has, as you assert, compromised the Committee's subsequent consideration of appropriate bioequivalence standards for locally acting oral dosage forms including vancomycin (VP Draft Guidance Resp. at 21).

⁶⁵ Vancomycin is not highly permeable, and therefore does not fall directly within the BCS Guidance classification of drugs for which a waiver of in vivo data could be requested. However, for drugs that act locally in the GI tract such as vancomycin, it is the poor permeability that generally assures no loss of bioavailability at the site of action due to absorption. For this reason, such drugs may be appropriate for in vitro dissolution testing under certain circumstances even though they are not Class I drugs as described in the BCS Guidance.

⁶⁶ CDER Division of Product Quality Research (DPQR) 2008 Vancomycin Solubility Study (Feb. 5, 2008) (DPQR 2008 Solubility Study).

⁶⁷ See note 64, above.

dissolution methodologies,⁶⁸ the dissolution data submitted by the generic applicant, and data showing that vancomycin HCl is “highly soluble” under BCS standards, FDA revised its generic vancomycin bioequivalence recommendation in February 2006. The revised recommendation (2006 Revised Recommendation) stated that “[v]ancomycin is a highly soluble drug and the reference listed drug (RLD) product is rapidly dissolving. Waivers of in vivo bioequivalence testing can be requested in [ANDAs], provided that the test product is rapidly dissolving at the conditions specified in the [BCS guidance].”⁶⁹ The 2006 Revised Recommendation noted that FDA had concluded that such testing would be more sensitive than clinical trials in detecting differences in product performance. In addition, the recommendation delineated the specific dissolution data recommended to demonstrate bioequivalence.⁷⁰ FDA provided the 2006 Revised Recommendation in individual letters to at least 16 parties, including multiple pharmaceutical companies that had requested information related to bioequivalence recommendations for generic vancomycin.⁷¹

4. ViroPharma’s 2006 Petition for Stay of Action

On March 17, 2006, you filed a petition for stay of approval of any ANDAs for generic vancomycin capsules on behalf of ViroPharma.⁷² Specifically, you requested that the Agency:

- (a) Require ANDA applicants for vancomycin capsules to use the most rigorous scientific method that will demonstrate a rate and extent of drug release to the site of action consistent with good medicine and science;
- (b) Require ANDA applicants for vancomycin capsules to demonstrate that the stability of a vancomycin capsule ANDA product is at least as good as that of Vancocin;
- (c) Require any ANDA applicant relying on Vancocin to provide evidence that its product is bioequivalent to Vancocin along the entire gastrointestinal tract;
- (d) Convene a joint meeting of the ACPS and the Advisory Committee for Anti-infective Drug Products, with industry participation, to examine the relevant data and information related to vancomycin delivery to the GI tract for the purpose of developing appropriate and consistent standards for the approval of new vancomycin capsule products;

⁶⁸ See also note 86, below, for additional detail on the scientific community’s developments regarding use of dissolution data to demonstrate bioequivalence.

⁶⁹ See, e.g. Letter fr. D. Conner, Director, Div. Bioequivalence, CDER Office of Generic Drugs to Dr. B. Leung, Infinum Capitol Corp. (Mar. 1, 2006), attached as Ex. 1 to VP May 31, 2006, Supp.

⁷⁰ Id.

⁷¹ FDA had distributed its previous recommendation of a clinical endpoint study methodology in the same manner. As discussed in section II.C.8(a), below, in 2007 FDA changed this “individual letter” practice of distributing bioequivalence recommendations for specific products to a process by which such recommendations generally are issued publicly as draft guidances.

⁷² VP Petition for Stay of Action, at 1 (Mar. 17, 2006). You amended the petition on March 30, 2006, again requesting a stay of any vancomycin ANDA or 505(b)(2) approval on the ground that the Agency had not established and applied appropriate standards for approving these vancomycin applications. VP Amended Petition for Stay of Action, at 1 (Mar. 30, 2006) (VP Am. Pet.)

- (e) Validate with both the FDA Medical Policy Coordinating Committee and the FDA Biopharmaceutics Coordinating Committee the scientific and medical appropriateness of the approval standards for a new locally acting vancomycin capsule product; and
- (f) Provide an opportunity for public review and comment on the appropriate approval standards for a new locally acting vancomycin capsule product.

(VP Am. Pet. at 1-2.)

Shortly thereafter you supplemented your petition to include data that you asserted demonstrated that Vancocin is not rapidly dissolving.⁷³

In response to your petition, FDA commissioned a study by FDA's Division of Product Quality Research (DPQR) within the Center for Drug Evaluation and Research (CDER) to determine the dissolution characteristics of Vancocin Capsules.⁷⁴ DPQR completed the study in February 2008, and concluded that Vancocin Capsules dissolved at a rate faster than 85% in 45 minutes at a range of predetermined pH conditions encountered in the GI tract, with the exception of two lots of the RLD drug.⁷⁵ The study also found that Vancocin Capsules dissolved at a rate faster than 85% in 30 minutes when the pH of the dissolution media was pH 1.2,⁷⁶ and, with the exception of one lot, all the products were found to dissolve over 90% in 60 minutes.⁷⁷ The study observed that Vancocin is not "rapidly dissolving" as defined in the BCS Guidance, however, which requires 85% dissolution within 30 minutes (rather than 45) at all of the predetermined pH levels.⁷⁸

FDA had also previously commissioned a DPQR study on the solubility of vancomycin under specific pH conditions that were within the extremes of normal physiological pH of the human GI tract.⁷⁹ As described above, under the BCS Guidance, a drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1-7.5. The high solubility boundary layer for vancomycin is based on its highest dose strength of 250 mg dissolved in 250 mL of aqueous media. Upon application of these criteria, the study found that at all BCS pH levels, Vancocin required less than 250 mL to dissolve the highest dosage strength of 250 mg.⁸⁰ Vancomycin therefore was confirmed to be highly soluble under BCS standards.

⁷³ VP June 30, 2006, Supp., at 36-41 (challenging bioequivalence recommendation on scientific grounds).

⁷⁴ DPQR 2008 Vancomycin Dissolution Study (Feb. 5, 2008) (DPQR 2008 Dissolution Study). While the study involved the examination of Vancocin capsules and of other vancomycin capsules, DPQR's conclusions with respect to the dissolution of vancomycin capsules were based only on the division's findings with respect to Vancocin (Id. at 14).

⁷⁵ Id. at 34.

⁷⁶ Id.

⁷⁷ Id. at 14.

⁷⁸ Id.

⁷⁹ DPQR 2008 Solubility Study.

⁸⁰ Id. at 17.

In July 2008, FDA convened the ACPS⁸¹ to consider bioequivalence for locally acting GI drug products with low solubility. At this meeting the Committee also discussed bioequivalence for highly soluble GI oral drug products, and the use of in vitro dissolution data over the relevant pH levels to demonstrate bioequivalence for highly soluble products.⁸² The Committee then discussed the role of excipients, or inactive ingredients, in such products, whether they can affect dissolution or drug performance, and if so, whether FDA should require a generic product seeking to use in vitro dissolution data to show bioequivalence to demonstrate that excipients in its product are qualitatively (Q1) and quantitatively (Q2) the same as the RLD.⁸³

5. FDA's 2008 Amendment to the Vancomycin Bioequivalence Recommendation

In December 2008, FDA issued the Draft Vancomycin BE Guidance. With this guidance, FDA amended the 2006 Revised Recommendation to incorporate the Agency's findings from the DPQR dissolution studies and other relevant information, including submissions to this citizen petition docket. FDA concluded that notwithstanding that vancomycin capsules are not "rapidly dissolving" under the BCS Guidance, in vitro dissolution studies still are an appropriate method of demonstrating bioequivalence for vancomycin capsules. As described in the Draft Vancomycin BE Guidance,⁸⁴ two key factors led FDA to this conclusion. First, vancomycin acts primarily in the colon, and GI transit times for drugs to reach the colon average 3 to 4 hours. Dissolution even at 60 minutes, which all but one Vancocin lot demonstrated in the 2008 DPQR Dissolution Study, ensures that even in patients with faster transit times than healthy subjects, vancomycin will be completely dissolved when it reaches the colon.⁸⁵ Second, as discussed in detail in section II.B.2(d), similar dissolution profiles across the pH ranges recommended in the bioequivalence recommendation ensure that generic and reference products will have equivalent release even in patients with extremely short GI transit times or in conditions that would not permit either the reference or the generic product to completely dissolve. FDA also considered the fact that the use of 30 minutes in the BCS scheme generally is considered to be a conservative baseline, and that the consensus among academic, industry, and regulatory scientists is that 85% dissolution at 60 minutes is sufficient to permit demonstration of bioequivalence by use of in vitro data.⁸⁶

⁸¹ Prior to its meeting in July 2008, the name of the ACPS was changed to the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. For the sake of consistency, we will continue to refer to this committee as the ACPS in this response.

⁸² See, e.g., Tr. of July 23, 2008, Meeting of FDA Advisory Committee for Pharm. Sci. (2008 ACPS Tr.), at 31-33, 36-38.

⁸³ Id. at 31, 83, 207-08.

⁸⁴ Draft Vancomycin BE Guidance at 2.

⁸⁵ See section II.B.2(g) below for a detailed discussion of this conclusion.

⁸⁶ Polli, J.E., Yu, L.X., Cook, J.A., Amidon, G.L., Borchardt, R.T., et al., "Summary Workshop Report: Biopharmaceutics Classification System--Implementation challenges and Extension Opportunities. *J. Pharm. Sci.* 2004; 93:1375-81 (BCS Implementation Article). As a general matter, the BCS Guidance is considered internationally to be conservative with respect to the class boundaries of solubility and permeability, and the dissolution criteria. Yu, L.X., Amidon, G.L., Polli, Z.E., Zhao, H., Mehta, M.U., Conner, D.P., Shah, V.P., Lesko, L.J., Chen, M.-L., Less, V.H.L., Hussain, A.S. "Biopharmaceutics Classification System: The Scientific Basis for Biowaiver Extensions." *Pharm. Res.* 2002;19:921-25.

The Draft Vancomycin BE Guidance details FDA's recommendation for establishing bioequivalence for generic vancomycin capsules. First, the draft guidance provides that in vitro dissolution studies may demonstrate bioequivalence for test formulations that are Q1/Q2 the same as the RLD with respect to inactive ingredients. FDA included the Q1/Q2 criterion because the Agency concluded that generic applicants might use different inactive ingredients that may affect the transport, dissolution, absorption, and/or effectiveness of the drug.⁸⁷ For proposed generic vancomycin products that are not Q1/Q2 the same as the RLD with respect to inactive ingredients, the draft guidance recommends in vivo bioequivalence studies with clinical endpoints, unless the ANDA sponsor can provide evidence that the differences in excipients will not affect the safety or effectiveness of the proposed generic drug product.⁸⁸

The draft guidance and its accompanying *Federal Register* notice make clear that the recommended bioequivalence methodologies are not the exclusive means by which an

In 2006 the World Health Organization (WHO) provided guidance to regulatory agencies around the world and recognized BCS-based biowaivers. WHO extended FDA's BCS-based biowaiver approach to highly soluble and poorly permeable (BCS Class III) drugs whose formulations exhibit very rapid dissolution, and to a select group of poorly soluble and highly permeable (BCS Class II) drugs that are highly soluble and rapidly dissolving at pH 6.8. In 2002 and 2007, FDA co-sponsored two scientific workshops on implementation and extensions of BCS-based biowaivers. BCS Implementation Article at 1376; Polli, J.E., Abrahamsson, B.S.I., Yu, L.X., Amidon, G.L., Baldoni, J.M., et al., Summary Workshop report: Bioequivalence, Biopharmaceutics Classification System and Beyond, *AAPS J.*, 2008;10(2):373-9 (BCS and Beyond Article). Over 400 national and international participants from government, industry, and academia attended these two workshops, signifying the importance of this dissolution-based biowaiver approach. The 2002 workshop report states “[c]onsensus held that this (rapid dissolution) definition should be broadened to include products that provide no less than 85% dissolution in 60 min.” BCS Implementation Article, at 1379. The 2007 workshop report states “[a] key highlight of the workshop was the continued scientific support for biowaivers for Class III compounds whose formulations exhibit very rapid dissolution” BCS and Beyond Article, at 374.

⁸⁷ Draft Vancomycin BE Guidance at 1. You correctly note that FDA does not expressly cite legal authority in the draft guidance. VP Mar. 25, 2010, Supp. at 27. This does not mean that FDA lacked authority to set forth this recommendation, however. As set forth above in section I.B, FDA has clear authority to determine bioequivalence standards for specific drug products in accordance with the statute and regulations. (See section 505(j)(7)(A)(i) of the FD&C Act; see also 21 CFR 320.1(f) and 21 CFR 324). FDA cited this authority in its general guidance that describes FDA's process for issuing guidances recommending bioequivalence methodologies for specific products, which is discussed in detail below. Draft guidance for industry on *Bioequivalence Recommendations for Specific Products*, at 2 (May 2007) (citing section 505(j)(8)(C) and 21 CFR 320.24). The fact that FDA did not expressly cite its authority in the Draft Vancomycin BE Guidance does not render that authority inoperative. (Note that FDA issued the final version of this guidance in June 2010, and further citations are to the final version (Specific Product BE Guidance).

⁸⁸ Draft Vancomycin BE Guidance at 1. Your assertion that the 2008 draft guidance constituted a break from the consideration given to products that fall directly within the BCS Guidance is misplaced. VP Draft Guidance Resp., at 19. Far from abandoning the scientific principles that provided the foundation of the BCS Guidance, FDA used those scientific principles as a springboard to investigate and identify more sensitive, accurate and reproducible methodologies for demonstrating bioequivalence. Also contrary to your assertion (*id.*) otherwise, the draft bioequivalence recommendation for vancomycin HCl capsules was consistent with the 2004 ACPS's discussion that dissolution testing should be acceptable to establish bioequivalence for locally acting GI products, and that PK studies are not appropriate for demonstrating the bioequivalence of vancomycin capsules because its drug levels are generally not detectable in the plasma or urine due to very limited absorption. Draft Vancomycin BE Guidance at 2.

ANDA applicant could meet the statutory requirement.⁸⁹ As the draft guidance expressly notes, the recommendations represent the Agency's "current thinking on this topic" and "an alternative approach" may be used if such "approach satisfies the requirements of the applicable statutes and regulations."⁹⁰ To provide additional information to persons considering the draft guidance, the recommendations also include a significant amount of background information and set forth the Agency's scientific rationale for the in vitro and in vivo bioequivalence recommendations.⁹¹

The Agency issued the Draft Vancomycin BE Guidance under a process FDA had introduced in May 2007.⁹² As described in FDA's Specific Product BE Guidance, FDA has disseminated product-specific bioequivalence recommendations in draft guidance form since 2007. The availability of bioequivalence recommendations for specific products is announced in the *Federal Register*. As a result, bioequivalence recommendations are disseminated more broadly than would have been possible using the previous "letter" format, in which product-specific letters only were sent to members of the public who had requested such information. This "product specific guidance" method also is intended to provide a meaningful opportunity for the public to consider and comment on those recommendations.⁹³

ViroPharma and others requested, and FDA granted, additional time to submit comments on the Draft Vancomycin BE guidance. ViroPharma submitted its comments on March 18, 2009, and in two additional submissions.⁹⁴ FDA also received and carefully considered comments from a variety of parties, including generic and other innovator drug manufacturers, doctors, patients, patient advocacy groups, and concerned citizens.⁹⁵

⁸⁹ Draft Vancomycin BE Guidance at 1.

⁹⁰ Id. See also availability of draft guidance on *Bioequivalence Recommendation for Vancomycin HCl*, 73 FR 76362, 76363 (Dec. 16, 2008).

⁹¹ Draft Vancomycin BE Guidance, at 2-3.

⁹² Specific Product BE Guidance. You submitted comments to the *draft* Specific Product BE Guidance on August 29, 2007. Letter fr. ViroPharma to FDA re. Draft Guidance for Industry on Bioequivalence Recommendations for Specific Products, Docket No. 2007-D-0168 (Aug. 29, 2007), attached as exhibit to VP Jan. 11, 2008, Supp., at 2.

⁹³ Specific Product BE Guidance at 1. You have requested information on the process by which FDA publishes draft guidances (VP Mar. 25, 2010, Supp. at 4). As a general matter, the Agency develops product-specific bioequivalence recommendations based on its understanding of the characteristics of the RLD, information derived from published literature, Agency research, and consultations within different offices in CDER, as needed, based upon the novelty or complexity of the bioequivalence considerations. Specific Product BE Guidance at 2-3. FDA does not, as you contend, publish product-specific guidances only when it lacks validation for the methodologies proposed therein and seeks evidence from outside sources (VP Mar. 25, 2010, Supp. at 22).

⁹⁴ Letter fr. ViroPharma to FDA Docket No. 2008-D-0626 (Dec. 19, 2008). Several parties opposed this request for an extension, claiming ViroPharma improperly was trying to delay approval of generic drugs. See, e.g. Feb. 2, 2009, Letter fr. M. Dotzel, Zuckerman Spaeder LLP, to FDA Docket No. 2008-D-0626, at 1. Upon consideration of the filings, FDA granted any interested party 30 additional days to file comments (*Draft guidance for industry on Bioequivalence Recommendation for Vancomycin HCl; Extension of Comment Period*, 74 FR 6640, 6640-41 (Feb. 10, 2009)). VP filed its comments on March 18, 2009. VP Draft Guidance Resp. ViroPharma submitted additional comments to the draft guidance docket on April 3, 2009, and May 18, 2009.

⁹⁵ See FDA Docket No. 2008-D-0626, available at <http://www.regulations.gov/search/Regs/home.html#docketDetail?R=FDA-2008-D-0626>.

6. The 2009 ACPS's Unanimous Endorsement of FDA's 2008 Vancomycin BE Recommendation

In August 2009, FDA convened the ACPS for the express purpose of considering the use of in vitro dissolution methods to establish bioequivalence for vancomycin capsule products. FDA convened this meeting to solicit external scientific expert opinion on the draft in vitro data recommendation, and to ensure that interested parties had a full opportunity to consider and comment on the proposed bioequivalence standard for generic vancomycin. The questions presented to the Committee for consideration were:

1. For potential Vancomycin HCl Capsule generic products that:

- (a) contain the same active and inactive ingredients in the same amounts as Vancocin Capsules,
- (b) meet currently accepted standards for assay, potency, purity, and stability (equivalent to those in place for Vancocin Capsules), and
- (c) are manufactured according to cGMP [current good manufacturing practices as set forth in FDA regulations]:

Do you accept the FDA recommendation to demonstrate bioequivalence through equivalent dissolution in media of pH 1.2, 4.5, and 6.8?

2. If your answer to (1) is no:

What potential difference between generic Vancomycin HCl Capsules and Vancocin Capsules is not accounted for in the FDA recommendation?

3. For potential Vancomycin HCl Capsule ANDA products that:

- (a) do not contain the same inactive ingredients in the same amounts as Vancocin Capsules,
- (b) meet currently accepted standards for assay, potency, purity, and stability, (equivalent to those in place for Vancocin Capsules), and
- (c) are manufactured according to cGMP:

Do you accept the FDA recommendation of a clinical endpoint bioequivalence study in patients to evaluate the effect of the different inactive ingredients?⁹⁶

Prior to the meeting, ViroPharma submitted a letter challenging certain statements made in the background materials that had been distributed to the Committee members and the public.⁹⁷ ViroPharma's letter and FDA's response to the letter were provided to the

⁹⁶ *Questions for the Committee*, FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (Aug. 4, 2009), available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM179396.pdf>.

⁹⁷ Letter fr. ViroPharma to FDA Docket No. 2009-N-0664 (July 31, 2009), at 4, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM175010.pdf>.

Committee members, and were made part of the public record pertaining to the meeting before the August ACPS meeting date.⁹⁸

FDA and industry representatives, including representatives of ViroPharma, presented materials at the meeting. Members of the public also had an opportunity to comment. The Committee conducted an extensive discussion of the scientific bases for the bioequivalence recommendation in the Draft Vancomycin BE Guidance, including many of the scientific concerns you have raised in your citizen petition and in comments to the draft guidance docket (discussed in detail below).

At the conclusion of the meeting, the Committee voted unanimously in favor of endorsing the bioequivalence recommendation set forth in the Draft Vancomycin BE Guidance.⁹⁹ Because the Committee voted unanimously on question #1, the group did not vote on question #2.¹⁰⁰ The Committee conducted a brief discussion of question #3, but FDA removed the question from a vote because the Committee did not have sufficient time to fully consider and make a recommendation on this question.¹⁰¹

7. ViroPharma's Freedom of Information Act Requests

In March 2006, ViroPharma filed with the Agency a request under the Freedom of Information Act (FOIA)¹⁰² for documents relating to the 2006 Revised Recommendation set forth in the letters sent to entities that had requested such information. ViroPharma made a second request in December 2008 for documents related to the Draft Vancomycin BE Guidance and any communications to third parties regarding the methodology set out in the Draft Vancomycin BE Guidance prior to December 15, 2008. FDA produced documents responsive to these requests on March 20 and October 28, 2009, and supplemented this production on December 9, 2009, February 24, 2010, and April 22,

⁹⁸ Id. at 1-3.

⁹⁹ Tr. of Aug. 4, 2009, Meeting of FDA ACPS (2009 ACPS Tr.), at 383-392.

¹⁰⁰ You erroneously contend that the August 2009 Advisory Committee proceedings were tainted by a discussion of the high costs of Vancocin and of bioequivalence studies with clinical endpoints, and that as a result, the Committee's endorsement of the in vitro dissolution data pathway is not reliable. VP Oct. 6, 2009, Supp. at 10-11. It is neither surprising nor inappropriate that the Committee discussed the lower cost of generic vancomycin. The potential benefit to consumers through increased competition in the drug industry is a primary purpose of the Hatch-Waxman Amendments. *Teva Pharm. Indus. v. Crawford*, 410 F.3d 51, 55 (D.C. Cir. 2005) (“Congress sought to strike a balance between incentives, on one hand, for innovation, and on the other, for quickly getting lower-cost generic drugs to market”); *Mead Johnson Pharm. Group v. Bowen*, 838 F.2d at 1332, 1333 (D.C. Cir. 1988). More broadly, courts have long recognized that “a primary purpose” of the FD&C Act is the protection of the “ultimate consumer’s economic interest.” *U.S. v. Article Consisting of 216 Cartoned Bottles*, 409 F.2d 734, 740 (2d Cir. 1969). See also n. 31, supra. Discussion of these policies during a committee meeting considering generic drug approval was not improper. There also is clear indication that the Committee members differentiated between cost concerns and the scientific questions related to the appropriate bioequivalence standard. See, e.g., 2009 ACPS Tr., at 219 (comment by Committee member Harriet B. Nemhard, Ph.D.) (“I appreciated the case made in terms of clinical practice and price and duplicating suppliers and so forth. But in terms of the bioequivalence, the innovator makes a case for addressing Q3 in the standards. I find that’s an interesting idea but I’m not sure the case was fully made”).

¹⁰¹ 2009 ACPS Tr. at 393-411.

¹⁰² Freedom of Information Act of 1966, Pub.L. 89-554, 80 Stat. 378.

2010. ViroPharma and FDA disagreed on several matters related to the Agency's production. ViroPharma sued FDA on December 16, 2008, alleging unlawful withholding of Agency records.¹⁰³ The parties filed cross-motions for summary judgment, and on March 16, 2012, the court granted in part and denied in part FDA's motion for summary judgment, and denied ViroPharma's motions for summary judgment and in camera review (judicial review of the documents that FDA withheld from production due to a claim of privilege). The court also directed the Agency to further explain the Agency's reasons for withholding certain documents.¹⁰⁴ To the extent that any issues you raise in your petition or supplements concern these FOIA requests and/or the adequacy of FDA's production,¹⁰⁵ the Agency declines to address those issues in this response due to the pending civil action.

II. DISCUSSION

A. FDA's Recommended Methodology for Demonstrating Bioequivalence for Vancomycin Capsules Is the Most Accurate, Sensitive, and Reproducible Approach Available

The fundamental question raised by your petition is whether the bioequivalence recommendation set forth in the Draft Vancomycin BE Guidance and unanimously endorsed by the ACPS in August 2009, is the most accurate, sensitive, and reproducible approach available among those set forth in 21 CFR 320.24(b), thereby permitting the approval of an ANDA that applies FDA's recommendation. Upon consideration of the foregoing history, the materials filed in the dockets for this citizen petition and the Draft Vancomycin BE Guidance, the discussion and unanimous endorsement of the August 4, 2009, ACPS that directly considered bioequivalence for vancomycin capsules, and the relevant scientific and legal authorities, FDA concludes for the reasons set forth below that your scientific challenges to the recommended bioequivalence methodology set forth in the Draft Vancomycin BE Guidance are unsupported, and that the recommendation is the most accurate, sensitive, and reproducible approach for demonstrating bioequivalence of generic vancomycin capsules.

¹⁰³ Complaint at ¶ 40-43, *ViroPharma Inc. v. U.S. Dept. of Health and Human Services*, Civil Action No. 08-2189 (D.D.C., filed Dec. 16, 2008) (Friedman, J.).

¹⁰⁴ Order, at 1, *ViroPharma Inc. v. U.S. Dept. of Health and Human Services*, Civil Action No. 08-2189 (D.D.C. Mar. 16, 2012).

¹⁰⁵ See, e.g. VP Jan. 15, 2010, Supp. at 6 (requesting that FDA confirm no responsive documents to ViroPharma FOIA request), 28-29; VP Mar. 25, 2010, Supp. at 1-2, 12-15.

1. FDA's 2008 Recommended Bioequivalence Methodology

The Draft Vancomycin BE Guidance is set forth in full directly below:

Contains Nonbinding Recommendations

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 (Q1) (i.e., contain all of the same inactive ingredients) and quantitatively (Q2) 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 Q1 and Q2 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 $f_2^{[106]}$ test 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.

¹⁰⁶ Dissolution profiles may be compared using the following equation that defines a similarity factor (f_2):

$$f_2 = 50 \text{ LOG } \left\{ \left[1 + 1/n \sum^n (R - T)^2 \right]^{-0.5} \times 100 \right\}$$

2. In Vivo Option

If the test product formulations are not Q1 and Q2 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.

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[107]}
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

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

¹⁰⁷ Approved label for Vancocin® HCl Capsules, USP © , 2005, ViroPharma Inc., Exton, PA, 19431.

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 tract,^{3[108]} and the dosage form is expected to be in contact with a relatively large fluid volume,^{4[109]} vancomycin is expected to be in solution long (e.g., hours) before it reaches the site of action in the lower GI tract.^{5[110]} 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 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.

¹⁰⁸ 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).

¹⁰⁹ 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).

¹¹⁰ 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).

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).^{5[11]}

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.

* * * *

B. ViroPharma's Scientific Challenges to the Bioequivalence Recommendation Lack Merit

You have asserted that, notwithstanding the 2009 ACPS's unanimous endorsement of this methodology, the vancomycin bioequivalence recommendation is scientifically flawed on several grounds. Upon careful review of your submissions, FDA disagrees.

¹¹¹ 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.

1. Clinical Endpoint Trials Are Not the Most Sensitive Method By Which Bioequivalence Can Be Established for Vancomycin

You argue that FDA must require data from in vivo clinical endpoint studies in CDAD patients to demonstrate bioequivalence. FDA has determined, however, that clinical endpoint studies are not always the most sensitive methodology to demonstrate bioequivalence for locally acting GI products due to increased variability compared to pharmacokinetic or in vitro dissolution studies. In particular, in vivo clinical endpoint studies measure formulation differences indirectly rather than directly, include confounding variables such as different severities of disease, may have variability in the definition of the instrument used to measure efficacy (i.e., what is being used for the primary endpoint), and may have difficulty in assessing dose response (the pattern of physiological response to varied dosage). Moreover, clinical endpoint studies require a longer study duration to assess clinical endpoint(s) than the time required to complete in vitro dissolution studies, and may not be able to use the most sensitive dose because of safety concerns related to the patient population stemming from a disparity between the dosing strength that may best reveal differences in formulation and the strength that is necessary to adequately treat the disease. There also is a lack of consistency between studies that contribute to a lack of sensitivity of clinical endpoint studies for locally acting GI products.¹¹² This conclusion is consistent with the ACPS discussions of this issue.¹¹³ This conclusion also is consistent with FDA's recommended bioequivalence methodology for a number of locally acting drug products, for which FDA has expressly determined that use of in vivo clinical endpoint trials to demonstrate bioequivalence is not the most sensitive method.¹¹⁴ FDA's recognition of the shortcomings of clinical endpoint studies for orally administered drugs is underscored in the *BA/BE Guidance*, in which the Agency generally recommends that "that the use of comparative clinical trials as an approach to demonstrate [bioequivalence] generally be considered insensitive and be avoided where possible."¹¹⁵

¹¹² See 2008 ACPS Tr. at 42-63.

¹¹³ Id.

¹¹⁴ See, e.g., May 7, 2008 Letter fr. FDA to W. Rakoczy, at 7 (rejecting a request to require in vivo bioequivalence testing, concluding that "given that [the acarbose tablet] acts locally in the GI tract and is not systemically absorbed, we believe that the appropriate methodology for establishing bioequivalence may be in vitro testing [for Q1/Q2 products] or in vivo testing with a pharmacodynamic endpoint"), available at <http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480552878>; Aug. 20, 2010 Letter fr. FDA to I. Hara, Warner Chilcott Co. LLC. at 11 (concluding comparative clinical endpoint studies "less sensitive, accurate and reproducible" than in vitro dissolution and pharmacokinetic studies for mesalamine, a locally acting GI product); Dec. 8, 2010 Letter fr. FDA to J. Jonas, Shire Development Inc., at 6-7 (denying request to require clinical efficacy studies to demonstrate bioequivalence for locally acting lanthanum carbonate oral chewable tablets, concluding that "comparative in vivo trials wold be less sensitive, accurate or reproducible than [pharmacodynamics] or properly designed and conducted in vitro dissolution and binding studies with respect to the capability to detect product differences").

¹¹⁵ BA/BE Guidance at 9.

2. The Recommended In Vitro Dissolution Study Adequately Accounts for Disease-Specific Attributes of the GI Tract

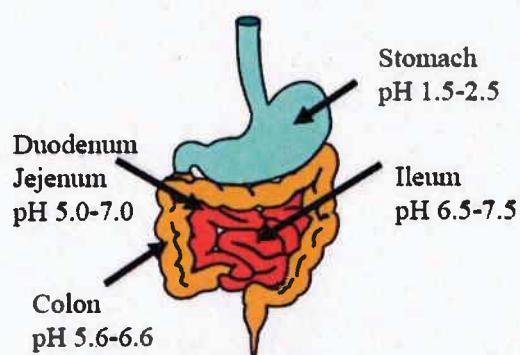
In your petition, you assert that the bioequivalence methodology set forth in the Draft Vancomycin BE Guidance is not the most sensitive, accurate, and reproducible for vancomycin because it fails to adequately take into account the disease states of CDAD and SAE patients on several grounds, and that the only methodology that is adequate is an in vivo study with clinical endpoints in patients with CDAD. FDA does not agree. Your specific points are addressed below.

(a) Background on the GI Tract of CDAD and SAE Patients

Some background on the GI tract of CDAD and SAE patients is helpful in addressing your claims. The GI tract refers to the esophagus, stomach, and intestine. The upper GI tract consists of the esophagus, stomach, and duodenum. The lower GI tract includes most of the small intestine and all of the large intestine. The small intestine has three parts: duodenum, jejunum, and ileum. The large intestine consists of cecum, colon, and rectum.

As shown in Figure 1, the mean gastric pH in healthy volunteers ranges between 1.5 and 2.5 under fasted conditions. In the intestine, there is a pH gradient, with pH values tending to rise moving down the small intestine. In the fasted state, the mean pH value in the duodenum increases from 5.0 at the pyloric sphincter to 6.0 at the distal end of the duodenum. The pH gradient in the jejunum ranges from 6.0 to 7.0, and increases further to 7.5 in the ileum.¹¹⁶ The pH of the colon can vary, depending on bacterial activity and undigested carbohydrates, with the result that the colon pH is lower than that of the terminal ileum and is generally about pH 6.0.¹¹⁷

Fig 1. Stomach and Intestine pH¹¹⁸



¹¹⁶ Willmann, S., Schmitt, W., Keldenich, J., Lippert, J., Dressman, J.B.. "A Physiological Model for the Estimation of the Fraction Dose Absorbed in Humans." *J Med Chem* 2004;47:4022-31.

¹¹⁷ Cummings, J.H., Pomare, E.W., Branch, W.J., Naylor, C.P.E., Macfarlane, G.T. "Short Chain Fatty Acids in Human Large Intestine, Portal, Hepatic, and Venous Blood." *Gut* 1987;28:1221-7.

¹¹⁸ Lionberger, R, OGD Slide Presentation, at 18, Aug. 4, 2009, ACPS Meeting,

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM179409.pdf>.

Table 1 below compares the gastrointestinal conditions of healthy subjects and CDAD and SAE patients at fasted state. In patients, it is possible that the pH profile may differ from that in healthy subjects. Some patients may have pH as high as 7.5.¹¹⁹ Table 2 details vancomycin solubility at different pH levels.

Table 1. Gastrointestinal conditions of healthy subjects and CDAD and SAE patients under fasted state.

	Healthy subject ¹²⁰	CDAD and SAE Patients ¹²¹
Stomach pH	1.0-2.5 ¹²²	4-7
Stomach fluid volume	45 ± 18 ml ¹²³	20-30 ml
Stomach transit time	0.25 hr ¹²⁴	Unknown but variable
Small intestine pH	4-7.4	pH 5 to >7
Small intestine fluid volume	Average 130 ml, range 10-150 ml	Low fluid volume
Small intestine transit time	3-4 hr	Unknown but variable
Large intestine pH	6-7	Unknown
Large intestine fluid volume	Average 10 ml, range as large as 125 ml	Unknown
Large intestine transit time	18 hr	Rapid transit with diarrhea
Colon	Smooth	Thickened dilated colon and pseudo membrane

Table 2. Vancomycin HCl solubility at different pH¹²⁵

Vancomycin HCl solubility and volume required to dissolve Vancomycin HCl in 250 mg Vancomycin HCl capsules, Data as mean±S.D., N=3 samples/test					
pH	1.0	3.0	4.0	5.0	7.5
Solubility (mg/ml)	140.3±0.7	191.7±0.2	2.98±0.03	9.5±0.2	17.5±0.2
Volume (ml)	1.8	1.3	83.9	26.3	14.3

¹¹⁹ Willmann S., et al., A Physiological Model for the Estimation of the Fraction Dose Absorbed in Humans, at 4.

¹²⁰ Sutton, S.C., "Role of Physiological Intestinal Water in Oral Absorption," *The AAPS J.* 2009, 11:277-285.

¹²¹ Unless noted otherwise, the information in this table related to CDAD and SAE patients was provided by ViroPharma. See

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM179424.pdf>.

¹²² Evans, D.F., Pye, G., Bramley, R., Clark, A.G., et al. "Measurement of Gastrointestinal pH Profiles in Ambulant Human Subjects." *Gut*, 1988, 29: 1035-1041.

¹²³ Schiller, C., Fröhlich, C.P., Giessmann, T., Siegmund, W., et al., "Intestinal Fluid Volumes and Transit of Dosage Forms as Assessed by Magnetic Resonance Imaging." *Aliment Pharmacol Ther.* 2005, 22(10):971-9.

¹²⁴ Ramsbottom, N., Knox, M.T., Hunt, J.N.. "Gastric Emptying of Barium Sulphate Suspension Compared With That of Water." *Gut*, 1977, 18:541-542.

¹²⁵ The data in this table are from the 2008 DPQR study determining the solubility of Vancocin oral capsules. DPQR 2008 Solubility Study at 17.

(b) Section 505(j) of the FD&C Act Does not Require an ANDA Applicant to Separately Demonstrate Safety and Effectiveness of Generic Products in Patient Populations

You generally maintain that various characteristics of the GI tract of the patient subpopulation can affect dissolution and performance of the vancomycin capsule, and that dissolution methodologies that do not reflect the *in vivo* environment of CDAD patients are inadequate to demonstrate bioequivalence. You mischaracterize the nature of the bioequivalence evaluation.

As described in section I.B, above, an ANDA applicant is not required to demonstrate through clinical endpoint trials that its product is safe and effective for the labeled conditions of use. Rather, it can rely on the finding of safety and effectiveness of the RLD as long as the product meets other requirements of the statute, including demonstrating that the proposed generic product is bioequivalent to the RLD. The purpose of bioequivalence testing is to evaluate whether the particular formulation described in the ANDA delivers the active ingredient to the site of action at the same rate and to the same extent as the RLD.

Vancocin is a simple capsule containing vancomycin and one inactive ingredient (polyethylene glycol 6000). As described in the Draft Vancomycin BE Guidance, the solubility and relatively fast dissolution rate of vancomycin ensures that the product forms a solution and stays a solution before it reaches the site of action in the GI tract.¹²⁶ If the proposed product is Q1/Q2 the same with respect to active and inactive ingredients to the RLD, then, as discussed below, the only difference that would affect the bioavailability at the site of action in the GI tract is a variation in the rates of dissolution of the two products, a property that can be measured accurately *in vitro* for highly soluble drugs.¹²⁷ Contrary to your underlying premise, an ANDA applicant for generic vancomycin does not have to submit data from tests that use all potential *in vivo* conditions of CDAD and SAE patients. Instead, data from a given range of conditions, discussed in detail below, are sufficient to demonstrate that the proposed product will perform the same as the RLD in all relevant conditions.

Although you cite various factors that may affect *in vivo* dissolution of vancomycin capsules, you have not provided any evidence to show that these patient-related factors, if evaluated *in vivo* in CDAD patients, would identify *differences in formulation* that might have clinical significance and that would not be identified by FDA's recommended *in vitro* dissolution testing. To the extent that the bioavailability of Vancocin could be affected by these factors, if at all, these factors can be expected to affect the bioavailability of a Q1/Q2 generic vancomycin product for which bioequivalence to

¹²⁶ Draft Vancomycin BE Guidance, at 2-3. See DPQR 2008 Dissolution Study at 34 (vancomycin products dissolve faster than 85% in 45 minutes); DPQR 2008 Solubility Study at 17 (concluding vancomycin products are highly soluble under BCS Guidance standards).

¹²⁷ Galia, E.; Nicolaides, E.; Hörter, D.; Löbenberg, R.; Reppas, C. and Dressman, J.B., "Evaluation of Various Dissolution Media for Predicting *In Vivo* Performance of Class I and II Drugs," *Pharm Res* 1998, 15(5), 698-705.

Vancocin is established through in vitro dissolution data to the same extent they would be expected to affect the bioavailability of Vancocin. FDA addresses the individual patient-related factors you cite in detail below.

(c) In Vitro Dissolution Media

You assert that FDA has not adequately accounted for the unique nature of fluid in the GI tracts of CDAD patients. Specifically, you assert that "the contents of the GI tract in patients with CDAD are highly abnormal and differ significantly from the simple, buffered solution suggested for use by OGD."¹²⁸ You claim that the GI contents of CDAD patients "include many components such as exudates, proteins, inflammatory mediators, cellular debris, blood and other biologic components that are very difficult if not impossible to simulate in an in vitro medium."¹²⁹ You suggest that the influence "of any of these factors on the availability at the site of action will not be predicted by the proposed in vitro testing."¹³⁰ You also note that other commentators to the Draft Vancomycin BE Guidance proposed use of Simulated Gastric Fluid and Simulated Intestinal Fluid in addition to the media proposed in the draft guidance.¹³¹

However, to design an appropriate in vitro dissolution study, the main objective is to select an in vitro condition which has a balance between adequately reflecting in vivo conditions in which vancomycin capsules are dissolved, and a condition that is sufficient for evaluation of the product formulation. The main factors in the selection of the dissolution media are the pH (addressed later), volume, and the potential addition of surfactants to help solubilize the drug after it leaves the formulation. Because of vancomycin's high solubility, the addition of surfactants like those found in simulated intestinal fluid is not recommended when conducting in vitro dissolution testing because they can hasten solubilizing and therefore affect the ability to identify differences in dissolution rate between vancomycin products. Dissolution testing using an aqueous solution without surfactants is as good as or better to evaluate the formulation performance for highly soluble drug products than are simulated gastric or intestinal fluid.¹³²

(d) Lower and Upper pH Levels

You claim that the pH levels FDA recommends for the in vitro bioequivalence dissolution testing for vancomycin capsules do not adequately account for the physiology

¹²⁸ VP June 30, 2006, Supp. at 26-27.

¹²⁹ Id. at 26.

¹³⁰ Id. at 26-27.

¹³¹ VP Draft Guidance Resp. at 11.

¹³² Hörter, D. and Dressman, J.B. "Influence of Physicochemical Properties on Dissolution of Drugs in the Gastrointestinal Tract," 2001, *Adv Drug Delivery Rev* 46(1-3), 75-87;

Nicolaides, E.; Galia, E.; Efthymiopoulos, C.; Dressman, J.B., and Reppas, C., "Forecasting the In Vivo Performance of Four Low Solubility Drugs From Their In Vitro Dissolution Data," 1999, *Pharm Res* 16 (12), 1876--82; Galia, E.; Nicolaides, E.; Hörter, D.; Löbenberg, R.; Reppas, C., and Dressman, J.B.

"Evaluation of Various Dissolution Media for Predicting In Vivo Performance of Class I and II Drugs," 1998, *Pharm Res* 15(5), 698--705.

and pH of the GI tract of patients most susceptible to CDAD, including elderly patients.¹³³ You also contend that the relevance of dissolution at the lower pH levels of 1.2 and 4.5 “is questionable,” that a pH level of 6.8 does not account for potential levels at 7.0 and higher,¹³⁴ and, more generally, that variability associated with dissolution testing complicates its use in bioequivalence assessment.¹³⁵ You claim that FDA disregarded scientific articles that observed the importance of accurate pH levels in dissolution testing for specific populations.¹³⁶ Finally, you contend that the pH range is inconsistent with the range used by FDA in its 2008 internal study of vancomycin solubility.¹³⁷

The dissolution characteristics of oral formulations are often evaluated in the physiologic pH range of 1.2 to 6.8, and FDA consistently recommends this pH range for dissolution testing.¹³⁸ The three dissolution media (pH 1.2, 4.5, and 6.8) in the recommended vancomycin dissolution study reflect a range of pH conditions that will ensure that test and reference products will release drug similarly over the range of in vivo environments that may be encountered in the patient population. FDA has determined that these three testing points cover a sufficient range to allow the conclusion that relative dissolution of test and reference products would be similar at any other pH conditions in the relevant portions of the GI tract.

With respect to the upper pH limit in particular, FDA has determined that 6.8 is the appropriate upper pH level for the vancomycin dissolution testing. As indicated above, it is commonly used as an upper pH condition for dissolution testing of IR products. It represents a higher pH than is often present in the small intestine. In addition, as indicated in the vancomycin solubility profile (Table 2), vancomycin has a higher solubility at pH 7.5 than 6.8. For the same formulation, the dissolution rate would increase with an increase in drug solubility due to pH changes; thus, if the test formulation dissolves more slowly than the RLD, a dissolution test at pH 6.8 will be more sensitive than pH 7.5 to detect the dissolution difference.¹³⁹

¹³³ VP June 30, 2006, Supp. at 28-29.

¹³⁴ Id. at 28-29.

¹³⁵ Id. at 32-33 (citing concerns with dissolution testing that may result from multiple calibration points, undefined parameters and differences in excipients).

¹³⁶ VP Draft Guidance Resp. at 14-15.

¹³⁷ Id. at 11-12.

¹³⁸ See BCS Guidance, at 2 (Aug. 2000); guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, at 6 (Aug. 1997).

¹³⁹ Guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, at 6 (Aug. 1997) (recommending upper pH level of 6.8 as sufficient). You point to the fact that FDA used an upper pH level of 7.5 in its DPQR 2008 Dissolution Study in support of your argument that FDA should require dissolution data up to the pH level of 7.5. Your reference to the highest level pH of 7.5 used in the DPQR 2008 Solubility Study is misplaced. FDA used the upper pH level of 7.5 in the solubility study, and determined that vancomycin has a higher solubility at pH 7.5 than 6.8. Accordingly, FDA concluded that the upper pH for dissolution assessment should be 6.8, because use of pH higher than that would be less sensitive due to the increased solubility.

In addition, these and the other precise specifications for dissolution comparison set out in the Draft Vancomycin BE Guidance and discussed in this petition response, including the Q1/Q2 requirement, adequately address your concerns regarding variability that may be associated with dissolution testing.

(e) Dissolution Media Volume

You next argue that fluid volume in the upper GI tract of CDAD patients is likely to be substantially lower than the 500 ml-1000 ml volumes cited by FDA in the Draft Vancomycin BE Guidance in support of the Agency's recommendation of a volume of 900 ml for the in vitro dissolution analysis.¹⁴⁰ You further assert that the authors of the scientific article FDA cites in support of its recommended fluid volume do not support FDA's dissolution methodology, because those authors proposed the values based on reports from healthy patients for a different purpose than comparative in vitro dissolution for vancomycin products. In addition, you claim that it cannot be assumed that the volume of fluid in an upper GI tract of a CDAD patient is likely to be the same as a healthy non-fasted individual, and is likely to be less.

Your arguments are misplaced. Normally, for the basket and paddle apparatus that FDA recommends in the Draft Vancomycin BE Guidance, the volume of the dissolution medium is 500 mL to 1000 mL, with 900 mL as the most common volume.¹⁴¹ FDA recommends 900 ml for the vancomycin dissolution study because it provides sufficient fluid volume to completely dissolve all vancomycin doses.

Based on the fluid volumes generally present in the GI tract, most vancomycin dissolution takes place in an in vivo environment where the entire dose can be dissolved. As shown in Table 2, the dissolution media volume at pH 1.2 and 6.8 to reach complete dissolution for a 250 mg vancomycin dose is less than 50 ml. At pH 4.0, vancomycin has the lowest solubility and the dissolution media volume to ensure "sink condition" (the volume of medium at least greater than three times that required to form a saturated solution of a drug substance) for full dissolution of 250 mg vancomycin dose is about 255 ml. Therefore, based on vancomycin solubility, the proposed 900 ml dissolution medium provides test conditions where the vancomycin capsule can completely dissolve.

Even if in particular individuals there is potentially insufficient physiological fluid volume for complete release of vancomycin HCl from formulations, FDA has determined that equivalent dissolution profiles at different pH conditions that would be encountered in the GI tract ($f_2 > 50$) will ensure that equivalent amounts of vancomycin from the generic and RLD formulations are available. Accordingly, assuming that the test product formulations are Q1 and Q2 the same as the RLD in a capsule, it is FDA's determination that Vancocin and a proposed vancomycin generic product will not behave differently in vivo provided they have comparable in vitro dissolution at the different pH conditions specified above.

¹⁴⁰ VP Draft Guidance Resp. at 12-13; VP June 30, 2006, Supp. at 38.

¹⁴¹ USP General Chapter on Dissolution <711> (USP 34-NF 29) (official through April 30, 2012).

In addition, if an individual has a low fluid volume in the GI tract, no vancomycin formulation can provide a higher concentration than the vancomycin solubility (the maximum amount of vancomycin that will dissolve in a specific amount of liquid) permits. Even at vancomycin's lowest solubility of 2.98 ± 0.03 mg/ml at pH 4.0 (see Table 2 above), the concentration of vancomycin is over 180-fold higher than the 0.016 mg/mL minimum inhibitory concentration (MIC) (the minimum antibiotic concentration needed to inhibit bacterial growth) estimated in the literature.¹⁴² In other words, even if some portion of Vancocin or a generic vancomycin product does not dissolve due to insufficient liquid, no significant safety and efficacy difference will be expected because there will be adequate concentration to kill the bacteria which causes CDAD.

(f) Solubility

You claim that while vancomycin is highly soluble at low pH levels, solubility is pH dependent, and that FDA's reliance on the highly soluble characteristic of vancomycin in healthy subjects is not relevant in the context of CDAD patients.¹⁴³ Specifically, you assert that the administration of vancomycin capsules to CDAD patients who have low gastric fluid volume "may greatly exceed the solubility of vancomycin, particularly in the presence of elevated intragastric pH observed in such patients."¹⁴⁴ In other words, you argue that the gastric fluid volume in certain CDAD patients is too low to completely solubilize the vancomycin dose and therefore that the vancomycin in a capsule will not be fully released.

Your assertions with respect to solubility are based on your concern about the fluid volume in the patient population. The previous section discusses this issue, and for the reasons set forth there, your assertions regarding solubility lack merit.

(g) Transit Times

You also challenge FDA's statement in the Draft Vancomycin BE Guidance 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."¹⁴⁵ You assert that the recommended dissolution method does not accurately account for potentially reduced transit times as short as 1-2 hours.¹⁴⁶ Your argument with respect to transit times is misplaced because, as previously stated, FDA's bioequivalence recommendation centers on the similarity of dissolution profiles between test and reference products. Test and reference products with similar dissolution profiles in the recommended tests will provide similar drug release in patients with much shorter GI

¹⁴² Dzink, J., Bartlett, J.G. "In Vitro Susceptibility of *Clostridium difficile* Isolates From Patients With Antibiotic-Associated Diarrhea or Colitis." 1980, *Antimicrob Agents Chemother* 17:695-8

¹⁴³ VP June 30, 2006, Supp. at 38.

¹⁴⁴ Id. at 38-39.

¹⁴⁵ Draft Vancomycin BE Guidance at 3.

¹⁴⁶ VP Draft Guidance Resp. at 15-17.

transit times. In addition, even the 1-2 hours transit time you mentioned is sufficient to provide complete release of vancomycin.¹⁴⁷

(h) Potential Systemic Absorption

You assert that FDA has not sufficiently taken into account the potential systemic absorption of vancomycin in CDAD patients as indicated in the Vancocin labeling.¹⁴⁸ The Vancocin Capsule label states: “[v]ancomycin is poorly absorbed after oral administration.”¹⁴⁹ This is the primary reason that the in vivo bioavailability study was waived during the NDA approval.¹⁵⁰ Vancomycin permeability is very low and vancomycin is poorly absorbed in patients. Therefore, recommending in vivo pharmacokinetic studies comparing generic and RLD products offers little benefit, as neither product would be expected to produce detectable plasma vancomycin concentrations. Even if the rare subset of patients with increased permeability could be identified for study and the in vivo plasma vancomycin concentrations in these patients could be measured and quantified,¹⁵¹ generic and RLD vancomycin HCl capsules with the same excipients and similar dissolution profiles would be expected to have the same plasma concentration profiles in these patients.

(i) Site of Action in SAE Patients

You contend that FDA did not adequately take into account the site of action in SAE patients in the upper GI tract and small intestine because FDA’s position that there is sufficient upper GI transit time for a vancomycin capsule to fully solubilize before it reaches the site of action in the lower GI tract, does not address the SAE site of action in the upper GI tract.¹⁵² Again, you misconstrue the bioequivalence analysis. In those SAE patients who may have infection in the upper GI tract, equivalent in vitro dissolution profiles at multiple pH conditions will ensure equivalent amounts of vancomycin are delivered to each site by both generic and RLD formulations, even in the upper GI tract.

(j) Predictability of In Vivo Performance

You maintain that there are cases where in vitro dissolution has not been predictive of in vivo performance.¹⁵³ The three drugs mentioned are mesalamine, mebendazole, and propantheline bromide. Without addressing the merits of ViroPharma’s claim that these are instances in which in vitro dissolution was not predictive of in vivo performance,

¹⁴⁷ DPQR 2008 Dissolution Study at 34 (vancomycin products dissolve faster than 85% in 45 minutes). For this reason, ViroPharma’s reference to the finding of Navaneethan and Giannella that CDAD has been observed in the small bowel in some patients (assuming this finding to be true), does not change our conclusions. VP May 18, 2009, Supp. at 1-2.

¹⁴⁸ VP June 30, 2006, Supp. at 17-20; VP Draft Guidance Resp. at 25-26.

¹⁴⁹ Vancocin PI, at 9.

¹⁵⁰ Biopharmaceutical Recommendation for Approval of Vancomycin Hcl 125 and 250 mg Capsules, Summary Basis of Approval for NDA 50606, at 40 (May 30, 1985).

¹⁵¹ See Vancocin PI at 3.

¹⁵² VP Draft Guidance Resp. at 28-29.

¹⁵³ VP June 30, 2006 Supp. at 33.

FDA notes that these three drugs all have significant differences from vancomycin that indicate the inappropriateness of this comparison. Vancomycin is a high solubility drug at all pH levels and Vancocin Capsules are an immediate release dosage form. The mesalamine products mentioned are modified release products, which means that they are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time rather than immediately. In addition, mesalamine solubility varies from high to low depending on pH.¹⁵⁴ With respect to mebendazole, it is a low solubility drug.¹⁵⁵ Finally, the published reports of propantheline bromide dissolution problems have been linked to excipient effects.¹⁵⁶ None of these examples is relevant to the dissolution of high solubility drugs using the same excipients, as is recommended in the Draft Vancomycin BE Guidance, because they differ in characteristics (solubility, release function, and inactive ingredients) that, as discussed in this response, form the core of FDA's consideration of the scientific appropriateness of using dissolution data to demonstrate bioequivalence.

3. Q1/Q2 Sameness Requirement for Using In Vitro Dissolution Method to Demonstrate Bioequivalence

(a) Q1 Sameness: Polyethylene Glycol 6000 NF Satisfies the Q1 Sameness Requirement for Generic Vancomycin Capsules

Vancocin labeling states that “[t]he [Capsules] contain vancomycin hydrochloride equivalent to 125 mg (0.08 mmol) or 250 mg (0.17 mmol) vancomycin. The [Capsules] also contain F-D & C Blue No. 2, gelatin, iron oxide, polyethylene glycol [PEG], titanium dioxide, and other inactive ingredients.”¹⁵⁷ The technical grade of PEG used in Vancocin Capsule is PEG 6000.¹⁵⁸

As a preliminary matter, FDA concludes that generic products should use a PEG with the same technical grade of 6000 as Vancocin to demonstrate Q1 sameness. Many inactive ingredients are available in different technical grades. Technical grades frequently are differentiated by physical characteristics (e.g., the particle size, morphology differences in different grades of lactose and microcrystalline cellulose) or chemical structures (molecular weight difference of polysorbate esters and polyethylene glycols).¹⁵⁹ Technical grades may also differ in impurities and impurity profiles. Usually excipients

¹⁵⁴ Fadda, H. M.; Sousa, T.; Carlsson, A. S.; Abrahamsson, B; Williams, J. G; Kumar, D.; and Basit Mol, A. W., “Pharmaceutics, Drug Solubility in Luminal Fluids from Different Regions of the Small and Large Intestine of Humans,” at 1527-32, *Molecular Pharmaceutics*, 2010: 7(5).

¹⁵⁵ Swanepoel E.; Liebenberg, W.; de Villiers, M.M., “Quality Evaluation of Generic Drugs by Dissolution Test: Changing the USP Dissolution Medium to Distinguish Between Active and Nonactive Mebendazole Polymorphs,” at 345-349, *Eur. J. Pharm Biopharm.* 2003 May; 55(3).

¹⁵⁶ Abd El-Fattah, Sawsan; Khalil, Saleh A.H., “Variations in Dissolution Rates of Sugar-Coated Chlorpromazine Tablets,” at 225–234, *International Journal of Pharmaceutics*, 1984: 18(3).

¹⁵⁷ Vancocin PI, at 8.

¹⁵⁸ ViroPharma, Presentation, at 30, Aug. 4, 2009 ACPS Meeting, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM179424.pdf>.

¹⁵⁹ Moreton, R.C. “Excipient Functionality.” May 2004 *Pharma Tech.* <http://pharmtech.findpharma.com/pharmtech/data/articlestandard//pharmtech/192004/94554/article.pdf>.

with different technical grades have different specifications and/or functionality, and performance.¹⁶⁰ According to FDA's guidance for industry on *Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (SUPAC IR Guidance), a change in the technical grade of an excipient is considered a Level 2 change, and requires the submission of a Prior Approval Supplement, including chemistry and dissolution documentation.¹⁶¹

As a general matter, if there are multiple grades of an inactive ingredient available and the NDA applicant specifies the technical grade of the excipient in the RLD labeling, generic products claiming to be Q1/Q2 to the corresponding RLD should contain the same technical grade of inactive ingredients used in the RLD, unless the ANDA applicant demonstrates that the difference in excipient technical grade does not affect drug product quality, manufacturability, performance, safety, and efficacy.¹⁶² In the majority of cases, if the inactive ingredient is the subject of a United States Pharmacopeia (USP)/National Formulary (USP/NF) monograph, inactive ingredients used in RLD and generic products comply with that monograph's provisions.

FDA has concluded that for the purposes of vancomycin capsules, PEGs with different molecular weight differ significantly in terms of physicochemical and toxicological properties.¹⁶³ Therefore, we would expect an ANDA applicant for generic vancomycin capsules to use PEG with a molecular weight of 6000 in order to demonstrate Q1

¹⁶⁰ SUPAC-IR Questions and Answers about SUPAC-IR Guidance (1997).

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124826.htm>.

¹⁶¹ Guidance for industry on *Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (Nov. 1995), at 8 (Level 2 change defined as "those that could have a significant impact on formulation quality and performance").

¹⁶² As provided in the Draft Vancomycin BE Guidance, if a product is not Q1/Q2 to vancomycin, it may use in vitro dissolution to demonstrate bioequivalence if "the ANDA sponsor provides evidence that the differences in excipients will not affect the safety or efficacy of the proposed generic drug product." Draft Vancomycin BE Guidance at 3. FDA notes that several comments to the Draft Vancomycin BE Guidance docket maintained that in certain instances FDA should retain some flexibility in requiring Q1/Q2 sameness. See, e.g., Wockhardt Ltd. Submission, at 1 (Feb. 6, 2010) (Docket No. 2008-626) (maintaining that dissolution data should be permissible to demonstrate bioequivalence notwithstanding "minor qualitative and quantitative changes in the test formulations which are not intended to affect the transport of [v]ancomycin through the GIT and/or effectiveness of the drug at the site"); Encap Drug Delivery Submission, at 1-2 (Feb. 5, 2009) (Docket No. 2008-626) ("it is recommended that the Q2 criteria be removed or be qualified to 'quantitatively similar'"). FDA will consider on a case-by-case basis any applications for products that deviate from the Q1/Q2 requirement that seek to rely on in vitro dissolution data to demonstrate bioequivalence.

¹⁶³ See, generally, Biondi, O., Motta, S., Mosessa. "Low Molecular Weight Polyethylene Glycol Induces Chromosome Aberrations in Chinese Hamster Cells Cultured In Vitro." 2002, *Mutagenesis*. 17: 261-264. PEGs with a molecular weight below ~600 are clear, viscous liquids, while at a molecular weight of ~1000 PEGs appear as white waxy solids. In general PEGS are water soluble, stable, nontoxic compounds that do not hydrolyse or deteriorate on storage. When administered orally the higher molecular weight PEGs appear to be less toxic than low molecular weight polymers because the latter are absorbed by the digestive tract, whereas larger polymers are absorbed more slowly or not at all.

sameness.¹⁶⁴ Use of PEG 6000 will ensure that any material differences that may exist between PEGs that might affect the performance of a proposed generic vancomycin capsule are not present.

Next, you assert that Vancocin contains a trade secret inactive ingredient whose identity and quantity are not publicly known. You assert that this ingredient potentially has a link to antibiotic potency, and therefore that only generic vancomycin capsules that include that inactive ingredient may be approved.¹⁶⁵ We do not agree. Vancocin has one inactive ingredient inside the shell capsule: polyethylene glycol 6000, and you have not demonstrated that the PEG 6000 used in Vancocin, or any components therein, have a unique link to antibiotic potency such that generic vancomycin products must use the specific PEG found in Vancocin in order to be Q1.¹⁶⁶ Rather, FDA has concluded that generic vancomycin capsule products that comply with the USP/NF monograph for PEG satisfy the Q1 requirement, provided that the generic vancomycin products demonstrate the other requirements for Q1 sameness discussed here and have acceptable drug product stability and other quality attributes.

(b) Q2 Sameness: The Concentration of Inactive Ingredients Should Not Differ More Than 5% From the RLD.

We conclude that in order to demonstrate Q2 sameness, the concentration or amount of PEG 6000 in generic vancomycin should not differ by more than 5% of the concentration or amount in Vancocin. “Quantitatively the same” has been determined by CDER, in the context of locally acting drugs, to mean that the concentration or amount of the inactive ingredient(s) in the test product would not differ by more than “5 percent of the concentration or amount in the reference listed drug.”¹⁶⁷

¹⁶⁴ We note that sameness in technical grade is not always required to demonstrate same formulation. See the draft guidance for industry on *Submission of Summary Bioequivalence Data for ANDAs*, at 4 (April 2009) available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM134846.pdf>.

¹⁶⁵ VP Draft Guidance Resp., at 44-46; VP Oct. 6, 2009, Supp. at 5-6; VP Dec. 18, 2009, Supp. at 1-3; VP July 25, 2010, Supp. at 12-14.

¹⁶⁶ FDA has fully considered your arguments related to this issue, but has refrained from including the full discussion here in order to preserve any of your confidential commercial or trade secret information contained therein.

¹⁶⁷ Draft guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*, at 8 (April 2003); FDA Citizen Petition Response re: Derma-Smoothe/FS (fluocinolone acetonide 0.01% Topical Oil (Docket No. 2004-P-0215) at 13-14 (Mar. 25, 2009) (locally acting topical oil considered Q2 if quantity of each inactive ingredient no more than 5% different than RLD)). See also SUPAC IR Guidance at 7 (no new bioequivalence data required for changes in total additive effect of all excipient changes of 5% or less).

4. Q3 Sameness Is Unnecessary to Demonstrate Vancomycin Bioequivalence When Using In Vitro Dissolution Data

You propose that FDA should consider requiring “Q3” sameness for generic vancomycin.¹⁶⁸ Upon consideration of your arguments and the relevant scientific materials, FDA concludes that Q3 sameness is not required for demonstrating bioequivalence of vancomycin capsules.

Q3 sameness is a relatively new concept in bioequivalence evaluations, and generally means the formulations have the same structural characteristics in terms of components, concentration, and microstructure.¹⁶⁹ In the August 4, 2009, ACPS Meeting that concerned the Draft Vancomycin BE Guidance, Dr. Patrick K. Noonan from Virginia Commonwealth University suggested the following factors for Q3 sameness for vancomycin capsules:

- Individual ingredient quality attributes
 - Testing beyond pharmacopeial requirements
 - Particle size
 - PEG molecular weight distribution
 - Polymorphic control
- Manufacturing process variables
 - Temperature, humidity, pressure
 - API milling speed
- PEG melt characteristics
 - Hot melt viscosity¹⁷⁰

FDA declines to adopt Dr. Noonan’s Q3 criteria for vancomycin, or otherwise to require ANDA applicants to demonstrate Q3 sameness.

For complex formulations other than solutions, such as topical creams, gels, and ointments, it is possible that Q1/Q2 formulations may result in different drug product properties based on different manufacturing process (e.g., a drug product manufactured by simply blending all components may have different dissolution and stability characteristics from the one manufactured by a hot melt process). However, vancomycin capsule is a simple solid oral dosage form and it need not maintain its microstructure to exert its pharmacological action because it goes through a dissolution process *in vivo* before it reaches the site of action. FDA reviewers routinely examine dissolution and stability characteristics, and ensure that any difference in manufacturing process from the RLD will not affect finished drug product quality and performance.

¹⁶⁸ VP Draft Guidance Resp. at 42-43.

¹⁶⁹ Wilkin, J., Presentation: The Pursuit of Alternative Methodologies For Demonstrating Bioequivalence for Generic Topical Dermatologic Drug Products: DPK, Q3, Cakes, and 2 PIs, Presentation, ACPS Meeting (Oct. 22, 2003).

¹⁷⁰ 2009 ACPS Tr., at 144-148.

In addition, under “Quality by Design” (QbD) principles, ANDA applicants are encouraged to identify and monitor critical attributes of excipients, drug substance, in-process material, and finished products, as well as critical process parameters. Within FDA’s current “Question-based review” (QbR) system, ANDA reviewers will evaluate these critical attributes and critical process parameters to ensure approval of quality generic products.

5. FDA’s DPQR Vancomycin 2008 Dissolution Study Was Not Faulty

As described above, OGD commissioned a study in 2006 with CDER’s DPQR to determine the dissolution characteristics of Vancocin Capsules.¹⁷¹ DPQR completed the study in February 2008, and concluded that vancomycin drug products were found to dissolve faster than 85% in 45 minutes at a range of predetermined pH conditions encountered in the GI tract, with the exception of two lots of the RLD drug.¹⁷² The study observed that vancomycin capsules are not “rapidly” dissolving as defined in the “BCS Guidance,” however, which requires 85% dissolution within 30 minutes at the predetermined pH levels.¹⁷³ DPQR repeated the study in 2009 and confirmed the 2008 results.¹⁷⁴

You assert that the DPQR Vancomycin 2008 Dissolution Study was faulty on several grounds: (1) FDA used expired vancomycin capsules; (2) FDA used test products that had “meaningfully high overages;” and (3) FDA improperly used a noncompendial method for assessing dissolution characteristics of oral vancomycin.¹⁷⁵

Upon review of the study, FDA finds your concerns regarding the 2008 dissolution study unsupported. First, the dissolution experiments described in the 2008 report were conducted in 2006, when the lots used to assess Vancocin dissolution had not yet expired. Second, as you note, samples of vancomycin products other than Vancocin also were evaluated in the 2008 study. Although FDA assessed the dissolution of these products, the Agency did not use data from any non-Vancocin product in determining that Vancocin dissolved more than 85% in 45 minutes. Similarly, although certain proposed vancomycin products demonstrated vancomycin release in the 109-116% range, these products were not used in determining the dissolution of vancomycin in Vancocin. Your concerns regarding FDA’s use of a noncompendial method for assessing dissolution characteristics of oral vancomycin are addressed below.

¹⁷¹ DPQR 2008 Dissolution Study.

¹⁷² Id. at 34.

¹⁷³ Id. at 14.

¹⁷⁴ DPQR 2009 Dissolution Study (July 30, 2009).

¹⁷⁵ VP Draft Guidance Resp., Appendix A at 63-64.

6. Use of the High Performance Liquid Chromatographic Assay Method for Vancomycin Capsules Is Appropriate to Determine In Vitro Dissolution Profiles

FDA does not indicate in the Draft Vancomycin BE Guidance a specific analytical procedure for generating dissolution profiles. Rather, for products that are the subject of product-specific guidances, the Agency generally recommends the approaches laid out in FDA's guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.¹⁷⁶ Those approaches depend on the existence of the USP official compendial test and the nature of the dissolution test employed for the RLD.¹⁷⁷ To determine the appropriate methodology to assess dissolution of vancomycin capsules, FDA took several steps, including: (1) review of the USP monograph requirements on vancomycin HCl and vancomycin HCl capsules; (2) evaluation of the practices that ViroPharma, the RLD holder; and (3) analysis of the suitability of using a high performance liquid chromatographic (HPLC) method to assess comparative dissolution of vancomycin HCl capsule formulations. As part of this evaluation, FDA also considered whether USP vancomycin reference standards and/or other qualified vancomycin reference standards can be used in HPLC analysis of comparative dissolution of vancomycin HCl capsule formulations. From this analysis, FDA concludes that use of an HPLC method to assess comparative dissolution of vancomycin capsules is appropriate, and that USP vancomycin reference standards and/or other qualified vancomycin reference standards can be used in HPLC analyses.

You assert that FDA should not permit ANDA applicants to use an HPLC method to assess comparative dissolution of vancomycin HCl capsule formulations.¹⁷⁸ FDA disagrees. Your specific arguments on this issue are addressed in detail below.

(a) Existing USP Monograph Requirements on Vancomycin HCl Active Pharmaceutical Ingredient (API) and Vancomycin HCl Capsules

The USP vancomycin HCl drug substance monograph directs that the assay performed to assess compliance with USP standards of strength should be the USP microbial assay, with specification of not less than (NLT) 900 µg of vancomycin per mg on the anhydrous basis against a USP Vancomycin Hydrochloride reference standard (RS).¹⁷⁹ Vancomycin is a mixture of similarly structured compounds, with vancomycin B being the compound of greatest abundance.¹⁸⁰ The vancomycin components vary in microbiological activity; therefore, the microbiological assay yields a result representing a concentration-weighted summation of the individual components' activities.

¹⁷⁶ Guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (Aug. 1997) at 5.

¹⁷⁷ Id.

¹⁷⁸ VP June 25, 2010, Supp.; VP July 20, 2010, Supp..

¹⁷⁹ USP Monograph on Vancomycin Hydrochloride, USP 32 - NF 29 through Second Supplement (remains official until April 30, 2012), at 4565-66.

¹⁸⁰ Best, G.K. Best, N.H., and Durham, N.N. "Chromatographic Separation of the Vancomycin Complex." 1968, *Antimicrob. Agents Chemother.*, 4 115.

The USP vancomycin HCl drug substance monograph directs that the Chromatographic Purity test should be performed by an HPLC method with peak area percentage of NLT 85% of vancomycin B and no more than (NMT) 5% of any other peak.¹⁸¹ USP Vancomycin Hydrochloride RS is used to prepare the resolution solution, but is not used for calculation of the purity. This HPLC test was adopted for vancomycin in USP 23 in 1995.¹⁸² Due to the complexity of the vancomycin chromatograms, the fundamental assumption for the evaluation of vancomycin HCl is that the molar absorptivities of the vancomycin-related compounds in the drug substance are approximately equal. This assumption was confirmed by several spectroscopic and chromatographic experiments.¹⁸³ The basic assumption of similar molar absorptivities permits measurement of vancomycin B and other related components. Wavelength selection is not critical, because most vancomycin related substances have similar UV absorption spectra, with the optimum wavelength determined by sensitivity requirements.

USP directs that the Limit of Monodechlorovancomycin (MDCV) test also should be performed by HPLC method with weight/weight (w/w) percentage NMT 4.7%. In the USP reference standard for this test, Vancomycin B with Monodechlorovancomycin RS, the purity of vancomycin B is expressed as mg per mg. This test was added in the Second Supplement to USP 30 in 2007.¹⁸⁴ The same assumption made in Chromatographic Purity is applied in the MDCV test as well: the molar absorptivity of MDCV is approximately equal to that of vancomycin B.

The USP drug product monograph directs that the quantitative analysis of vancomycin HCl oral capsule content should be performed using USP microbial assays.¹⁸⁵ USP also states that the microbial assay should be used in the quality control dissolution test. There is no assay provided in the USP vancomycin capsule monograph expressly directed toward comparative dissolution of vancomycin HCl capsules, so FDA must determine the most appropriate comparative assay.

FDA will require all ANDA applicants to apply USP monograph requirements for vancomycin hydrochloride and vancomycin hydrochloride capsules for stability and quality control of APIs and drug products.

¹⁸¹ HPLC uses different types of stationary phases, a pump that moves the mobile phase(s) and analyte through the column, and a detector to provide a characteristic retention time for the analyte. Analyte retention time varies depending on the strength of its interactions with the stationary phase, the ratio/composition of solvent(s) used, and the flow rate of the mobile phase. Rather than a summation of component activities like that generated by the microbiological assay, the HPLC method measures vancomycin B and other related components multiple times over the course of the execution of the assay. In other words, multiple, precise measurements of the presence of vancomycin B in two products over a set time period function as a surrogate for similar dissolution rate for those products.

¹⁸² USP monograph of Vancomycin Hydrochloride, USP 23 - NF 18 (1995), page 1620.

¹⁸³ Inman, E.L. "Determination of Vancomycin Related Substances by Gradient High-Performance Liquid Chromatography. 1987, *J. Chromatography A*, 410 363-372.

¹⁸⁴ *Pharmacopeial Forum* 30(6), at 2055

(<http://www.usp.org/USPNF/revisions/usp30nf25secondSupplement05.html>).

¹⁸⁵ USP Monograph for Vancomycin Hydrochloride Capsules, USP 30 - NF 29 through second supplement (remains official until April 30, 2012), at 4566-67.

(b) Analytical Practices of RLD Holder for Analyzing Vancomycin HCl APIs and Vancocin Capsules

In light of your reference to ViroPharma's use of the microbial assay to assess batch variance,¹⁸⁶ FDA reviewed the Company's practices for analyzing Vancocin, and has concluded that nothing in ViroPharma's practices provides support for a determination that HPLC is not an appropriate method for assessing comparative dissolution. Due to the confidential nature of this information, the company's specific practices will not be discussed in this citizen petition response.

(c) Previous Comparative Dissolution Assessment of Vancomycin HCl Capsules by FDA

The Agency used an HPLC method to assess dissolution in the 2008 and 2009 DPQR Dissolution Studies.¹⁸⁷ As indicated in the 2008 study report, FDA's DPQR validated the HPLC analytical method used "according to USP category I for accuracy, precision, linearity, specificity and analytical range."¹⁸⁸ The study report also provided a detailed schedule of the validation parameters used.¹⁸⁹

In your citizen petition filings, ViroPharma asserts that this validation was insufficient because FDA did not establish the relationship between biological assay testing and the HPLC assay. Without understanding this relationship, you claim, "it is possible that quantification of a single peak [via HPLC] is not an appropriate method of analysis or that only a set of specific and well-defined conditions for preparing and handling test and reference materials will provide reliable data."¹⁹⁰ This assertion is incorrect, because FDA does not seek to demonstrate something that would require cross-validation to the microbial methodology — for example, that the HPLC methodology demonstrates exactly what the microbial assay would demonstrate. Rather, the Agency seeks to establish the comparative dissolution rate of vancomycin using the most sensitive validated assay available, which, in the Agency's determination, is the HPLC method. While the Agency's guidance on dissolution testing for immediate release solid oral dosage forms instructs FDA to look to USP-recommended dissolution methodologies in certain circumstances,¹⁹¹ the guidance does not recommend use of, or cross-validation to, a USP methodology in all circumstances in which dissolution is assessed.

¹⁸⁶ VP July 20, 2010, Supp. at 2-3.

¹⁸⁷ DPQR 2008 Dissolution Study at 9-10; DPQR 2009 Dissolution Study at 8. FDA notes that in the 2009 Vancomycin Dissolution study, the Agency used an ultra-performance liquid chromatographic (UPLC) method to evaluate dissolution rather than the HPLC method. DPQR 2009 Vancomycin Dissolution Study, at 8. As indicated in the DPQR 2009 Dissolution Study, FDA validated this methodology. Id. at 8-10. The UPLC method functions very similarly to the HPLC methodology, but as indicated in the study report, has certain benefits including speed of analysis. Id. at 8. While these benefits exist, they are not of such a nature that FDA would require ANDA applicants to use a UPLC method rather than the HPLC method. FDA will accept either method so long as it is adequately validated.

¹⁸⁸ DPQR 2008 Dissolution Study at 10. See also DPQR 2009 Dissolution Study at 8.

¹⁸⁹ DPQR 2008 Dissolution Study at 10. See also DPQR 2009 Dissolution Study at 8-9, 10.

¹⁹⁰ VP June 25, 2010, Supp. at 2.

¹⁹⁰ Guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, at 5.

You also assert that there were differences in the results between the 2008 and 2009 DPQR Dissolution Studies for Vancocin products from the same batch that demonstrate that the HPLC methodology has not been fully validated.¹⁹² This is not the case. As indicated above, FDA fully validated the methods used in the 2008 and 2009 Dissolution Studies through accepted methods. There are multiple potential sources for differences in dissolution data of products from the same batch tested on two separate occasions, including product change over time, and capsule-to-capsule variations. None of these factors is relevant to whether the methods themselves were adequately validated.

(d) No Official USP Standard is Expressly Indicated for Assessing Comparative Dissolution

The Draft Vancomycin BE Guidance recommends “[d]issolution testing for stability and quality control: USP method.” As mentioned above, FDA will require all ANDA applicants to apply USP monograph requirements for vancomycin hydrochloride and vancomycin hydrochloride capsules for stability and quality control of APIs and drug products.

You argue that current generic applicants also must use the USP microbial method for assessing comparative dissolution of the test and reference products.¹⁹³ The microbial method is not an adequate replacement for the HPLC test. The USP microbial method is not expressly indicated for assessing comparative dissolution rates of two products, and the USP vancomycin capsule monograph does not otherwise include a comparative dissolution methodology. In other words, a methodology for measuring the comparative dissolution of two different vancomycin HCl capsule formulations is beyond the scope of the USP monograph. Use of the HPLC assay to measure comparative dissolution does not replace the USP microbial dissolution test, but rather is complementary to this quality control method, and is used to assess bioequivalence if the proposed generic formulations meet the Q1/Q2 criteria.

(e) Limitations of Microbial Assay, and the Growing Recognition of Superior Utility of HPLC Methodology for Measuring Comparative Dissolution

The USP microbial dissolution tests for vancomycin capsules were primarily adopted as a quality control tool to replace the use of disintegration tests, which had been official in the USP since 1950.¹⁹⁴ As you acknowledge, the USP vancomycin dissolution method with microbial assay is insufficient as the analytical technique for undertaking vancomycin bioequivalence analysis:

The USP vancomycin dissolution test was not developed for use as a bioequivalence method. Rather, its use has been in the release of batches of

¹⁹² VP July 20, 2010, Supp. at 7.

¹⁹³ VP July 20, 2010, Supp. at 3.

¹⁹⁴ Cohen, J.L., Hubert, B.B., Leeson, L.J., Rhodes, C.T., Robison, J.R., Roseman, T.J., Shefter, E. “The Development of USP Dissolution and Drug Release Standards. 1990, *Pharm Res.* 7 (10), 983-987.

vancomycin hydrochloride capsules. It does not measure the rate of dissolution of vancomycin capsules, but only whether a certain percent dissolution has occurred at a single time point. It is difficult to use, because of its narrow linear working range. It is not particularly precise. Its variability is sufficiently large to make interpretation of the f2 test problematic. In sum, the USP vancomycin dissolution test is unlikely to be capable of generating the type of dissolution profiles needed to permit the comparisons required in OGD's proposed vancomycin capsule BE method.¹⁹⁵

By contrast, the USP monographs increasingly have recognized the general value of the HPLC methodology for various vancomycin analyses. Since the vancomycin monographs were first published, HPLC has become the official method for purity determinations for vancomycin HCl (added in 1995),¹⁹⁶ and for the test for Limit of monodechlorovancomycin (added in the 2nd supplement to USP 30 in 2007).¹⁹⁷ The HPLC method was adopted because of the recognition of its usefulness and effectiveness in a variety of settings, such as monitoring process changes, stability profiling, establishing improved accuracy in chemical purity determination, and tightening in-process controls.¹⁹⁸

Such a trend of generally recognizing the superiority of HPLC compared to the microbial assay in a variety of circumstances is supported by a recent report from the World Health Organization (WHO), which provided that:

EDQM (European Directorate for the Quality of Medicines & HealthCare, the WHO custodian centre for antibiotics) has a long record of experience in monitoring the stability of official European Pharmacopoeia (Ph. Eur.) reference standards for antibiotics. Due to the inherent variability of the microbiological assay methods, it was decided some years ago to replace them by stability indicating methods such as reverse phase high liquid chromatography (rp-HPLC) for monitoring the stability of the Ph. Eur. Reference standards. It was therefore believed to be of benefit to estimate the degradation at elevated temperature by rp-HPLC in addition to microbiological assays with the aim of collecting data for future replacement of the method . . .

Considering that the precision of the liquid chromatography method is much better than the precision of the microbiological assay, it is believed that with respect to the variability of these methods, any significant change in the impurity profile (by HPLC) will be detected ahead of any significant loss of potency.¹⁹⁹

¹⁹⁵ VP July 20, 2010, Supp. at 3.

¹⁹⁶ USP Monograph of Vancomycin Hydrochloride, USP 23 - NF 18 (1995), page 1620.

¹⁹⁷ *Pharmacopeial Forum* 30(6) at 2055.

¹⁹⁸ Vila et al., *Analytical Methods for Vancomycin Determination in Biological Fluids and in Pharmaceuticals*. at 395-399 (2007).

¹⁹⁹ WHO/BS/10.2151. Collaborative Study for the Establishment of the Second International Standard for Vancomycin. Expert Committee on Biological Standardization, Geneva, 18 to 22 Oct 2010.

- (f) The HPLC Method Together With the Dissolution Conditions Recommended by the Draft Vancomycin BE Guidance and the f_2 Requirement Is Much More Stringent than the Use of the Microbiological Assay

The literature recognizes that, in contrast to the inherent variability of the microbiological assay methods mentioned above, the HPLC method is much more sensitive, accurate, precise, and robust.²⁰⁰ The utility of the HPLC method has also been demonstrated during the method validations by DPQR. The sensitivity and wide linearity range of HPLC methods allows a single method to be applicable throughout the full time course of dissolution studies, including the early time periods recommended in the Draft Vancomycin BE Guidance. The accuracy and precision of HPLC methods ensure that the statistical analysis is meaningful. The specificity of HPLC methods also allows selective monitoring of components and dissolution homogeneity.²⁰¹

In the Draft Vancomycin BE Guidance, the comparative dissolution conditions are clearly specified, emphasizing multiple media and multiple early time points. It provides that the dissolution data should be generated in three different media with USP Apparatus 1 (basket), rotating at 100 rpm, in a volume of 900 ml at 37° Celsius. Samples are to be taken at 5, 10, 20, 30, and 45 minutes, or as needed for profile comparison. This approach was taken because the HPLC method is sensitive, accurate and precise enough to detect the possible variation in the early time points, if any, and generates sufficient data for f_2 statistical analysis, which measures the closeness between the two dissolution profiles.²⁰²

The Draft Vancomycin BE Guidance not only requires sampling at early time points (5, 10, and 20 minutes), but also requires dissolution to be performed in three dissolution media with a range of pH from 1.2 to 6.8 to precisely characterize the dissolution behavior and reveal any potential difference between the generic vancomycin HCl capsules and the RLD. Such difference, if any, will be detected by HPLC because of its high sensitivity, accuracy and precision. These data generated from the comparative dissolution studies then will be subjected to the f_2 analysis to statistically demonstrate the equivalence between two dissolution profiles.

This stringent measurement of comparative dissolution, along with the quality control requirements set forth in the USP monograph, and the stability requirements recommended in relevant FDA guidances, ensure the product bioequivalence to the RLD.

²⁰⁰ Best, et al. "Chromatographic Separation of the Vancomycin Complex," at 15; Inman. "Determination of Vancomycin Related Substances by Gradient High-Performance Liquid Chromatography," at 363-372; Vila et al., "Analytical Methods for Vancomycin Determination in Biological Fluids and in Pharmaceuticals," at 395-399 (2007).

²⁰¹ The bioassay is a functional assay that considers the overall contribution of multiple components. If an individual component released heterogeneously (i.e., was not released at the same rate in each vancomycin product), the bioassay would not be able to detect the difference. In contrast, the HPLC method can reveal how much of each component is in the solution at a given time point if a heterogeneous dissolution happens.

²⁰² Tsong, Y., Sathe, P.M., Shah, V.P. *In Vitro Dissolution Profile Comparison. Encyclopedia of Biopharmaceutical Statistics: Second Edition* (April 2003).

FDA therefore concludes that the HPLC method is the most appropriate methodology available to assess the comparative dissolution of vancomycin capsule formulations.

(g) Appropriate Reference Standards for Use in the HPLC Analysis

As a general matter, HPLC methods are used in a comparative mode, which requires the use of reference standards for quantitation. The quality of reference standards is critical to ensuring accurate results, and these materials should be highly purified and well-characterized. As the Agency indicated in its draft guidance for industry on *Analytical Procedures and Method Validation*, reference standards from the USP/NF and other official sources do not require further characterization.²⁰³ When there is no official source, a reference standard should be of the highest purity available and well-characterized to assure the purity, strength, identity, and quality of the material. Methods using noncompendial reference standards must incorporate any purity correction factor into calculations. Working reference standards are usually materials that were characterized and had their purity established against a primary reference standard. These sometimes are used in cases in which it is more cost effective to certify an in-house lot than to purchase USP reference materials for routine analysis.

Currently there are two USP reference standards available for vancomycin, Vancomycin HCl RS and Vancomycin B with Monodechlorovancomycin RS. The former is indicated for use in the Microbial Assay and the latter for the Limit of Monodechlorovancomycin by HPLC methodology in accordance with the USP monograph. Vancomycin B with Monodechlorovancomycin RS has weight/weight strength of Vancomycin B, which is the major component of Vancomycin, and is controlled by the Chromatographic Purity test in the same monograph. As a USP reference standard, it meets the requirements for the purity, strength, identity, and quality, and is intended to be used in HPLC analysis.

By using USP Vancomycin B with Monodechlorovancomycin RS, the HPLC method essentially quantifies vancomycin B as a surrogate to vancomycin. This approach is appropriate for use to evaluate comparative dissolution for the following reasons:

- Vancomycin B is the compound of greatest abundance in vancomycin.²⁰⁴
- Vancomycin B is the most critical component recognized by USP and specifically controlled by Chromatographic Purity test in the monograph.²⁰⁵
- The dominance of vancomycin B in vancomycin HCl has been consistently demonstrated at mid-90s percentage in the corresponding DMFs and ANDAs as a result of current purification technology.

²⁰³ Draft guidance for industry on *Analytical Procedures and Method Validation* (Aug. 2008).

²⁰⁴ Best et al., *ChromatoGraphic Separation of the Vancomycin Complex*, at 15.

²⁰⁵ USP Monograph on Vancomycin Hydrochloride, USP 32 - NF 29, at 4565-66

Therefore, the Vancomycin B with Monodechlorovancomycin RS can be used without further qualification as a reference standard for quantitative analysis of vancomycin B by HPLC method to assess comparative dissolution.

While the USP Vancomycin HCl reference standard does not similarly quantify vancomycin B as a surrogate to vancomycin, the reference standard meets USP requirements for identity and quality, and may be used in the HPLC method for comparative dissolution assessment of vancomycin capsules. Because the HPLC method will assess both the RLD and the ANDA product against the same USP reference standard, it will reveal differences in dissolution between the RLD and proposed generic product as a result of formulation differences.

Based on the foregoing considerations, FDA has concluded that a fully validated HPLC method using USP reference standards (or other qualified reference standards), coupled with the dissolution requirements in the draft guidance and f_2 criteria, is the appropriate methodology for assessing comparative dissolution of generic vancomycin capsules.²⁰⁶

7. Recent Articles by Omar Vesga and Colleagues Do Not Provide a Scientific Basis for Prohibiting Use of In Vitro Dissolution Data for Demonstrating Bioequivalence of Generic Vancomycin Capsules

You next cite two articles by Dr. Omar Vesga and his colleagues in which the authors claim that generic parenteral vancomycin products that pass in vitro potency assays have different in vivo performance from Vancocin. You claim that these papers indicate that there is no in vitro test or combination of in vitro tests that would ensure bioequivalence for generic vancomycin and reliably predict in vivo performance of the product.

These papers refer to the parenteral dosage forms of vancomycin, not the capsule solid oral dosage form at issue here. There are multiple ANDAs approved for the parenteral dosage form. As discussed below, FDA has considered these publications and your related arguments, and has determined that they provide no basis for rejecting use of the in vitro bioequivalence methodology set forth in the Draft Vancomycin BE Guidance to demonstrate bioequivalence of generic vancomycin capsules.²⁰⁷

(a) The 2009 Article Does Not Provide a Basis for Challenging FDA's Recommended In Vitro Dissolution Bioequivalence Methodology

First, you reference a 2009 paper published by Vesga and his research group entitled "*Application of microbiological assay to determine pharmaceutical equivalence of*

²⁰⁶ Your suggestion that "in light of the inaccurate vancomycin dissolution data already received from the generic industry, to ensure the validation of any method proposed by a generic firm, FDA would need to independently validate the method in any event" is misplaced. VP July 20, 2010, Supp. at 12, n.41. FDA requires any ANDA sponsor to provide evidence that any methodology it uses to assess comparative dissolution has been validated. FDA evaluates the sufficiency of such evidence upon review of the individual ANDAs as part of the review process. Any deficiencies in the validation method would be identified at that time.

²⁰⁷ Draft Vancomycin BE Guidance at 1-2.

*generic intravenous antibiotics.*²⁰⁸ You note that despite the fact that “physicochemical methods [like the high performance liquid chromatographic (HPLC) method] are preferred over bioassays to determine [drug] concentration,” the authors of the article rejected use of such methods due to the fact that “significant variations in concentration are characteristic of vancomycin thereby making the ability to distinguish between concentration and potency integral to any analysis.”²⁰⁹ Instead, you assert, the authors identified “a microbiological assay using large plates designed to determine potency and concentration of pharmaceutical-grade antibiotics for injection and a statistical method to assess the in vitro equivalence of generic products with respect to the innovator.”²¹⁰

Although the authors identified this in vitro method to assess parenteral vancomycin, they (and you) argue that the method provides insufficient characterization of the vancomycin capsule due to the degradation products contained within that dosage form.²¹¹ You assert that as a result of this limitation, and because “noncompedial” HPLC methods do not measure potency and the established USP bioassay does not measure concentration of degradation products, there is no feasible, sufficiently validated in vitro test or combination of tests that would ensure bioequivalence for generic vancomycin and reliably predict in vivo performance of the product.²¹²

FDA agrees that the methods in that article are limited in that they only evaluate product potency and do not measure the purity of the antibiotics, and therefore, that the microbial assay developed would not be sufficient to provide the data necessary to demonstrate pharmaceutical quality, including purity. There is no support, however, for your claim that the article demonstrates that there is no feasible, sufficiently validated in vitro test or combination of tests that would ensure bioequivalence for generic vancomycin capsules and reliably predict in vivo performance of the product. Currently, as described above, vancomycin capsule ANDA applicants are requested to submit both microbial potency and HPLC data from validated methodologies. The measurement of comparative dissolution using a validated HPLC method, along with the quality control requirements including the microbial potency requirements set forth in the USP monographs for vancomycin, and the stability requirements recommended in relevant FDA guidances, ensure the product’s bioequivalence.

(b) The 2010 Article on Parenteral Vancomycin Does Not Provide a Basis for Challenging FDA’s Recommended In Vitro Dissolution Bioequivalence Methodology

You next address a 2010 article published by Vesga and his research group entitled “Generic Vancomycin Products Fail In Vivo Despite Being Pharmaceutical Equivalents

²⁰⁸ Andres, F., Zuluaga et al., “Application of Microbiological Assay to Determine Pharmaceutical Equivalence of Generic Intravenous Antibiotics,” 2009, 9 BMC *Clinical Pharmacology* 1, 10 (Zuluaga Article).

²⁰⁹ VP Nov. 21, 2011, Supp. at 2.

²¹⁰ Id. at 2.

²¹¹ Id.

²¹² Id. at 3.

of the Innovator.”²¹³ You assert that Vesga demonstrated that all of the generic products he evaluated failed to demonstrate in vivo equivalence despite the fact that each generic was “undistinguishable from the innovator based on concentration and potency, protein binding, in vitro antibacterial effect … and serum pharmacokinetics.”²¹⁴ You cite four reasons identified by Vesga as causes of this failure to demonstrate the same in vivo performance: (1) antibiotics are secreted in nature and industrial production of an API involves complicated biosynthesis, purification, and manufacturing processes that are difficult to replicate; (2) two molecules can look similar without being identical and can display different biological effects; (3) generic manufacturers may not know the character of excipients employed by innovator manufacturers sufficient to avoid polymorphs; and (4) antimicrobials interact with the host and confront an invader organism, which creates a dynamic triangle with numerous possibilities of biologic variation.²¹⁵

Vesga claims that his study demonstrated that parenteral vancomycin products that are equivalent in potency as measured by microbial assay demonstrated different in vivo performance in animal models. As a preliminary matter, the study was deficient in at least three ways. First, the study did not establish the chain of custody and storage conditions of the U.S.-sourced products used by Vesga.²¹⁶ If the products were stored inappropriately under conditions that could lead to the formation of impurities, then material used by the investigator would not be representative of the products in the U.S. marketplace. Second, the study did not characterize the purity of the products used in the study. If the purity of the products used in the study differed from those currently in the marketplace, then the study’s findings would not be relevant. Third, Vesga claims that crystalline degradation products (CDP-1) would be present at two to three times more in generic vancomycin parenteral products and that this could explain the in vivo findings of different potency. Vesga did not characterize the CDP-1 levels in the products used in his study, however, and, thus, his claim was unsupported.²¹⁷ Table 3 below contains the result of FDA’s Division of Pharmaceutical Analysis (DPA) laboratory evaluation of the purity of FDA-approved vancomycin injection products (including CDP-1 levels). FDA found that the maximum CDP in any tested product was 2%, and not at the levels Vesga speculated were present.²¹⁸

²¹³ Vesga, O. et al., “Generic Vancomycin Products Fail In Vivo Despite Being Pharmaceutical Equivalents of the Innovator,” 2010, 54 *Antimicrobial Agents and Chemotherapy* 8, 3271-1279 (Vesga Article).

²¹⁴ VP Nov. 21, 2011 Supp. at 4 (internal quotation to article omitted).

²¹⁵ VP Nov. 21, 2011, Supp. at 4-5.

²¹⁶ Vesga Article at 3272-3273.

²¹⁷ Id. at 3277-3278.

²¹⁸ CDER Division of Pharmaceutical Analysis, Memorandum re: Evaluation of Vancomycin Marketplace Products by UPLC-MS, at 2 (Sept. 19, 2011); CDER Division of Pharmaceutical Analysis, Memorandum re: Evaluation of Vancomycin in Marketplace Products, at 1 (April 15, 2011).

Source	% CDP-1 (BP method)	% CDP-1 (UPLC-UV method)	% CDP-1 (UPLC-MS method)
Sandoz	1.8	1.1	1.6
Baxter (lot 1)	0.6		
Baxter (lot 2)		0.3	0.7
Hospira	1.4	0.5	1.3
APP (lot 1)	1.2		
APP (lot 2)		ND	0.9
Bioniche (lot 1)	2.0		
Bioniche (lot 2)		0.2	1.4
Akorn (lot 1)	1.9		
Akorn (lot 2)		0.6	1.5

With respect to the particular points you raised regarding the Vesga article:

- (1) FDA allows the API of generic products to be produced by different manufacturing processes, so the generic sponsor does not have to replicate the innovator's API manufacturing process.²¹⁹ However, the API used in generic products should meet the identity, potency, purity, and other quality standards as the API used in the brand product.²²⁰
- (2) As discussed above, vancomycin can be specifically identified at the molecular level by current, validated analytical methods including the HPLC method.
- (3) In the United States, the generic injectable vancomycin products must contain the same excipients in the same amount as the RLD product,²²¹ so this point is not relevant.
- (4) There is biologic variation, but this variation affects both the brand and the generic product equally. For example, if the organism changes the host, both the brand and generic antibiotics are exposed to the changed host environment and would be equally affected by the same biological variability because they provide equivalent exposure of the same active ingredient to the host and organism.

Thus these differences do not support your argument that in vivo efficacy studies for generic vancomycin capsules are necessary to demonstrate bioequivalence.

²¹⁹ See generally, 21 U.S.C. 355(j)(2) (does not require demonstration of same manufacturing process as reference listed drug); 21 CFR 314.94(a)(9)(i) (requiring information related to manufacture of ANDA product).

²²⁰ 21 U.S.C. 355(j)(2)(A)(ii)(I) (same active ingredient requirement).

²²¹ 21 CFR 314.94(a)(9)(iii).

(c) The Vesga Article Does Not Demonstrate That Potential Manufacturing Differences Alter In Vivo Performance Such That In Vivo Data Are Necessary to Demonstrate Bioequivalence

You next assert that FDA's current recommendation that generic vancomycin capsules need only demonstrate Q1/Q2 sameness fails to adequately account for potential wide variation in manufacturing and formulation conditions, which you refer to inaccurately as "Q3" sameness. In support of this position, you claim that Vesga has demonstrated that manufacturers that are not required to copy the manufacturing conditions of the innovator can alter the in vivo performance of vancomycin, and that current in vitro testing methods are insensitive to such manufacturing-associated differences.²²²

Your claims about different manufacturing processes are not relevant to Q3 equivalence. As discussed above, "Q3" sameness generally means the formulations have the same structural characteristics in terms of components, concentration, and microstructure.²²³ The products evaluated in this article were all solutions that are, by definition, Q3 equivalent. Solutions of dissolved drugs have no specific structural arrangement of matter or microstructure. Once a drug is dissolved, there is no trace of the solid structure the material had before it dissolved. The Q3 concept is intended to describe differences in solid structure and thus is not relevant to solutions.

For generic vancomycin capsules, we previously have discussed in section II.B.4 above, why Q3 sameness is not required to demonstrate bioequivalence. The Vesga Article's concerns about manufacturing processes for the parenteral products are related to the potential for different manufacturing processes to produce different impurities. As discussed above, chromatographic methods can characterize the impurities present in vancomycin capsules and thus, would identify whether a difference in manufacturing process had a significant impact on product impurities.

You also argue that in light of the Vesga and Zuluaga Articles, FDA must provide a scientific rationale for its currently recommended in vitro dissolution methodology and assess (1) the potential insensitivity of the recommended methodology with respect to product purity of the API used in parenteral formulations; (2) the "wholly unstudied and untested" impact of small deviations in excipient profiles on generic products; (3) the potential impact of differences in degradation profiles as a function of process and formulation differences, and "what, if any, data support OGD's conclusion that such differences would not result in in vivo performance differences when generics need only meet [current good manufacturing practices]."²²⁴

²²² VP Nov. 21, 2011, Supp. at 4.

²²³ Wilkin, Jonathan, Presentation: *The Pursuit of Alternative Methodologies For Demonstrating Bioequivalence for Generic Topical Dermatologic Drug Products: DPK, Q3, Cakes, and 2 PIs.*

²²⁴ VP Nov. 21, 2011, Supp. at 6.

FDA permits generic versions of Vancocin Capsules to demonstrate bioequivalence using an in vitro dissolution test if they are Q1/Q2 the same as Vancocin (or can demonstrate that differences in excipients do not affect the safety or effectiveness of the product), and meet appropriate chemistry, manufacturing and control quality standards. These quality standards include both antimicrobial potency and standards for ensuring purity using HPLC methods. The Vesga and Zuluaga Articles do not provide evidence that products with equivalent potency and purity would behave differently in vivo; they only considered potency testing and did not characterize the purity of the products used in the study.²²⁵

(d) The ACPS Does Not Need To Be Reconvened To Consider the Vesga and Zuluaga Articles and/or Q3 Sameness

You assert that members of the August 2009 ACPS that considered use of an in vitro bioequivalence methodology for vancomycin expressed concern that tight manufacturing controls and more rigorous manufacturing site inspections should be conducted for generic vancomycin products as compared to other generic products. In light of the members' concerns and Vesga's work (which was not considered by the Committee), you claim that a new advisory committee meeting that includes Dr. Vesga is necessary to consider (1) whether Q3 sameness should be required; and (2) the impact of Vesga's "evidence" that in vivo performance cannot be reliably predicted by existing in vitro tests.²²⁶

At the 2009 ACPS meeting, Committee members mentioned the importance of manufacturing controls, inspections, and postmarketing evaluations, but they did not indicate that vancomycin should be subject to more rigorous evaluation than other products.²²⁷

Of note, representatives of ViroPharma presented the "Q3" issue at the August 2009 meeting.²²⁸ The Committee discussed but did not endorse your recommendation that Q3 sameness be required for demonstrating vancomycin bioequivalence using in vitro data.²²⁹ Further, the Vesga and Zuluaga Articles do not provide the complete characterization of the purity of the products studied that would be needed as an initial matter to evaluate their conclusions, nor does either Article present any issues that support the need for an additional advisory committee meeting.

²²⁵ Generic and reference products are permitted to have some differences in impurities. As part of the ANDA submission, the generic sponsor provides information on the purity of its product. In the ANDA review process these impurity levels are reviewed for acceptability based in part on what is known about the purity of the reference product. In addition, compendial (USP) standards are also considered and an overall conclusion about the acceptable purity for generic product is made. See the guidance for industry on *ANDAs: Impurities in Drug Products* (Nov. 2010).

²²⁶ VP Nov. 21, 2011, Supp. at 7.

²²⁷ 2009 ACPS Tr. at 144-152.

²²⁸ ViroPharma Slide Presentation, at 19, 31, Aug. 4, 2009 ACPS Meeting, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM179424.pdf>.

²²⁹ See, e.g., 2009 ACPS Tr. at 161-166; 219-20, 298 ("I find that [Q3] sameness an interesting idea, but I'm not sure the case was fully made") (comment of Dr. Nembhard).

You thus have not demonstrated that there is a need for the ACPS to consider any of these issues, or to reconsider its 2009 unanimous endorsement of the bioequivalence recommendation in the Draft Vancomycin BE Guidance.

(e) Your Request That the Agency Take Into Special Account Risks That May Be Posed to Patients By Non-Bioequivalent Generic Vancomycin Capsules Before Permitting In Vitro Data to Demonstrate Bioequivalence Disregards the Statutory Requirements of Section 505(j)

You refer to comments submitted to the citizen petition docket by members of the scientific and medical communities and to the World Health Organization's position on consideration of patient populations. You assert that the Agency must take into account the severity of the risks to patients that may be posed by substituting inequivalent generic vancomycin capsules before permitting in vitro data to demonstrate bioequivalence.

FDA will not approve a generic drug unless it determines that the drug can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. As such, we apply the most appropriate scientific standards (including the identification of recommended bioequivalence studies) to all generic drugs to ensure that only drugs that meet this rigorous standard are approved. FDA does not lower the criteria for ANDA approval (including the standards for finding sameness of generic and reference products), for those drugs where inequivalence is not expected to have a significant impact on patients. The converse is also true — the approval standards are sufficiently rigorous and robust that they do not need to be raised even where the patient populations are particularly sensitive or the product is intended to treat a life-threatening condition.

Regarding the sufficiency of in vitro equivalence testing to evaluate the bioequivalence of generic oral capsule vancomycin products to the reference product, this was the primary focus of the 2009 meeting of FDA's Advisory Committee for Pharmaceutical Science. Their unanimous conclusion was that in vitro testing was the most appropriate method for assessing bioequivalence for oral vancomycin products.

8. ANDA Applicants Are Not Required To Submit "Failed" Bioequivalence Studies

You next assert that FDA must require all ANDA applicants for generic vancomycin to submit all bioequivalence studies they have conducted in order to prevent fraud on the Agency and to avoid "gerrymandering" of favorable dissolution results, citing the recently amended 21 CFR 314.94(a)(7).²³⁰ As of 2009, this regulation requires ANDA applicants to submit all bioequivalence studies conducted on a drug product formulation for which approval is sought. But FDA expressly declined to apply the rule retroactively. As stated in the preamble to the final rule: "[w]ith respect to ANDAs, amendments or

²³⁰ VP Draft Guidance Resp. at 49; VP Dec. 2, 2009, Supp. at 6; VP June 25, 2010, Supp. at 10.

supplements submitted prior to [July 15, 2009], applicants are not required to report additional BE studies that were conducted with their applications.”²³¹

C. FDA Has the Legal Authority to Accept In Vitro Dissolution Data To Establish Bioequivalence for Generic Vancomycin

In addition to your scientific challenges to the vancomycin bioequivalence recommendation, you dispute FDA’s legal authority to accept in vitro data to demonstrate bioequivalence of generic vancomycin products on myriad grounds. None of your legal arguments has merit, as we explain in detail below.

1. The Draft Vancomycin BE Guidance In Vitro Methodology Complies With the Legal Requirement That an Applicant Use the Most Accurate, Sensitive and Reproducible Methodology Available

As described in detail in section I.B., Congress has given FDA broad authority to determine the appropriate method by which an ANDA applicant can establish bioequivalence for generic vancomycin (section 505(j)(8) of the FD&C Act). This authority is reflected in various provisions of the statute (e.g., section 505(j)(7)(a)(iii)), and serves as the cornerstone of bioequivalence regulations set forth in section 320.24(a): “FDA may require in vivo or in vitro testing, or both, to ... establish the bioequivalence of specific drug products.” Subsection 320.24(b) outlines different methods by which bioequivalence may be demonstrated, and permits, in addition to the delineated methods, “[a]ny other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence.”²³²

You assert that, as a legal matter, an ANDA applicant for vancomycin capsules must provide data from clinical endpoint bioequivalence studies, rather than in vitro data, because such studies are listed higher on the descending scale of acceptable bioequivalence methodologies set forth in 21 CFR 320.24(b), and otherwise are “feasible.”²³³ Section 320.24(b) sets forth methodologies in descending order of preference as a general matter. The ultimate selection of the appropriate bioequivalence method is determined on a case-by-case basis, however, and “depends upon the purpose of the study, the analytical methods available, and the nature of the drug product.”²³⁴

²³¹ Requirements for Submission of Bioequivalence Data; Final Rule, 74 FR 2849, 2858 (Jan. 16, 2009).

²³² 21 CFR 320.24(e).

²³³ VP Oct. 6, 2009, Supp. at 14, n.63.

²³⁴ 21 CFR 320.24(a) (emphasis added). See also Abbreviated New Drug Application Regulations: Final Rule, 57 FR 17950, 17972 (April 28, 1992) (“[t]he preferred method for establishment of bioequivalence ... is determined on a case-by-case basis, depending on the drug under study”).

FDA has determined, for the reasons set forth above in section II.A and C, that the most accurate, sensitive, and reproducible approach available for demonstrating vancomycin capsule bioequivalence is one using in vitro dissolution data, and not clinical study data, which is the least sensitive for this product. This decision is fully consistent with the regulations.

2. Section 320.24(b)(1)(ii) Does Not Provide the Sole Basis for Permitting In Vitro Data To Demonstrate Bioequivalence

You assert that subsection 320.24(b)(1)(ii), which describes a bioequivalence approach in which in vitro data is correlated with in vivo data, is the exclusive circumstance in which FDA may accept in vitro studies to establish bioequivalence.²³⁵ You appear to be invoking the interpretative maxim *expressio unius est exclusio alterius*, which provides that the expression of one item of an associated group or series should be interpreted to exclude another left unmentioned. As courts have noted, however, this canon does not apply when the Agency has indicated, as it clearly has here, that the enumeration is not intended to be exclusive.²³⁶ Subsection 320.24(e) expressly provides that bioequivalence may be demonstrated by “[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence” in addition to those set out in subsections 320.24(b)-(d).²³⁷ Your attempt to narrow section 320.24 therefore is unavailing, and more generally is inconsistent with the broad discretion granted FDA to determine an appropriate bioequivalence methodology.²³⁸

3. There Is No Default Requirement for In Vivo Data to Demonstrate Bioequivalence

You next argue that the bioequivalence regulations “establish a general rule in 21 CFR 320.21 that to demonstrate bioequivalence ANDA sponsors must submit information obtained in vivo, unless a sponsor can meet the criteria for a waiver set forth in 21 CFR 320.22.”²³⁹ Your argument lacks merit because there is no such “general rule” requiring in vivo data, as is evident from the plain language of the bioequivalence regulations. Section 320.1(f) defines “[b]ioequivalence requirement” as “a requirement imposed by the Food and Drug Administration for in vitro and/or in vivo testing of specified drug products which must be satisfied as a condition of marketing.”²⁴⁰ Section 320.24(a) provides that “FDA may require in vivo or in vitro testing, or both, to measure the

²³⁵ VP Supp. Oct. 6, 2009, Supp. at 12; VP Draft BE Guidance Resp. at 8.

²³⁶ *Ohio v. U.S. Dep’t of the Interior*, 880 F.2d 432, 446-47 (D.C. Cir. 1989) (rejecting invocation of maxim where Congress expressly noted related list included but was not limited to certain elements of damage awards).

²³⁷ 21 CFR 320.24(e). You assert that 320.24(e) is limited to special in vivo situations involving animal drugs or isotopically labeled drugs, based on statements in a preamble to the 1977 regulations. VP July 25, 2008, Supp. at 6. The plain language of this provision – “[a]ny other approach deemed adequate by FDA” — cannot reasonably be construed to be so restricted, however. *Thomas Jefferson University v. Shalala*, 512 U.S. 504, 515 (1994) (rejecting petitioner’s effort to limit plain language of broad regulation).

²³⁸ VP Supp. Dec. 2, 2009, at 4. For these reasons, your related assertion that the regulations must be amended for an applicant to rely solely on in vitro dissolution studies is misplaced.

²³⁹ VP July 25, 2008, Supp. at 1-2.

²⁴⁰ 21 CFR 320.1(f).

bioavailability of a drug product or establish the bioequivalence of specific drug products.”²⁴¹ Section 320.24(b) then lists methodologies — in vivo, in vitro, and “any other approach deemed adequate by FDA” — to measure bioequivalence. These provisions are consistent with the discretion accorded the Agency by Congress in section 505(j)(8)(C) of the FD&C Act (FDA “may establish alternative, scientifically valid methods to show bioequivalence” for drug products, including vancomycin).

Your related assertion — that FDA’s acceptance of in vitro data to demonstrate bioequivalence under its section 320.24 authority renders section 320.22 superfluous — is unavailing. If FDA establishes an in vivo data requirement for a proposed generic product, then subsection 320.21(b)(2) permits an ANDA applicant to seek waiver of such a requirement in the manner specified in subsection 320.22.²⁴² If FDA does not require in vivo data to demonstrate bioequivalence in the first instance, then sections 320.21(b)(2) and 320.22 do not apply. In other words, the waiver procedure set forth in section 320.22 applies only after FDA determines that in vivo data should be submitted.²⁴³

Notably, the text of section 320.21 (“Requirements for submission of bioavailability and bioequivalence data”) itself, which you cite as the authority for your position, evidences the regulation’s limited function. Section 320.21(a) pertains to the requirement for NDA applicants to demonstrate bioavailability of a proposed new drug product, and requires such an applicant to provide “(1) [e]vidence measuring the in vivo bioavailability of the drug product that is the subject of the application; or (2) [i]nformation to permit FDA to waive the submission of evidence measuring in vivo bioavailability” (emphasis added).²⁴⁴ Section 320.21(b), by contrast, pertains to the ANDA requirement of demonstrating bioequivalence, and does not contain an in vivo data requirement. Rather, the bioequivalence data provision requires an ANDA applicant to submit “[e]vidence demonstrating that the drug product that is the subject of the abbreviated new drug application is bioequivalent to the reference listed drug [...], or (2) [i]nformation to show that the drug product is bioequivalent to the reference listed drug which would permit FDA to waive the submission of evidence demonstrating in vivo bioequivalence as provided in paragraph (f) of this section.” Sub-paragraph (2) requires conformance with section 320.22 when an applicant seeks waiver of an Agency-imposed in vivo data requirement. Your interpretation, which would require clinical testing of patients in all cases unless the narrow exceptions set forth in section 320.22 are met, also runs counter to the guiding principle, articulated in section 320.25, that “no unnecessary human research should be done.”²⁴⁵

²⁴¹ 21 CFR 320.24(a).

²⁴² 21 CFR 320.21(b)(2) and (f).

²⁴³ For these reasons, your assertions that FDA seeks to rely on section 320.24 as an authority for waiver of an in vivo data requirement for vancomycin, and for other recent generic drug approvals also are unavailing. VP July 25, 2008, Supp. at 3, 5-7.

²⁴⁴ 21 CFR 320.21(a).

²⁴⁵ 21 CFR 320.25(a) (entitled “Guiding Principles”) (“The basic principle in an in vivo bioavailability study is that no unnecessary human research should be done”).

In addition, the regulatory history shows that FDA has not established a default in vivo data requirement. Indeed, the history makes clear that FDA intended to exercise the full scope of its statutory discretion to determine the appropriate bioequivalence methodology. In the preamble to the 1992 final rule, FDA explained that, depending upon the drug, the Agency would determine the appropriate bioequivalence methodology on a case-by-case basis:

Bioequivalence can be established by pharmacodynamic measurement as well as by in vitro techniques and bioequivalence studies with clinical endpoints. The preferred method for establishment of bioequivalence . . . is determined on a case-by-case basis, depending on the drug under study.²⁴⁶

FDA pointed out that Congress had authorized both in vivo and in vitro methods to establish bioequivalence: “[h]ad Congress intended to require only direct measurements of the rate and extent of absorption in the human body, it would not have also permitted in vitro studies to satisfy the bioequivalence requirements.”²⁴⁷ In the same preamble, FDA rejected a suggestion that the Agency amend a separate regulation — subsection 314.94(a)(7)(iii), which sets forth the required contents of an ANDA — to state that waivers from an in vivo bioequivalence requirement are available under 21 CFR § 320.22.²⁴⁸ The Agency reasoned that “[s]ection 314.94(a)(7), generally, and § 314.94(a)(7)(iii), specifically, do not require in vivo bioequivalence.”²⁴⁹ FDA further noted, “[i]nformation to show bioequivalence may, depending upon the drug product, come from an in vivo or an in vitro study.”²⁵⁰

You cite language from the 1989 preamble to the proposed rule regarding FDA’s intent to eliminate a provision for a blanket waiver of in vivo bioavailability for generic drugs, the former section 320.22(d)(5).²⁵¹ FDA sought to remove this blanket waiver because it “ha[d] no evidence to show that in vitro data alone are regularly sufficient to assure bioequivalence.”²⁵² Contrary to your contention, FDA’s elimination of a blanket waiver did not “explicitly relinquish” the Agency’s statutory discretion to determine the appropriate bioequivalence methodology on a case-by-case basis.

To further support your argument, you similarly cite FDA’s elimination of an automatic waiver of in vivo tests for “an oral dosage form that is not intended for systemic absorption.”²⁵³ FDA explained in the preamble to the 1992 final rule that it removed the automatic waiver because in vivo tests “may be required for certain products.”²⁵⁴ The Agency reasoned that “requests for waiver of in vivo . . . bioequivalence for these products need to be reviewed on a case-by-case basis,” and noted that “the regulation

²⁴⁶ *Abbreviated New Drug Application Regulations: Final Rule*, 57 FR at 17972 (emphasis added).

²⁴⁷ Id.

²⁴⁸ Id. at 17960.

²⁴⁹ Id.

²⁵⁰ Id.

²⁵¹ VP July 25, 2008, Supp. at 6, n.18 (citing 21 CFR 320.22(d)(5) (1983)).

²⁵² *Abbreviated New Drug Application Regulations, Proposed Rule*, 54 FR at 28912 (emphasis added).

²⁵³ VP July 25, 2008, Supp. at 6, n.18; VP Draft Guidance Resp. at 40.

²⁵⁴ *Abbreviated New Drug Application Regulations: Final Rule*, 57 FR at 17975.

does permit applicants to request a waiver of the requirement for the submission of evidence in the form of in vivo . . . bioequivalence data provided the product meets the criteria in § 320.22.”²⁵⁵ This language describes applicants’ ability to request waivers under section 320.22, but does not “explicitly relinquish” FDA’s statutory discretion to make independent determinations of the appropriate bioequivalence methodology pursuant to subsection 320.24(a) in the first instance.

You also seek to draw support from FDA’s correction, in subsection 320.21(f), of an erroneous reference to section 320.24 instead of section 320.22.²⁵⁶ Subsection 320.21(f) originally read as follows: “[i]nformation to permit FDA to waive the submission of evidence . . . demonstrating the in vivo bioequivalence shall meet the criteria set forth in § 320.24.” In 1998, FDA amended this provision to change the section referenced: subsection 320.21(f) now refers to section 320.22. FDA explained that “Section 320.21(f) inaccurately includes a reference to criteria set forth in § 320.24 as containing information under which FDA could waive the requirement for submission of evidence demonstrating in vivo . . . bioequivalence.”²⁵⁷ This correction does not have the significance that you claim. FDA does not dispute that section 320.22 contains criteria relating to waivers that an applicant may request, and that those criteria are what subsection 320.21(f) was intended to reference. But the correction did not affect subsection 320.24(a), which does not pertain to waivers, but rather, sets out FDA’s authority for determining what type of data is required for demonstrating bioequivalence in the first instance.

Finally, there is no merit to your claim that FDA cannot allow an ANDA applicant to demonstrate bioequivalence for vancomycin through in vitro data without receiving a waiver under the authority of the BCS Guidance.²⁵⁸ As discussed in above, FDA is not requiring ANDA applicants for generic vancomycin to submit in vivo data, so they do not need to request a waiver for such a requirement. Even if FDA were to impose an in vivo data requirement for which a generic applicant might seek a waiver, the BCS Guidance does not provide the authority for waivers of in vivo data, nor does it describe the totality of the circumstances in which such waivers may be available. It merely sets out the Agency’s thinking on some scenarios in which such waivers may be appropriate. Your related suggestion that the BCS Guidance sets forth an exhaustive list of the circumstances in which a waiver of in vivo bioequivalence is available is contrary to the clear language of the statute, which provides that FDA has broad discretion to establish bioequivalence standards.²⁵⁹

²⁵⁵ Id.

²⁵⁶ VP July 25, 2008, Supp. at 6-7.

²⁵⁷ *Bioavailability and Bioequivalence Requirements: Abbreviated Applications; Proposed Revisions*, 63 FR 64222, 64223 (Nov. 19, 1998).

²⁵⁸ VP Draft Guidance Resp. at 19-20.

²⁵⁹ Section 505(j)(8)(C) of the FD&C Act. See also 21 CFR 320.24(a).

4. FDA Need Not Amend Section 320.22 To Consider Q1/Q2 Sameness in Determining Bioequivalence

You next claim that FDA can only consider Q1/Q2 sameness in bioequivalence determinations in the context of a waiver of an in vivo data requirement for the classes of products specified in 21 CFR 320.22(d), which subsection involves consideration of inactive ingredient similarity and/or sameness. Your argument misconstrues FDA's authority to make bioequivalence determinations. FDA's discretion to determine the appropriate bioequivalence methodology for a product is authorized by the statute and section 320.24 of the regulations, not sections 320.21 and 320.22. As described above, section 320.22(d) is a narrow provision that provides a process by which applicants can apply for a waiver of an in vivo data requirement that FDA otherwise has imposed on a specific product or product. The specific provision that you cite, 320.22(d)(3), concerns oral solutions and involves consideration of inactive ingredient sameness. Citation to inactive ingredient sameness here does not preclude FDA's consideration of Q1/Q2 sameness in the context of a 320.24(a) determination. Nor is FDA, as you contend, attempting to amend 320.22(d)(3) to include products like vancomycin by permitting the use of Q1/Q2 sameness to support bioequivalence of generic vancomycin. Section 320.22 simply is not relevant to the recommended in vitro dissolution bioequivalence methodology for generic vancomycin.

5. FDA Is Not Precluded From Considering Exceptions to the Q1/Q2 Requirement

In the Draft Vancomycin BE Guidance, FDA indicates that it may permit in vitro dissolution data to demonstrate bioequivalence for products that are not Q1/Q2, if the applicant can demonstrate that the differences in excipients will not affect the safety or efficacy of the product. You maintain that accepting such evidence would constitute rulemaking without giving the public notice and an opportunity to comment, citing 21 CFR 314.94(a)(9)(iii)-(v), which relate to inactive ingredients in proposed generic products.²⁶⁰

Some statutory and regulatory background is necessary to address your argument. Section 505(j)(2) of the FD&C Act requires an ANDA applicant to submit information related to the inactive ingredients in a proposed generic product.²⁶¹ Consistent with the statute, subsection 314.94(a)(9)(ii) provides that “[u]nless otherwise stated in paragraphs (a)(9)(iii) through (a)(9)(v) of this section, an applicant shall identify and characterize the inactive ingredients in the proposed drug product.”²⁶² This subsection also requires an applicant to “provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product.”²⁶³

²⁶⁰ VP Mar. 25, 2010, Supp. at 27.

²⁶¹ 21 U.S.C. 355(j)(2)(vi).

²⁶² 21 CFR 314.94(a)(9)(ii).

²⁶³ Id.

In subsections 314.94(a)(9)(iii)-(a)(9)(v) (relating to parenteral, ophthalmic, and otic dosage forms, respectively), FDA has more stringent limitations on inactive ingredients to account for the fact that each of these drug products represents an individual pharmaceutical system with its own characteristics and requirements, and that inactive ingredients are added to maintain these systems.²⁶⁴ FDA “presume[s] different inactive ingredients in these products unsafe unless the applicant can rebut the presumption by demonstrating that the different inactive ingredient will not affect the safety of its proposed product.”²⁶⁵ For example, subsection 314.94(a)(9)(iii) provides that “a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug,” but that “an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.”²⁶⁶

You assert that the option set out in the Draft Vancomycin BE Guidance for ANDA applicants to use in vitro data for non-Q1/Q2 products if the applicant can show the differences do not affect safety or effectiveness, should not be available to ANDA applicants until FDA amends section 314.94(a)(9) to include a Q1/Q2 sameness requirement for products like vancomycin.²⁶⁷ But subsection 314.94(a)(9) is not related to what is permissible in demonstrating bioequivalence. Instead, subsections 314.94(a)(9)(iii)-(v) reflect the Agency’s determination of what generally is required in inactive ingredients to ensure safe use of certain products due to the fact that those products function as individual pharmaceutical systems. That context is completely different from the demonstration of bioequivalence using in vitro data.

You also assert that FDA may not consider in vitro data for products that are not Q1/Q2 because the August 2009 ACPS discussed but did not formally vote on this question.²⁶⁸ Although FDA acknowledges the fundamentally important role that advisory committees play in the regulatory approval process, FDA is not limited to accepting only data endorsed by an advisory committee. As the advisory committee regulations explicitly state, “[t]he Commissioner has sole discretion concerning action to be taken and policy to

²⁶⁴ *Abbreviated New Drug Applications; Proposed Rule*, 54 FR at 28883-884.

²⁶⁵ Id. at 28884.

²⁶⁶ Id. See also 21 CFR 314.94(a)(9)(iv) (“a drug product intended for ophthalmic or otic use shall contain the same inactive ingredients and in the same concentration as the reference listed drug ... However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product, except that, in a product intended for ophthalmic use, an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the listed drug...”); 21 CFR 314.94(a)(9)(v) (“[g]enerally, a drug product intended for topical use, solutions for aerosolization or nebulization, and nasal solutions shall contain the same inactive ingredients as the reference listed drug. However, an abbreviated application may include different inactive ingredients provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product”).

²⁶⁷ VP Mar. 25, 2010, Supp. at 27.

²⁶⁸ VP Dec. 2, 2009, Supp. at 4-5; VP Mar. 25, 2010, Supp. at 27 n.137.

be expressed on any matter considered by an advisory committee.”²⁶⁹ FDA is not bound by an advisory committee recommendation, and is empowered to act even in the absence of an advisory committee vote.

6. FDA Has Authority To Waive an In Vivo Bioequivalence Data Requirement

As described in detail above, FDA has the legal authority to establish bioequivalence standards for drug products, and in particular, to determine that in vitro dissolution studies may be submitted to establish bioequivalence of a generic drug product. Neither the statute nor the regulations impose a default in vivo data requirement for demonstrating bioequivalence, and thus, an ANDA applicant need not secure a waiver prior to the Agency accepting in vitro studies, unless FDA has determined that in vivo data is required. For generic vancomycin capsules, FDA has concluded that ANDA applicants may submit in vitro data under the specifications set forth above to establish bioequivalence for vancomycin capsules. An applicant therefore need not secure a waiver under section 320.22 to establish bioequivalence using in vitro dissolution data.

Even if there were a “default” in vivo data requirement for all NDAs so that a waiver under section 320.22 were required, FDA has determined that the Agency would waive such a requirement for generic vancomycin capsule applicants that meet the criteria for in vitro data set forth above under 21 CFR 320.22(e). Section 320.22(e) provides that “FDA, for good cause, may waive a requirement for the submission of evidence of . . . bioequivalence if waiver is compatible with the protection of the public health.”²⁷⁰ FDA concludes that such a waiver would be for good cause and compatible with the public health for generic vancomycin capsules for several reasons. As discussed above, vancomycin is one of only two FDA-approved treatments for the fast-moving, life-threatening colitis associated with CDAD. As detailed in your citizen petition supplements,²⁷¹ increased incidence of CDAD infections as well as more severe instances of the disease have been extensively reported in the medical literature and general media.²⁷² Medical literature also indicates that in light of the high demand and high cost of Vancocin Capsules, doctors and hospitals have begun administering vancomycin parenteral solution to patients orally to treat CDAD.²⁷³ This formulation has never been approved for oral use or for use in this fashion, and thus raises potential public health concerns including a risk of dosage errors. The availability of safe and effective generic

²⁶⁹ 21 CFR 14.5(b).

²⁷⁰ 21 CFR 320.22(e).

²⁷¹ VP June 30, 2006, Supp. at 10-14.

²⁷² Hall, A.J., Curns, L.C. McDonald, U.D. Parashar, B.A. Lopman, Centers for Disease Control and Prevention, “Abstract: Gastroenteritis Deaths on the Rise in the United States: The Emerging Roles of Clostridium difficile and Norovirus” at 190 (presented at 2012 International Conference on Emerging Infectious Diseases), available at http://www.iceid.org/images/iceid_2012_finalprogram_final.pdf.

²⁷³ Can. J. Hosp. Pharm. 2010 Sep-Oct; 63(5): 366–372; see also Generic Pharmaceutical Association, Presentation, Aug. 4, 2009 ACPS Meeting, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM179425.pdf>.

vancomycin capsules would mitigate these concerns consistent with the fundamental purposes of Hatch-Waxman: to make available to consumers safe and effective generic drug products.²⁷⁴

7. The FD&C Act Does Not Require That Individual Bioequivalence Recommendations Be Published in the Orange Book When an RLD Is Listed

You contend that subsection 505(j)(7)(A)(i)(III) of the FD&C Act requires FDA to publish a specific bioequivalence requirement for all listed drugs prior to (and irrespective of the likelihood of approval of) a pharmaceutically equivalent second drug, and that the Agency's failure to do so for vancomycin capsules violated the FD&C Act.²⁷⁵ Your contention is unfounded. Section 505(j)(7)(A)(i) provides that "the Secretary shall publish and make available to the public" three sets of information: "(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) ...; (II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and (III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published."²⁷⁶ The Orange Book lists approved drugs together with the approval date and the application number at the time the NDA is approved or shortly thereafter.²⁷⁷ The Agency fulfills the third prong of this statutory directive by including on the list of approved products a "therapeutic equivalence" code for each product once another product that is pharmaceutically equivalent to the listed product is approved.²⁷⁸ These therapeutic equivalence codes indicate the type of bioequivalence data FDA required prior to approving the therapeutically equivalent product(s).²⁷⁹

²⁷⁴ *Teva Pharm. Indus. v. Crawford*, 410 F.3d at 55; H.R. Rep. No. 98-857(I), at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2647-48 (stating that one of the purposes of the legislation is "to make available more low cost generic drugs"). Such a waiver also would promote FDA's general mission to protect the public health by ensuring only safe and effective products are marketed, and to ensure that the financial interests of consumers are protected. *U.S. v. Lane Labs-USA Inc.*, 427 F.3d 219, 227 (3d Cir. 2005) ("[t]he FDCA and its legislative history make it clear that Congress intended the statute to protect the financial interests of consumers as well their health").

²⁷⁵ VP Dec. 22, 2010, Supp. at 1-2.

²⁷⁶ 21 U.S.C. 355(j)(7)(A)(i)(III).

²⁷⁷ 21 CFR 314.3(b).

²⁷⁸ See 21 CFR 320.24(a) ("Information on bioequivalence requirements for specific products is included in the current edition of FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" and any current supplement to the publication"); *Abbreviated New Drug Application Regulations, Proposed Rule*, 54 FR at 28911 ("FDA satisfies [the section 505(j)(7)(A)(i)(III)] requirement through the use of therapeutic equivalence codes" in the Orange Book). Two products are considered "pharmaceutically equivalent" if they contain the same active ingredient(s), are of the same dosage form, route of administration, and are identical in strength or concentration (21 CFR 320.1(c)); *Orange Book*, introduction at v. Two products are considered "therapeutically equivalent" only if they are pharmaceutically equivalent and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the label. *Orange Book*, introduction at iv.

²⁷⁹ As described in the *Orange Book* Introduction, "[t]he coding system for therapeutic equivalence evaluations is constructed to allow users to determine quickly whether the Agency has evaluated a

You assert that FDA must publish information regarding bioequivalence requirements at the same time that the RLD is listed.²⁸⁰ The plain language of the statute does not mandate publication of this information at the time of the RLD listing, nor does it otherwise direct when FDA must fulfill this requirement. Notably, none of the courts that have considered FDA's compliance with section 505(j)(7)(A)(i)(III) have construed the statute in the manner you suggest or otherwise have found any legal deficiency in FDA's practice of listing bioequivalence data requirements for a listed drug at the time a pharmaceutically equivalent drug is approved.²⁸¹

In addition, your interpretation would render several other provisions of section 505(j) superfluous.²⁸² For example, section 505(j)(3)(b) requires the Agency to meet with an ANDA applicant to agree on the design and size of bioequivalence studies needed for approval if an applicant submits a reasonable written request for such a meeting. Under your view, the bioequivalence method would had to have been determined and published when FDA first approves and lists the RLD, and there would be no reason for such meetings with the ANDA applicant.

As a practical matter, your view would require the Agency to expend enormous resources to generate and evaluate the scientific data required to establish bioequivalence requirements, data the FD&C Act requires ANDA holders to provide in the ANDA.²⁸³ There is no evidence that Congress intended to place such a burden on the Agency through subsection 505(j)(a)(7)(A).²⁸⁴

8. Your Requests for an Opportunity to Comment on the Bioequivalence Recommendation for Generic Vancomycin Capsules Have Been Satisfied

In multiple submissions you have requested that FDA (1) publish and provide opportunity for public comment on FDA's vancomycin bioequivalence recommendation;²⁸⁵ (2) provide the scientific rationale underlying any bioequivalence recommendation;²⁸⁶ (3) refrain from approving any ANDA prior to publication of such

particular approved product as therapeutically equivalent to other pharmaceutically equivalent products (first letter) and to provide additional information on the basis of FDA's evaluations (second letter)." Id. at xiii. This additional information indicates the bioequivalence methodology utilized by the sponsor of the product. Id. at xv.

²⁸⁰ VP Dec. 22, 2010, Supp. at 1-2.

²⁸¹ See, e.g. *Schering Corp. v. FDA*, 51 F.3d at 398 (citing section 505(j)(7)(A)(i)(III) as evidence of Congressional intent to provide FDA discretion to determine appropriate bioequivalence methodology through the ANDA approval process).

²⁸² *Duncan v. Walker*, 533 U.S. 167, 174 (2001) ("It is our duty to give effect, if possible, to every clause and word of a statute. . . . We are thus reluctant to treat statutory terms as surplausage in any setting") (internal citation and quotation omitted).

²⁸³ 21 U.S.C. 355(j)(2)(A)(iv).

²⁸⁴ *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 351 and n.6 (2001) (uncontemplated increase of FDA's administrative burden in reviewing regulated products is improper).

²⁸⁵ See, e.g., Letter fr. T. Doyle, ViroPharma, to H. Winkle, Dir. CDER Office of Pharm. Sci., at 2 (Jan. 30, 2008).

²⁸⁶ See, e.g., VP Dec. 30, 2007, Letter at 10.

recommendation;²⁸⁷ and (4) seek expert opinion regarding vancomycin bioequivalence.²⁸⁸ FDA published the Vancomycin BE Draft Guidance for public comment in 2008, which, as described above, included the Agency's scientific rationale for permitting in vitro dissolution to demonstrate bioequivalence for vancomycin capsules.²⁸⁹ FDA convened the August 2009 ACPS meeting for the express purpose of gathering expert opinion on the proposed bioequivalence standard for generic vancomycin capsules in a public forum,²⁹⁰ at which the Agency's scientific rationale for the vancomycin bioequivalence methodology set out in the draft guidance was discussed in great detail.²⁹¹ Both of these events occurred prior to the approval of any vancomycin capsule ANDA. Your requests outlined above therefore have largely been satisfied. To the extent that the particular bases on which you requested these actions require additional discussion, we address those issues below.

(a) FDA Appropriately Distributed Bioequivalence Recommendations

You claim in your initial submissions that the 2006 Revised Recommendation should be rescinded because the “letter” method of distributing bioequivalence standards violated several statutes or policies including the *Freedom of Information Act*, the *Data Quality Act*,²⁹² FDA good guidance practices,²⁹³ FDA’s Standards of Conduct,²⁹⁴ and FDA’s historical controlled correspondence procedures.²⁹⁵ FDA concludes that these arguments are moot because the Agency has since issued guidance outlining the recommended bioequivalence methodology for vancomycin. In addition, FDA no longer uses the letter method as the primary means of publicly distributing bioequivalence recommendations.²⁹⁶ As described above, FDA consistently has issued product-specific recommendations through Specific Product BE Guidance process since 2007,²⁹⁷ and there is no reasonable expectation that FDA will cease this practice and return to a letter-only method of distributing bioequivalence recommendations in the future.²⁹⁸

You make a related claim that you were caught “unawares” when one party released the contents of its 2006 letter indicating that FDA may accept in vitro dissolution data, and

²⁸⁷ Id. at 11.

²⁸⁸ VP Draft Guidance Resp. at 39.

²⁸⁹ Draft guidance for industry on *Bioequivalence Recommendation for Vancomycin HCl; Availability*, 73 FR 76362 (Dec. 16, 2008).

²⁹⁰ *Advisory Committee for Pharmaceutical Science and Clinical Pharmacology; Notice of Meeting*, 74 FR 26249 (June 1, 2009).

²⁹¹ 2009 ACPS Tr. at 35-90, 294-328.

²⁹² (Pub. L. No. 106-554, 114 Stat. 2763 (2000) section 515 Appx. C).

²⁹³ Section 701(h) of the FD&C Act.

²⁹⁴ 21 CFR part 19.

²⁹⁵ VP May 31, 2006, Supp. at 7-14; VP Jan. 15, 2010, Supp. at 19-27.

²⁹⁶ Specific Product BE Guidance at 2-3. To note, FDA does provide bioequivalence recommendations by letter to members of the public who request such information for products for which specific product guidances are not yet available or for which final guidances have not been completed.

²⁹⁷ See <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>, last accessed on January 30, 2012 (listing 946 product-specific bioequivalence recommendations issued).

²⁹⁸ *Larsen v. U.S. Navy*, 525 F.3d 1, 4 (D.C. Cir. 2008) (claims moot when “there is no reasonable expectation ... that the alleged violations will recur”) (internal quotation omitted).

that FDA acted in violation of the Administrative Procedure Act by allegedly treating similarly situated parties differently by distributing this information only to specific parties, failing to provide a rationale for the Agency's decision, and for selectively disclosing information.²⁹⁹ As was customary at that time, FDA sent the 2006 Revised Recommendation for vancomycin to each party that had requested such information. Had ViroPharma requested that information, as numerous other entities (including multiple drug manufacturers) did, ViroPharma would have received the same information.³⁰⁰

To the extent that your challenge to the letter method is based on your desire for an opportunity to comment on any bioequivalence recommendation for generic vancomycin, you have been given extensive opportunity to advocate for your position on past and current recommended standards prior to the approval of any generic vancomycin product, through the advisory committee process, the draft guidance process, and this citizen petition process. Therefore, any notice-related concerns stemming from FDA's use of the letter method in 2006 have been adequately addressed.³⁰¹

(b) FDA Is Not Required to Provide Notice and Opportunity for Comment Prior to Amending a Recommendation for a Specific Drug Product

You contend that FDA must engage in notice-and-comment rulemaking prior to changing a bioequivalence recommendation for a specific generic drug product.³⁰² In support of your position, you cite the *Alaska Hunters* line of authority, under which the D.C. Circuit has held that “[w]hen an agency has given its regulations a definitive interpretation, and later significantly revises that interpretation, the agency in effect has amended its rule, something it may not accomplish without notice and comment rulemaking.”³⁰³ Your reliance on this precedent is misplaced.

Alaska Hunters requires that the contested agency decision be a “definitive interpretation” of a regulation to be subject to the notice-and-comment rulemaking

²⁹⁹ VP May 24, 2006, Supp. at 13 (citing 5 U.S.C. 706(2)(a)).

³⁰⁰ You also attempt to impugn FDA by referencing the fact that FDA did not send letters to these entities directly in the order in which the Agency received requests for information, and that different individuals signed several of the letters (VP May 21, 2006, Supp. at 13; VP Dec. 2, 2009, Supp. at 22-26). You do not assert, however, that FDA failed to provide the information to entities that had requested it, or that FDA intended to provide advantage to or impair any of those entities by accelerating or delaying a letter. Nor do you assert that any of the signatories lacked the authority to sign the letters. Notably, as evidenced in several of your numerous charts detailing when FDA received and sent correspondence (VP Dec. 2, 2009, Supp. at 22-26), FDA responded to all pre-existing requests for information within one month of the March 6 letter you reference. Although the process by which FDA disseminated the letters was not a precise “first-in first-out” process, nothing in your detailed examination of the postmark dates evidences bad faith or negligence on FDA’s part.

³⁰¹ *Novartis v. Leavitt*, 435 F.3d 344, 349 (D.C. Cir. 2006) (no notice and comment required when drug manufacturer otherwise received opportunity to comment on dosage form designation).

³⁰² VP May 31, 2006, Supp. at 8, 22; VP May 17, 2007, Supp. at 9, 12; VP Dec. 30, 2007, Supp. at 10-11; VP Dec. 2, 2009, Supp. at 4.

³⁰³ *Alaska Professional Hunters Assoc. v. FAA*, 177 F.3d 1030, 1034 (D.C. Cir. 1999).

requirement.³⁰⁴ By their very nature, recommended bioequivalence standards are not “definitive interpretations” of the bioequivalence regulations. Instead, they are *recommendations* and do not preclude an applicant from pursuing an alternative method under section 320.24. Indeed, the Draft Vancomycin BE Guidance expressly states that the proposed methods “represent the Agency’s current thinking on a topic and should be viewed only as recommendations.”³⁰⁵ They are nonbinding and “do not establish legally enforceable responsibilities.”³⁰⁶ FDA therefore is not required to employ notice-and-comment rulemaking to amend a bioequivalence recommendation for a specific drug product.³⁰⁷

(c) The Agency Is Not Required to Provide Notice and Opportunity for Comment on a Bioequivalence Recommendation Before Approving an ANDA That Applies the Recommendation

You similarly assert that FDA must provide notice and an opportunity to comment on an amended bioequivalence recommendation (and the administrative record underlying the amended bioequivalence recommendation) prior to approval of a generic product consistent with that amended recommendation.³⁰⁸ Under your theory, each time FDA allows an ANDA applicant to demonstrate bioequivalence using a new methodology, it changes the Agency’s interpretation of the bioequivalence regulations, and thus, FDA first would be required to conduct notice-and-comment rulemaking. This argument relies upon a misunderstanding of the function of the bioequivalence regulations. They do not set out bioequivalence recommendations for individual products. Rather, the regulations

³⁰⁴ *Envil. Integrity Project v. EPA*, 425 F.3d 992, 998 (D.C. Cir, 2005) (finding improper EPA’s promulgation of final regulations inconsistent with prior Agency decisions and proposed regulations without notice-and-comment rulemaking (NCRM)); *Paralyzed Veterans of Am. v. D.C. Arena L.P.*, 117 F.3d 579, 586 (D.C. Cir. 1997) (requiring NCRM for “fundamental modification of [a] previous interpretation”); *Mercy Medical Skilled Nursing Facility v. Thompson*, No. 01-2014, 2004 U.S. Dist. LEXIS 27365, at *5 (D.D.C. May 14, 2004) (secretary’s manual violated APA “because it constitutes a change in the Secretary’s definitive interpretation made without [NCRM]”); *Tripoli Rocketry Assn. v. ATF*, 337 F. Supp. 2d 1, 13 (D.D.C. 2004) (Agency reversal of applicability of regulation-based exemption improper without NCRM).

³⁰⁵ Specific Product BE Guidance at 1; Draft Vancomycin BE Guidance at 1.

³⁰⁶ Draft Vancomycin BE Guidance at 1. At several points you demonstrate confusion on the term “recommended” as it is used to describe bioequivalence standards for specific drug products, asserting at various times that the recommendations set forth in the Draft Vancomycin BE Guidance serve as FDA’s preliminary *and* final action on the matter of generic vancomycin bioequivalence. VP Mar. 25, 2010, Supp. at 4-6, 24-25. You misconstrue the Agency’s use of the term “recommended” and the nature of the recommended bioequivalence standards. Bioequivalence standards, whether set forth in draft or final guidance, are recommended standards that benefit ANDA applicants by providing guidance on how to develop ANDAs for specific products. They are not requirements, and do not preclude an applicant from using another method of demonstrating bioequivalence so long as the application meets the requirements under the statute, nor do they bind FDA from changing the recommendations on the basis of subsequent scientific or legal developments.

³⁰⁷ For these reasons, FDA declines to identify all locally acting drug products for which it changed a bioequivalence standard “without public process.” VP Dec. 30, 2007, Supp. at 10.

³⁰⁸ VP May 31, 2006, Supp. at 22; VP Dec. 30, 2007, Supp. at 10-11; VP Draft Guidance Resp. at 52. You similarly argue that FDA must provide notice and an opportunity to comment on circumstances in which an ANDA applicant may qualify for an exception to the Q1/Q2 sameness requirement for in vitro data (VP Draft Guidance Resp. at 48). For the reasons set forth above, this argument fails as well.

set out procedures for establishing bioequivalence. As detailed above, FDA has followed this regulatory process in accordance with the parameters set out therein, and has determined that in vitro dissolution is the optimal methodology to demonstrate bioequivalence of vancomycin capsules under section 320.24 of the regulations.

Moreover, your argument conflicts directly with two provisions of the FD&C Act. First, FDA cannot delay review or deny approval of an ANDA on the grounds that the Agency has not published and provided a public comment period for a change in a bioequivalence recommendation for a generic product. FDA decides whether to approve an ANDA based on the Agency's evaluation of the scientific information provided in the application, under the requirements of the FD&C Act and regulations, and in reliance upon the Agency's scientific experience and judgment. If the applicant complies with all applicable statutory requirements, the statute directs the Agency to approve the application regardless of whether the Agency has published applicable bioequivalence recommendations.³⁰⁹ The Agency's delay or denial of an ANDA's approval to provide third parties an opportunity to comment on a related bioequivalence recommendation would be inconsistent with this provision of the FD&C Act.

Second, as discussed in detail above, the FD&C Act expressly grants FDA wide discretion to "establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect." The bioequivalence regulations similarly provide that FDA may employ "any ... approach deemed adequate by [it] to measure bioavailability or bioequivalence."³¹⁰ Inserting a notice-and-comment requirement before FDA applies a new bioequivalence methodology to one or more applications would restrict this broad authority. Of the many courts that have recognized FDA's broad discretion to determine bioequivalence standards (see section I.B., above), none has suggested that the Agency must, or even should, employ notice-and-comment rulemaking to establish bioequivalence criteria for any drug product.³¹¹

Your proposal for notice-and-comment rulemaking not only lacks any legal support; it also would impose practical hurdles on FDA's ability to advance the purposes of the Hatch-Waxman Amendments. Your proposed notice-and-comment procedure would stifle innovation in developing bioequivalence methodologies and would greatly slow the approval process for products that satisfy the statutory requirements for approval. You make a related assertion that FDA's determinations of acceptable bioequivalence methods for certain "other" drug products without opportunity for public comment demonstrated the Agency's widespread "abandonment" of clinical endpoint studies "behind closed doors" in violation of FDA's policy on transparency.³¹² As explained above, FDA is not required to provide an opportunity for public notice and comment

³⁰⁹ Section 505(j)(4) of the FD&C Act.

³¹⁰ 21 CFR 320.24(b).

³¹¹ For these reasons, your argument that FDA should provide public notice of and an opportunity to comment on what type of exceptions to the Q1/Q2 sameness requirements FDA will accept lacks merit (VP Draft Guidance Resp. at 48).

³¹² VP Dec. 30, 2007, Supp. at 3, 8.

prior to making bioequivalence determinations for specific drug products.³¹³ Nonetheless, the Agency has convened multiple advisory committee meetings concerning bioequivalence standards, has developed a public process for providing notice and opportunity to comment on proposed bioequivalence recommendations prior to their final adoption in the Specific Product BE Guidance, and has issued over 946 bioequivalence recommendations through this new process.³¹⁴ These actions demonstrate the Agency's commitment to openness and transparency.

(d) FDA Is Restricted From Publicly Disclosing Certain Data in Pending ANDAs

Prior to approving any generic vancomycin capsule product, you request that FDA provide the scientific basis for the draft bioequivalence recommendation for generic vancomycin and the data underlying the recommendation.³¹⁵ FDA provided this information in the Draft Vancomycin BE Guidance, in the background materials for the August 2009 ACPS, and in section II.B., above.³¹⁶ FDA also provided data underlying the Agency's scientific determinations in these materials and directly to you in response to your FOIA requests. Your requests therefore have been granted in this respect. However, the Agency cannot release any scientific data provided by an individual ANDA applicant prior to approval of the ANDA, because of the statutory and regulatory prohibitions against public disclosure of the existence of an ANDA and/or the data contained therein.³¹⁷ To the extent that your request seeks such data, your petition is denied.

9. Vancocin Is Not Eligible for 3-year Exclusivity Under Section 505(j)(5)(F)(iv) of the FD&C Act Because of the Limitation on Such Exclusivity for Certain Antibiotic Products Set Forth in Section 505(v) of the FD&C Act

(a) Approval of ViroPharma's December 2011 Supplemental NDA

On December 14, 2011, FDA approved Supplemental New Drug Application (sNDA) 50-606/S-028 for Vancocin Capsules. This "Prior Approval" Efficacy Supplement³¹⁸ sought updates to the prescribing information in Vancocin labeling, supported by your

³¹³ VP Dec. 30, 2007, Supp. at 3-4; VP April 3, 2009 Supp. at 5.

³¹⁴ See note 90, infra.

³¹⁵ See, e.g. VP Letter to H. Winkle, Director, FDA Office Pharm. Science, at 2 (Jan. 30, 2008).

³¹⁶ Draft Vancomycin BE Guidance at 1-3; Briefing Information, ACPS Meeting (Aug. 4, 2009), available at

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM173220.pdf>; Addendum, Background Information, ACPS Meeting (Aug. 4, 2009), available at

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM175010.pdf>.

³¹⁷ 21 CFR 314.430(b)-(d)(1). There also are civil and criminal restrictions on the release of trade secret and confidential commercial information (21 U.S.C. 331(j) (prohibiting disclosure of any information acquired constituting a trade secret under the FD&C Act); 18 U.S.C. 1905 (prohibiting Federal employees from disclosing trade secret information procured during course of employment)).

³¹⁸ Prior approval efficacy supplements are described in 21 CFR 314.70(d).

submission of two clinical safety and efficacy studies. In addition, the labeling changes in the sNDA brought the Vancocin labeling into compliance with the Physician Labeling Rule (PLR).³¹⁹ After your sNDA was approved, you filed a supplement to your petition asserting that as a result of the modified labeling, Vancocin is entitled to 3 years of exclusivity against generic competition under section 505(j)(5)(F)(iv),³²⁰ and that generic products could not be approved with any “carve outs” from the Vancocin labeling because any such omissions would render the generic products “less safe or effective” than Vancocin for the remaining non-protected conditions of use.³²¹ Upon review of your supplement, the applicable law, and the labeling changes approved in the sNDA, FDA concludes that Vancocin is not eligible for a 3-year exclusivity period due to the limitation on such exclusivity for certain antibiotic products set forth in section 505(v) of the FD&C Act.

(b) Relevant Statutory and Regulatory Framework

The availability of a 3-year exclusivity period for supplements to previously approved drug products is described in section 505(j)(5)(F)(iv) of the FD&C Act. It provides that “[i]f a supplement to an application approved under subsection (b) . . . contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b).”³²²

However, as explained further below, section 505(v) of the FD&C Act limits the availability of this exclusivity for certain antibiotic drug products. To understand the relevance of section 505(v) to your exclusivity claim, a brief summary FDA’s regulation of antibiotics is set forth below.

At the time the Hatch-Waxman Amendments were enacted, antibiotics like vancomycin were approved under section 507 of the FD&C Act and were not eligible for the patent certifications and exclusivity protection provided by Hatch-Waxman, which applied only to drugs approved under section 505 of the FD&C Act.³²³ In the *Food and Drug Administration Modernization Act of 1997* (the Modernization Act), Congress eliminated the separate approval pathway for antibiotics.³²⁴ Section 125 of the Modernization Act

³¹⁹ Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 FR 3922 (Jan. 24, 2006), promulgated in 21 CFR 201.56, 201.57.

³²⁰ The same exclusivity is available to prevent approval of products under section 505(b)(2) in section 505(c)(3)(E)(iv). For purposes of this response, we will refer in this discussion only to the exclusivity provided under section 505(j), but the Agency’s conclusions on this issue are applicable to the exclusivity provided for in both sections 505(j) and 505(c).

³²¹ VP Dec. 22, 2011, Supp.

³²² Section 505(j)(5)(F)(iv) of the FD&C Act. See also 21 CFR 314.108(b)(5).

³²³ Drug Price Competition and Patent Term Restoration Act of 1984, 98 Stat. 1585, 1585; see also *Glaxo, Inc. v. Heckler*, 623 F. Supp. 69 (E.D.N.C. 1985). Hatch-Waxman’s patent term extension provisions did apply to antibiotics, allowing patent term extensions for certain patents claiming antibiotic drugs (see 35 U.S.C. 156(f)(4)(B)(1984)).

³²⁴ Food and Drug Administration Modernization Act of 1997, Pub. L. 105-115, 111 Stat. 2296.

expressly repealed section 507 of the FD&C Act, and provided that drugs approved under section 507 would thereafter be considered to have been reviewed and approved under section 505.

For the purposes of Hatch-Waxman requirements and protections, the Modernization Act created a clear distinction between antibiotic drugs for which the first application was received after the Modernization Act's effective date of November 21, 1997, and those antibiotic drugs for which the first application was received before this date. The latter are commonly referred to as "Old Antibiotics." Applications for antibiotic drugs for which the first application was received subsequent to the enactment of the Modernization Act were treated as any other 505 drug and, among other things, were subject to Hatch-Waxman provisions (including, among others, patent listing, patent certification, and eligibility for exclusivity). In contrast, section 125(d)(2) of the Modernization Act expressly exempted Old Antibiotics from certain enumerated provisions of section 505, including those related to patent listing, patent certification, and exclusivity.³²⁵ The Agency subsequently determined that the section 125(d)(2) exemption applied to all antibiotic moieties for which applications had been submitted prior to November 21, 1997, including applications that had been withdrawn, refused for filing, or had failed to obtain approval. FDA explicitly identified vancomycin as a moiety in that group.³²⁶

On October 8, 2008, Congress enacted section 4 of the *QI Program Supplemental Funding Act of 2008* (the QI Act), entitled "Incentives for the Development of, and Access to, Certain Antibiotics."³²⁷ The QI Act incorporated Old Antibiotics into the Hatch-Waxman regulatory scheme for the first time, with certain limitations. Among other things, the QI Act removed the Modernization Act's enumerated exemptions in section 125(d)(2) for Old Antibiotics,³²⁸ and created in section 505(v) a limited opportunity for an application containing an Old Antibiotic to obtain Hatch-Waxman

³²⁵ Section 125(d) of the Modernization Act states:

Exception. – The following subsections of section 505 (21 U.S.C. 355) shall not apply to any application for marketing in which the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application for marketing received by the Secretary of Health and Human Services under section 507 of such Act (21 U.S.C. 357) before the date of the enactment of this Act: (A)(i) Subsections (c)(2), (d)(6), (e)(4), (j)(2)(A)(vii), (j)(2)(A)(viii), (j)(2)(B), (j)(4)(B), and (j)(4)(D); and (ii) The third and fourth sentences of subsection (b)(1) (regarding the filing and publication of patent information); and (B) Subsections (b)(2)(A), (b)(2)(B), (b)(3), and (c)(3) if the investigations relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

³²⁶ *Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs; Proposed Rule*, 65 FR 3623, 3627 (January 24, 2000).

³²⁷ *QI Program Supplemental Funding Act of 2008*, Pub. L. No. 110-379, 122 Stat. 4075.

³²⁸ Section 505(v)(4) of the FD&C Act.

exclusivity, if that application (or supplemental application) was submitted after the QI Act's enactment.³²⁹ Specifically, section 505(v)(2)(A) provides that:

Notwithstanding any provision of the Food and Drug Administration Modernization Act of 1997 or any other provision of law, a sponsor of [an Old Antibiotic] shall be eligible for, with respect to the drug, the 3-year exclusivity period referred to under clauses (iii) and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv) of section (j)(5)(F), subject to the requirements of such clauses, as applicable.³³⁰

However, this new availability of 3-year exclusivity for Old Antibiotics was not without limitation. Rather than simply placing new applications and supplements for Old Antibiotics under the pre-existing Hatch-Waxman regulatory scheme, Congress prescribed specific limits to this eligibility under section 505(v)(3)(B) of the FD&C Act. The QI Act provides that 3-year exclusivity period is not available for "any condition of use for which the [Old Antibiotic] . . . was approved before the date of the enactment [of the QI Act]."³³¹

The QI Act does not expressly define what constitutes a "condition of use . . . approved before the date of enactment." As an initial matter, FDA concludes that this limitation must exclude from exclusivity some applications and supplements containing new clinical studies that otherwise would qualify a non-Old Antibiotic product for 3-year Hatch-Waxman exclusivity under 505(j)(5)(F)(iv) (i.e., those "reports of new clinical investigations . . . essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement"). To conclude otherwise would render the limitation in 505(v)(3)(B) meaningless — such a reading would exclude from 3-year Hatch-Waxman exclusivity only those studies that already do not qualify for such exclusivity. Thus, to give content to this limitation, FDA must find that there is a higher hurdle for exclusivity for an Old Antibiotic than there is for another kind of product seeking 3-year exclusivity.³³²

The legislative history of the QI Act indicates that Congress enacted the provision to encourage development of truly novel antibiotics and novel uses of Old Antibiotics, including those that qualified as Old Antibiotics because they had been previously submitted to the Agency, despite the fact that they had never been marketed. Congress sought to balance the need to encourage development of new antibiotic drugs to combat the growing number of disease-resistant bacterial infections and the desire to ensure access to previously approved antibiotics through approval of generic versions of such antibiotics. As described by Senator Burr: "Section 4 [of the QI Act], entitled 'Incentives

³²⁹ Section 505(v)(1) of the FD&C Act. Congress also included separate exclusivity incentives for Old Antibiotics that had been submitted for review but had not been approved prior to 1997. Section 505(v)(2) of the FD&C Act.

³³⁰ Section 505(v)(2)(A) of the FD&C Act.

³³¹ Section 505(v)(3)(B) of the FD&C Act.

³³² When Congress includes limiting language in one section of a statute but omits it from another, "it is generally presumed that Congress acts intentionally and purposefully in the disparate inclusion or exclusion." *Russell v. United States*, 464 U.S. 16, 23 (1983) (internal quotation omitted).

for the Development of and Access to Certain Antibiotics,’ is an important step forward to help spur research on new antibiotics and provide incentives for the creation of additional generic antibiotics.”³³³ By adding new exclusivity provisions, the legislation created incentives for sponsors to find new uses for Old Antibiotics, and bring “old but never approved” antibiotics to the market.³³⁴ By incorporating Old Antibiotics into the Hatch-Waxman patent certification scheme (which allowed, among other things, for challenges to applicable patents pre-approval), the QI Act also facilitated approval and marketing of generic copies of antibiotics approved under section 507.³³⁵

Upon review of the statute and the available legislative history, FDA interprets 505(v)(3)(B) to permit 3-year Hatch-Waxman exclusivity for Old Antibiotics only for a significant new use for an Old Antibiotic (such as a new indication for a previously approved antibiotic, or a new approval for a submitted but never previously approved antibiotic), not for refinements in labeling related to previously approved uses for Old Antibiotics. This interpretation is consistent with the balance sought by Congress in the QI Act to reward and provide incentives for companies to develop innovative new uses of Old Antibiotics while also facilitating antibiotic access generally through generic approvals and limiting the time period in which the innovator product is the only product on the market.³³⁶

(c) Vancocin Is Not Eligible for 3-Year Exclusivity Under Section 505(v) of the FD&C Act Because Approval of the December 2011 Supplement Did Not Constitute Approval of a New Condition of Use

Prior to evaluating whether the labeling changes approved in December 2011 meet the requirements for exclusivity set forth in section 505(j)(5)(F)(iv), the Agency must determine whether Vancocin, as an Old Antibiotic, is eligible for the 3-year exclusivity in light of the restrictions of section 505(v) of the FD&C Act. FDA first concludes that Vancocin meets the requirements of section 505(v)(2)(A), in that the sNDA approved in December 2011 was an application for marketing submitted after the enactment of section 505(v), in which the drug that is the subject of the application contains an

³³³ 154 Cong. Rec. S 9638, 9638 (Sept. 26, 2008) (statement of Sen. Burr); see also 153 Cong. Rec. S 5624, 5625 (May 7, 2007) (statement of Sen. Hatch when originally proposing bill in 2007) (“[t]he Hatch amendment is intended to be an initial step in the fight against the resistant strains of bacteria by increasing incentives and innovation”); 154 Cong. Rec. H10170, 10171 (Sept. 27, 2008) (statement of Rep. Sullivan) (“[T]his bill provides an important correction in FDA policy regarding the development of antibiotics.”).

³³⁴ See 153 Cong. Rec. S. 5624, 5630 (May 7, 2007) (statement of Sen. Kennedy) (“The amendment strikes the right balance between innovation and access, and closes a loophole that eliminated the incentives to bring old but never approved antibiotics to market”).

³³⁵ See 154 Cong. Rec. at S 9638 (statement of Senator Burr) (indicating that the Modernization Act “had negatively impacted generic drug companies’ ability to obtain approval of and market generic equivalents of antibiotics approved under section 507”).

³³⁶ As Senator Kennedy stated in the context of making available to Old Antibiotics the 5-year exclusivity for new chemical entities, “the [Old Antibiotic] amendment would make certain molecules that are part of old active ingredients eligible for recognition as new active ingredients, provided they will be used for a new indication. This provision includes limits that would prevent pharmaceutical manufacturers from abusing the process to extend the life of old active ingredient drugs” (153 Cong. Rec. S 5759, 5823 (May 9, 2007) (emphasis added)).

antibiotic drug that was the subject of an application approved by the Secretary under section 507 of the FD&C Act. The question then becomes whether Vancocin is subject to the limitation in section 505(v)(3)(B), which precludes exclusivity if the December 2011 labeling supplement was for approval of labeling changes based on new clinical studies in a “condition of use . . . approved before the date of enactment.”

You contend that Vancocin’s labeling has undergone “fundamental and extensive changes” that constitute “numerous new conditions of use” for Vancocin. Specifically, you contend that the Vancocin labeling changes include the following:

- Inclusion of a clinical studies section supporting one of the already approved indications (CDAD)
- Inclusion of the clinical data in the adverse reactions section related to use in CDAD patients
- A direction for monitoring renal function in CDAD and SAE patients over 65 years of age based on a risk of nephrotoxicity
- An advisory to clinicians to be aware of the importance of appropriate duration of the Vancocin treatment (7-10 days) for geriatric CDAD patients, who may take longer to respond to therapy
- A new indication for use, because the CDAD indication changed from “treatment of antibiotic-associated *pseudomembranous colitis* caused by *C. difficile*” to “treatment of *C. difficile*-associated diarrhea”
- A new dosing regimen for CDAD patients because the dosage and administration of the 125 mg capsules changed from “500 mg to 2 g administered orally for 7-10 days” to “125 mg orally 4 times a day for 10 days.”³³⁷

As explained in detail below, FDA concludes that the revision of the Vancocin label to incorporate clinical data that supports and refines labeling regarding already approved conditions of use, does not constitute approval for a condition of use that has not been “approved before the date of enactment” within the meaning of section 505(v)(3)(B). Therefore, these labeling changes do not merit 3-year exclusivity under the limitation on such exclusivity for an Old Antibiotic subject to section 505(v)(3) of the FD&C Act. First, FDA finds that the first four changes cited above relate to and refine the currently approved indication for treatment of CDAD in already identified patient populations, and do not constitute a significant expansion in the conditions of use of the product.

Second, FDA does not find that Vancocin’s modified labeling supports a “changed indication.”³³⁸ “Antibiotic-associated *pseudomembranous colitis* caused by *C. difficile*” and “*C. difficile*-associated diarrhea” are not mutually exclusive definitions. “*Pseudomembranous colitis*” implies that the diagnosis was made pathologically (through endoscopy) rather than a clinical diagnosis using the toxin assay in stool. Diagnoses are typically made (both in the clinical trials that ViroPharma submitted in support of its labeling sNDA and in general clinical practice) based upon a positive *C. difficile* toxin

³³⁷ VP Dec. 22, 2001, Supp. at 6-7. We note that many of your modifications were required to bring your labeling into compliance with the PLR.

³³⁸ Id. at 7.

assay associated with diarrhea and may not necessarily be associated with the prior use of antibiotics.³³⁹ Thus the labeling changes clarified the previously approved indication but did not constitute a new indication.³⁴⁰

Third, FDA rejects your claim that the new labeling included a new dosing regimen. Rather, the dosing regimen you claim is new — “125 mg orally 4 times a day for 10 days” — is encompassed within and is at most a refinement of the prior regimen of “500 mg to 2 g administered orally for 7-10 days.” Nor can you claim that this refinement is an innovation, as “125 mg administered 4 times daily” dose of vancomycin has been adopted as the “standard dose” since the 1980s.³⁴¹ Antibiotic guides, such as the *Sanford Guide to Antimicrobial Therapy*, recommend the “125 mg po qid × 10-14 days” regimen (as listed for “*C. difficile* toxin positive antibiotic-associated colitis”).³⁴²

Notably, ViroPharma’s position that these studies were essential to the approval of a new indication and new dosing regimen are inconsistent with the contents of the sNDA that contained those studies, and the letter detailing the approval of the sNDA. As indicated in the approval letter, the Agency determined that the supplement supported “updates to the prescribing information” and “conversion of the current label into the [PLR] format.”³⁴³ In addition, had you intended to seek approval for a new indication or a new dosing regimen (or a new active ingredient, new dosage form, or new route of administration), you would have been required by statute to have conducted an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients under the *Pediatric Research Equity Act* (PREA).³⁴⁴ You did not submit any such assessments in your sNDA or otherwise reference PREA’s requirements by seeking a deferral or waiver of this requirement. Moreover, your approval letter, to which you did not object, confirmed that PREA was not triggered by your sNDA. This

³³⁹ Bartlett, J.G., Gerding, G.N., “Clinical Recognition and Diagnosis of *Clostridium difficile* Infection.” *Clin Infect Dis.* 2008; 46 Suppl 1:S12-8. This labeling change also provided for clarity and consistency throughout the label and would have been made along with changes for the Physician’s Labeling Rule conversion without the data from these trials.

³⁴⁰Your claim that *staphylococcus aureus* is no longer included as an indication Vancocin’s labeling is unsupported, and contradicted by the Company in its own advertising. Your website states “[o]ur product VANCOVIN® is the only antibiotic approved to treat two significant bacterial infections of the lower digestive tract. The product is . . . indicated for the treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains) and antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*.” We note that the Vancocin labeling change from “may be administered orally for treatment of enterocolitis caused by . . . [*s. aureus*], to the statement that the drug is “also used for the treatment of enterocolitis caused by [*s. aureus*]” is a minor change in syntax. In addition (a) the sNDA did not include any data or information supporting this change; (b) the use information on [*s. aureus*] (still) appears in the “Indications and Usage” section of the label; and (c) dosing instructions for staphylococcal enterocolitis are provided in the “Dosage and Administration” section of the labeling.

³⁴¹ Bartlett, J.G. “The Case for Vancomycin as the Preferred Drug for Treatment of *Clostridium difficile* infection.” *Clin Infect Dis.* 2008; 46: 1489-1492.

³⁴² Gilbert, D.N., Moellering, R.C., Eliopoulos, G.M., Sande, M.A., “The Sanford Guide to Antimicrobial Therapy,” 38th ed. *Antimicrobial Therapy*; 2008:16.

³⁴³ See letter fr. Katherine A. Laessig, FDA, to ViroPharma, Inc., Approval of sNDA, NDA 50-606/028 (December 14, 2011).

³⁴⁴ Pub. L. No. 108-155, 117 Stat. 1936 (2003), codified in section 505B(a) of the FD&C Act.

confirms that you, like the Agency, did not believe your labeling changes constituted a new indication, new dosing regimen, or other PREA-triggering change.

The Agency would not discourage any sponsor's effort to modify labeling to provide doctors and patients with current information based on clinical data, and the Agency actively encourages sponsors to bring their labels into compliance with the PLR. Revising the labeling and providing clinical data that supports or, at most, refines information about already approved conditions of use, however, does not give rise to an approval for a condition of use that has not been previously approved and therefore merits the limited 3-year exclusivity available for an Old Antibiotic product. As we have noted previously, the unique history of development of antibiotic regulation reflects Congressional policy judgments that balance the incentives for new antibiotic development and development of new uses for Old Antibiotics against the desire to speed availability of generic antibiotic products in the marketplace.³⁴⁵ FDA's decision here that Vancocin is not eligible for 3-year exclusivity because of the limitation of section 505(v)(3) is consistent with those policies.³⁴⁶

10. Neither ViroPharma Nor Congress is Entitled to Receive Prior Notice of Agency Approval Action

In your December 2011 supplement, you also request that in the event FDA determines it appropriate to approve any generic or 505(b)(2) applications referencing Vancocin prior to December 15, 2014, the Agency provide both you and members of the U.S. Senate Health, Education, Labor, and Pensions (HELP) Committee and the U.S. House of Representatives Energy and Commerce Committee with 30 days notice prior to final approval of any such application.³⁴⁷ Under applicable statutory and regulatory provisions, FDA generally is prohibited from disclosing any information regarding the filing of an application or approvability of a drug product before the Agency has approved the application, unless its existence has been "previously disclosed or acknowledged."³⁴⁸ Although the existence of ANDAs for generic vancomycin has been publicly acknowledged, FDA cannot provide you or rank-and-file members of Congress information related to approval of such any application before it is approved. Accordingly, your request for prior notice related to the impending approval of ANDA or 505(b)(2) applications is denied.

³⁴⁵ Letter to M. Labson, et al., from J. Woodcock re. Docket No. 2009-P-0038 (Mar. 17, 2009).

³⁴⁶ FDA also notes that even if Vancocin were not subject to the limitation on 3-year exclusivity in 505(v)(3)(B), three-year exclusivity, itself, is not a bar to ANDA approval if the Agency determines that the information protected by that exclusivity can be removed from the ANDA labeling and the ANDA will remain safe and effective for the remaining non-protected conditions of use. See 21 CFR 314.127(a)(7) (providing that FDA will refuse to approve an ANDA that omits labeling protected by exclusivity unless FDA determines that the omission does not render the ANDA less safe or effective for the remaining non-protected conditions of use).

³⁴⁷ VP Dec. 22, 2011, Supp. at 25.

³⁴⁸ See 21 CFR 314.430(b).

D. FDA Developed and Amended the Vancomycin Capsule Bioequivalence Recommendations Through a Lawful and Sound Process

In addition to your scientific and legal challenges, you assert that the actions of certain FDA employees during the development of the vancomycin capsule bioequivalence recommendation so tainted the process that the current and previous recommendations should be rescinded, and that the Agency should not approve generic vancomycin products using the methodologies set forth in the Draft Vancomycin BE Guidance. FDA takes such assertions very seriously, and has reviewed carefully the issues you have raised. Upon consideration of your filings and of the record you submitted in support of your petition, we conclude that the bioequivalence recommendation for generic vancomycin capsules set forth in the 2008 Draft Vancomycin BE Guidance and in this response has a sound scientific basis. It is the result of thorough Agency review, aided by extensive expert and public consideration and comment.

FDA acknowledges that the process employed in undertaking certain Agency actions, or the Agency's failure to take certain actions, during the course of developing the bioequivalence recommendation for vancomycin was not always optimal. The effect of any early procedural missteps, if any, however, has been remedied by subsequent procedurally and scientifically sound actions. FDA's current bioequivalence methodology recommendations are scientifically sound, and ViroPharma and other interested stakeholders have been given any process that they were due. Moreover, the facts do not support your allegations of wrongdoing by Agency employees. Accordingly, we deny your request that FDA rescind the bioequivalence standard for vancomycin capsules and refrain from approving any ANDAs consistent with the recommendation due to the alleged deficiencies in process.

1. ViroPharma's Improper Use of the Petition Process and Improper Reference to Predecisional Agency Materials

We address two preliminary matters before addressing the substance of your process claims. First, FDA notes that you have petitioned FDA in a fashion analogous to interrogatories in civil discovery, demanding answers to more than 170 individual factual questions related to the Agency's development of the vancomycin bioequivalence recommendation.³⁴⁹ This is an improper use of the citizen petition process. The petition procedure enables parties to "petition the Commissioner to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action."³⁵⁰ "Administrative action" is defined in relevant part as "every act, including the refusal or failure to act, involved in the administration of any law by the Commissioner."³⁵¹ The "action" you request the Agency to take here — to respond directly to factual questions regarding certain Agency decisions — is secondary to your underlying challenge of those decisions. In the interest of a thorough evaluation of the

³⁴⁹ See, e.g., VP Jan. 15, 2010, Supp. at 5-30.

³⁵⁰ 21 CFR 10.25(a).

³⁵¹ 21 CFR 10.3(a).

many issues you raise, however, FDA has incorporated these questions and the events referenced therein in its consideration of your petition.

Second, you extensively cite FDA employee statements made or actions taken during the consideration of and prior to the Agency's amendment of the vancomycin bioequivalence recommendation in 2006 and 2008, as evidence that FDA, and OGD in particular, believed it lacked scientific and legal authority to recommend in vitro dissolution data, and acted improperly in order to "hide" this deficiency. As explained below, the examples that you cite do not support your claim. Of more fundamental concern, your reliance on FDA employee predecisional statements or actions overlooks a cornerstone principle of the administrative process. As courts have long recognized, Agency employees must enjoy the free exchange of scientific opinions while making a decision, without the threat of public scrutiny of the deliberative process. Perhaps best expressed in the FOIA context, courts consistently warn against the chilling effect of predecision review of scientific determinations, holding that "scientists should be able to withhold nascent thoughts where disclosure would discourage the intellectual risk-taking so essential to technical progress."³⁵²

Importantly, this policy does not exclude the public from participation in the bioequivalence recommendation development process, nor does it preclude public review and challenge of the Agency's final determinations. Indeed, as illustrated in this instance, FDA has provided extensive notice of and actively has solicited comment on FDA's proposed bioequivalence recommendations before approving any proposed generic vancomycin product and before finalizing the Draft Vancomycin BE Guidance. Rather, the policy "allows agencies a space within which they may deliberate."³⁵³ Your effort to characterize Agency deliberations as duplicitous is unsupported, and provides no basis to rescind Draft Vancomycin BE Guidance or to refrain from approving an ANDA consistent with the recommendation.

2. Public Statements Made by FDA Employees Regarding Bioequivalence Recommendations for Generic Vancomycin Capsules Were Not Misleading

You assert that FDA employees publicly misrepresented the Agency's activities in light of FDA's subsequent amendment of the recommendations in 2006 and 2008. These purported misrepresentations, you maintain, evidence a culture of secrecy that taints the Agency's decision-making process.³⁵⁴ Your principal claim is that OGD's process of developing the vancomycin recommendation was improperly secretive because you were not aware of each deliberative step that the Agency took before it amended the recommendation. As discussed above, Agency employees must enjoy the free exchange of scientific opinions while making a decision without the threat of public scrutiny of the deliberative process. Your characterization of this effort as secretive because you were not a party to internal Agency discussions is misplaced. Upon review of your assertions,

³⁵² *Chemical Mfg. Assn. v. CPSC*, 600 F. Supp. 114, 118 (D.D.C. 1984).

³⁵³ *Wolfe v. Dep't Health and Human Services*, 839 F.2d 768, 776 (D.C. Cir. 1988).

³⁵⁴ VP Draft Guidance Resp. at 33-36.

the Agency concludes that there is no evidence that OGD engaged in improper activities to hide from public scrutiny its review of bioequivalence methodologies for generic vancomycin.

(a) FDA Employees Did Not Misrepresent the Status of Generic Vancomycin Bioequivalence Recommendations

You assert that before FDA amended the bioequivalence recommendation in 2006 and 2008, Agency employees made public statements that misrepresented the Agency's intention to amend the bioequivalence recommendation soon thereafter.³⁵⁵ For example, you cite a statement made by OGD Director of Science, Lawrence Yu, Ph.D., at the October 2004 ACPS meeting, that FDA used a clinical-study approach for demonstrating vancomycin bioequivalence. You then infer that such statements "hid" the fact that the Agency was considering the use of in vitro data.³⁵⁶ These comments in no way were made in bad faith, or in an attempt to hide the Agency's ongoing review of the bioequivalence methodologies. Rather, these statements reflected FDA's then-current conclusions regarding a method or methods by which an ANDA applicant could establish bioequivalence for generic vancomycin. Nor did such statements convey that FDA considered its pre-2006 or post-2006 recommendation to be the Agency's final conclusion on generic vancomycin bioequivalence on which you could justifiably rely. On the contrary, the Agency expressly indicated that such bioequivalence standards continued to be evaluated. The very topic of the 2004 ACPS meeting was the ongoing development of appropriate standards for demonstrating bioequivalence for locally acting drug products.³⁵⁷ Immediately after the statement you cite, Dr. Yu told the Committee, "[w]hat we want is [...] to develop a scientific basis for the choice of [bioequivalence method], [for] which we need your input on [the] role of pharmacokinetic studies, [the] role for in vitro dissolution studies, [the] role of the clinical studies."³⁵⁸ In fact, the Agency noted in several of the bioequivalence letters distributed to parties that had requested the information,³⁵⁹ and after the 2006 change in the recommendation in responses made to Congressional inquiries made on your behalf,³⁶⁰ that the proposed methods were subject to change as a result of your citizen petition.

³⁵⁵ VP May 31, 2006, Supp. at 3-6; VP Draft Guidance Resp. at 33-34.

³⁵⁶ VP May 31, 2006, Supp. at 4 (citing 2004 ACPS Tr. at 274-75). You similarly cite to statements made by FDA representatives between February 2006 and the December 2008 publication of the Vancomycin BE Draft Guidance that referenced the 2006 Revised Recommendation. VP Draft Guidance Resp. at 33-34.

³⁵⁷ 2004 ACPS Tr. at 273.

³⁵⁸ Id. at 275.

³⁵⁹ See, e.g., Letter fr. G. Buehler, OGD Director to [redacted] (Jan. 9, 2004), attached as Ex. 5, VP Mar. 25, 2010, Supp. (in letter setting forth the pre-2006 recommendation for in vivo clinical endpoint studies noting that if an in vitro method "is adequately developed in the future, the FDA might consider comparative in vivo bioassays that correlate with clinical activity as evidence to establish bioequivalence"); Letter from D. Conner, Director, OGD Div. of Bioequivalence to [redacted], at 1 (Nov. 1, 2006), attached as Exh. 15 to VP Mar. 25, 2010, Supp. (in letter setting forth 2006 bioequivalence recommendation, "our advice is preliminary. A citizen petition Docket No. 2006P-0124 was submitted to the Agency on March 17, 2006. The response to the citizen petition may result in a revision to the recommendations").

³⁶⁰ Letter fr. S. Mason, FDA Acting Asst. Commissioner for Legislation to the Hon. A. Specter, at 2 (Oct. 19, 2007) (referencing the citizen petition docket and FDA's ongoing consideration of the bioequivalence recommendation for generic vancomycin).

Even if these employee statements somehow misrepresented the status of the bioequivalence recommendations, which they did not, your attempt to impugn the Agency's decision-making process on the basis of these statements is misplaced. FDA regulations make clear that views of individual FDA staff expressed at meetings or otherwise, do not constitute a final or official administrative action or position.³⁶¹ Courts have rejected efforts to cite statements made by FDA employees regarding bioequivalence to demonstrate the Agency's official position on the issue. In *Serono Labs., Inc. v. Shalala*, the D.C. Circuit expressly rejected a party's efforts to cite individual employee statements that revealed pre-decisional disagreement among FDA chemists as evidence that the final Agency action was infirm.³⁶²

(b) OGD Employee Statements Regarding General Bioequivalence Principles or Other Drug Products Were Not Misrepresentations

You next claim that OGD employees made statements about bioequivalence in general that misrepresented the Agency's activities related to generic vancomycin. For example, you cite a statement made in February 2006 by then-OGD Director Dr. Gary Buehler at the annual meeting of the Generic Pharmaceutical Association that bioequivalence of locally acting drug products was "an ongoing topic of research" at FDA. You contend that this statement was a misrepresentation because FDA disseminated the 2006 Revised Recommendation shortly thereafter.³⁶³ But Dr. Buehler's statement was and remains true: bioequivalence of locally acting drug products was at the time, and continues to be, an ongoing topic of research at FDA. Nothing in this statement can be construed to indicate that FDA would not issue an amended bioequivalence recommendation for generic vancomycin when the Agency determined that it was scientifically appropriate to do so.

You similarly cite a 2005 statement by OGD's Director of the Division of Bioequivalence I, Dale Conner. You quote Dr. Conner as stating that "[b]ioequivalence study designs with clinical endpoints are used for some oral drug products that are not systemically absorbed, such as sucralfate tablets" and that "[w]ith suitable justification, bioavailability and bioequivalence may be established by in vitro studies alone,' including some locally acting products."³⁶⁴ You state that "Dr. Conner offered only one

³⁶¹ 21 CFR 10.65(a) ("[a]ction on meetings and correspondence does not constitute final administrative action subject to judicial review"); 21 CFR 10.85(k) ("A statement or advice given by an FDA employee orally, or given in writing but not under this section [pertaining to advisory opinions] or 10.90, is an informal communication that represents the best judgment of that employee at that time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.").

³⁶² *Serono Labs., Inc. v. Shalala*, 158 F.3d at 1321 (rejecting reference to documents that revealed pre-decisional disagreement among FDA chemists as to whether an active ingredient in an ANDA product was the same in RLD); *Fisons Corp. v. Shalala*, 860 F. Supp. at 867-68 (rejecting citation to prior public statements made by Agency employees about how generic impurities would be considered in an ANDA review as evidence of an Agency policy or practice of waiving a bioequivalence requirement, citing subsections 10.65(a) and 10.85(k)).

³⁶³ VP May 31, 2006, Supp. at 4-5.

³⁶⁴ *Id.* at 4.

example of a locally acting drug suitable for such an in vitro waiver; cholestryramine resins.”³⁶⁵ You assert that Dr. Conner’s statement and reference to cholestryramine resins implicitly conveyed the Agency’s position that in vitro data would not be sufficient to demonstrate bioequivalence for any other locally acting product such as generic vancomycin.³⁶⁶ However, nothing in Dr. Conner’s statement expressed or even implied that cholestryramine resins are the only locally acting product for which in vitro data would be sufficient. This is not a reasonable conclusion to draw from the cited statement.³⁶⁷

(c) FDA Employees Do Not Have a Duty to Inform the Public That the Agency Is Considering a Scientific Matter

You next address instances when FDA employees have “not” spoken. For instance, you reference a January 2008 meeting between the Agency and ViroPharma at which, you assert, Dr. Yu indicated that OGD’s 2006 recommendation was based on sound science. You claim this was a misrepresentation because Dr. Yu must have known, but did not share, FDA’s conclusion that vancomycin was not rapidly dissolving in light of the DPQR 2008 Dissolution Study that was issued the following month.³⁶⁸ You assume that Dr. Yu both knew of and had a duty to disclose the details of the DPQR study before the study was finalized and before FDA considered any results. Again, this conclusion is unsupported, and, as discussed above, fails to recognize the important policy protecting the free exchange of scientific ideas during the decision-making process.

You also assert that FDA representatives should have responded to generic manufacturer Akorn Incorporated (Akorn)’s representation at the July 2008 ACPS that it had data demonstrating vancomycin was rapidly dissolving. You allege that FDA should have disclosed the conclusions of the DPQR 2008 Dissolution Study at the time Akorn presented its data, and that FDA’s failure to do so conveyed to the committee the Agency’s implicit endorsement of Akorn’s presentation.³⁶⁹ Your argument is misplaced for several reasons. Under the FD&C Act and FDA regulations, the Agency generally is

³⁶⁵ Id.

³⁶⁶ VP May 17, 2007, Supp. at 3-4. See also VP Dec. 30, 2007, Supp. at 5 (asserting that the exclusion of a drug product from general summary presentations about bioequivalence indicates FDA’s recognition of its error in approving generics of the unmentioned drug product). You similarly claim that an informational poster presented at a November 2006 meeting was intentionally misleading because it referenced the bioavailability of BCS Class 1 products together with other generic products but did not expressly indicate that a majority of the products reviewed were not BCS-characterized products. Such a presentation by no means indicates, as you assert, that “OGD was more interested in promoting public acceptance of the ‘sameness’ of generic drugs and OGD’s own ability to regulate them than portraying accurately the results of its research” (VP Dec. 30, 2007, Supp. at 6).

³⁶⁷ You also cite as indicative of OGD’s “penchant for revisionist history” an article by Dr. Gary Buehler regarding the development of bioequivalence review since 1974 (VP Mar. 25, 2010, Supp. at 8-12). This mischaracterization of Dr. Buehler’s article is neither accurate nor productive, and your discussion fails to recognize that FDA’s approach to bioequivalence has evolved against a backdrop of scientific and regulatory developments. Dr. Buehler did not, as you imply, mischaracterize the history of FDA’s consideration of bioequivalence in order to support the use of in vitro data to demonstrate bioequivalence.

³⁶⁸ VP Draft Guidance Resp. at 32-33.

³⁶⁹ VP Draft Guidance Resp. at 18, 25.

prohibited from disclosing any determinations regarding the filing or approvability of any pending ANDA for a generic drug product before it has reached a final decision on whether to approve or not approve the application.³⁷⁰ For FDA to have responded to Akorn's data in the manner you propose would have been in violation of these restrictions. Such a response also would have undermined the purpose of an advisory committee meeting, which is to foster open comment from interested parties.³⁷¹ Reflecting this purpose, FDA regulations prohibit non-committee members from responding to other presentations.³⁷² Your related assertion that in response to Akorn's presentation, Dr. Yu should have informed the committee that FDA was drafting a guidance for vancomycin bioequivalence and that ViroPharma had made certain arguments regarding absorption in patients to the Agency, lacks merit for similar reasons.³⁷³

3. FDA Properly Developed the Generic Vancomycin Bioequivalence Recommendation

(a) FDA Properly Developed the 2006 Generic Vancomycin Bioequivalence Recommendation

You argue that the internal process by which FDA developed the 2006 Revised Recommendation was unsound. Specifically, you claim that Dr. Yu unilaterally made the decision in 2006 to permit in vitro dissolution data to demonstrate bioequivalence for generic vancomycin in violation of OGD procedures in an effort to shield from review "his" conclusion to permit in vitro data.³⁷⁴ This claim is based on a statement Dr. Yu made in a 2009 e-mail in which he said that he made the decision in 2006 to permit in vitro data and others "went along."³⁷⁵ Notwithstanding this e-mail exchange, it is clear from the Agency documents you have included in support of your petition, that FDA conducted a thorough review in 2006 involving numerous members of the Agency.³⁷⁶ For example, the internal bioequivalence review memorandum endorsing the 2006 amendment that you cite was signed by two OGD scientists and three OGD managers including the Director of the Division of Bioequivalence, the OGD Associate Director of Medical Affairs, and OGD's Director of Science.³⁷⁷ You also assert that certain OGD

³⁷⁰ 21 CFR 314.430(d)(1).

³⁷¹ As the committee chair stated at this meeting prior to the public comment period, "[t]he FDA and this Committee place great importance on the open public hearing process. The insights and comments provided can help the Agency and this Committee in their consideration of the issues before them. That said, in many instances, and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair." 2008 ACPS Tr. at 91.

³⁷² 21 CFR 14.29(f).

³⁷³ VP Draft Guidance Resp. at 25.

³⁷⁴ VP Dec. 2, 2009, Supp. at 3.

³⁷⁵ VP Dec. 2, 2009, Supp. at 3 (quoting Aug. 6, 2009, e-mail from L. Yu to C. Parise, D. Nguyen) (attached as Ex. C to supplement).

³⁷⁶ VP Jan. 15, 2010, Supp., Ex. 15; see also VP Jan. 15, 2010, Supp., Ex. 11 (exhibits include multiple e-mails among many members of OGD confirming concurrence with the vancomycin recommendation).

³⁷⁷ VP Jan. 15, 2010, Supp., Ex. 15.

employees improperly excluded Dr. Hixon, then Associate Director of Medical Affairs, from the review process.³⁷⁸ This is unfounded: the documents on which you rely show that Dr. Hixon was involved in the review process and approved the recommendation.³⁷⁹

You next contend that the 2006 recommendation was not finalized prior to its release, citing two signed versions of the OGD vancomycin bioequivalence review memorandum with different dates.³⁸⁰ You are correct that FDA modified its internal bioequivalence review memorandum after the Agency sent several letters setting forth the in vitro recommendation. Although this process was imperfect, these modifications were editorial in nature and did not alter the substantive bioequivalence recommendation, or the bases on which OGD rested its recommendation. For example, in the first February 8, 2006, version, the information in the “Formulation” section of the memo is set forth in paragraph form. The same information is set forth in a table format in the February 24, 2006, version. Nothing substantive in the documents changed, and the same individuals signed off on both versions.³⁸¹ You also question the sign-off process for the February 8, 2006, memorandum due to the fact that each individual signed the first memorandum on the same day.³⁸² There is no basis to infer wrongdoing on this ground, and FDA declines your request that the Agency review employee records to determine where each signatory was on February 8, 2006.

Finally, you assert that FDA erroneously relied on data submitted by an ANDA applicant in concluding that vancomycin is rapidly dissolving as defined in the BCS Guidance thereby justifying the use of in vitro dissolution data.³⁸³ In response to this concern, which you first voiced in March 2006, FDA conducted its own dissolution study, the findings of which were memorialized in the 2008 DPQR Dissolution Study report discussed above and confirmed in the 2009 DPQR Dissolution Study.³⁸⁴ Both these studies demonstrated that vancomycin capsules are not rapidly dissolving under the BCS Guidance definition. The 2006 citation to the BCS Guidance therefore was inaccurate. As explained above, however, the BCS Guidance does not describe the only instances in which FDA may consider in vitro dissolution data in evaluating bioequivalence. More notably, FDA acknowledged this error, conducted its own in vitro dissolution data studies to investigate the claim, reexamined and refined the bioequivalence recommendation, and solicited the expert ACPS’s opinion, which unanimously endorsed use of in vitro data notwithstanding the fact that vancomycin does not fall within the BCS Guidance criteria.

³⁷⁸ VP Jan. 15, 2010, Supp. at 7-9, 11-12.

³⁷⁹ See, e.g., VP Jan. 15, 2010, Supp., Ex. 11 (exhibit includes multiple e-mails to and from D. Hixon regarding “vancomycin recommendation,” including Jan. 20, 2006, e-mail fr. L. Lee to D. Hixon stating that “we have about 10 controlled correspondences for this drug and would like to know what you think about the recommendation”); Ex. 15 (OGD bioequivalence review memorandum signed by D. Hixon as concurring).

³⁸⁰ VP Jan. 15, 2010, Supp. at 8-9, 20.

³⁸¹ Compare VP Dec. 15, 2009, Supp., Ex. 15 at 8 (Bioequivalence Review for Generic Vancomycin (Feb. 8, 2006)) with Ex. 21 (Bioequivalence Review for Generic Vancomycin at 8 (Feb. 24, 2006)).

³⁸² VP Jan. 15, 2010, Supp. at 8-9, 20.

³⁸³ VP June 3, 2006, Supp. at 36-37; VP April 3, 2009, Supp. at 2-3.

³⁸⁴ DPQR 2008 Dissolution Study; DPQR 2009 Dissolution Study.

Thus, any impact of the Agency reliance on inaccurate data in establishing the 2006 recommendation has been mitigated.

(b) FDA Properly Developed the 2008 Amendment to the Generic Vancomycin Bioequivalence Recommendation

You also challenge several aspects of the process by which FDA developed and made public the 2008 amendment to the vancomycin bioequivalence recommendation. You make the unsupported assertion, based on the Agency's October 2008 response to an inquiry from the Alliance for Aging Research (Alliance), that FDA relied on a generic applicant's (Akorn's) faulty data in developing the bioequivalence methodologies that are recommended in the Draft Vancomycin BE Guidance.³⁸⁵ In July 2008, Alliance asked FDA to make available data correlating in vitro testing with in vivo clinical results for use of vancomycin in CDAD patients.³⁸⁶ In its response to Alliance in October 2008, FDA explained that it did not have such correlating data, but that in vitro data presented in the July 2008 ACPS meeting by generic manufacturer Akorn related to the dissolution of vancomycin "was consistent with" the Agency's draft bioequivalence recommendation.³⁸⁷ FDA's letter to Alliance was not accurate because FDA did not rely on Akorn's data. As explained above, the Agency relied on the results of its Internal DPQR 2008 Dissolution Study³⁸⁸ in formulating the Draft Vancomycin BE Guidance, which results FDA confirmed in the second internal dissolution test in 2009.³⁸⁹ In addition, FDA mistakenly disclosed in the October 2008 letter to Alliance, the fact that the Agency anticipated issuing the Draft Vancomycin BE Guidance in December of that year. Nonetheless, there is no indication that you or any other party was harmed by this inadvertent disclosure of the impending draft guidance.

You also assert that FDA selectively disclosed the substance of the December 2008 recommendation to Akorn prior to publishing the notice of availability of the Draft Vancomycin BE Guidance in the *Federal Register*, based on the fact that the company referenced comparable dissolution profiles and Q1/Q2 sameness in its presentation at the 2008 ACPS meeting on bioequivalence of low-solubility drug products.³⁹⁰ This allegation is unfounded. FDA did not "tip off" Akorn as to the draft guidance standard. FDA's thinking on Q1/Q2 sameness previously had been published in policy documents related to other locally acting products. For example, in FDA's May 2008 citizen petition response concerning Acarbose Capsules, another locally acting oral GI drug product, the Agency endorsed the use of in vitro dissolution data to demonstrate bioequivalence for that product, and included a recommendation for Q1/Q2 sameness of inactive ingredients.³⁹¹ Q1/Q2 sameness also has been used by the Agency for some time in

³⁸⁵ VP April 3, 2009, Supp. at 1-3; VP June 25, 2010, Supp. at 11.

³⁸⁶ Letter to FDA fr. D. Perry, Exec. Dir., Alliance for Aging (Aug. 28, 2008).

³⁸⁷ Letter fr. FDA to D. Perry, Exec. Dir., Alliance for Aging, at 2 (Oct. 24, 2008).

³⁸⁸ Draft Vancomycin BE Guidance at 2 (referencing 2008 FDA dissolution study in scientific rationale for draft recommended standard).

³⁸⁹ DPQR 2009 Dissolution Study.

³⁹⁰ VP Draft Guidance Resp. at 34; VP Dec. 2, 2009, Supp. at 4; VP Mar. 25, 2010, Supp. at 18-22.

³⁹¹ Letter fr. FDA to W. Rakoczy re. bioequivalence of generic acarbose products (May 7, 2008), at 7.

bioequivalence analyses for other locally acting drug products.³⁹² Your related charge that FDA selectively disclosed the 2008 recommendation to Akorn in order to “enlist” the company to “cultivate an appearance of independent validation” of FDA’s revised standard is similarly unfounded.³⁹³

Shortly after FDA published the notice of availability for the Draft Vancomycin BE Guidance in the *Federal Register*, the Agency made public a version of the Draft Vancomycin BE Guidance containing certain revised citations in the footnotes to the scientific literature supporting the bioequivalence recommendation.³⁹⁴ FDA posted the revised version on its Web site consistent with the processes described in the Specific Product BE Guidance³⁹⁵ and on the Agency’s Guidance Web page.³⁹⁶ FDA did not reissue notice of the revisions in the *Federal Register*, although it is clear from the Agency documents you cite that FDA employees attempted in good faith to make the revised guidance public.³⁹⁷ This clearly was not, as you contend, an effort by one FDA employee to circumvent Agency process³⁹⁸ or evidence of the Agency’s “equivocation on the parameters of the dissolution requirements” or “penchant for behind-closed-door behavior.”³⁹⁹ Moreover, any prejudice to you that may have resulted from the failure to post a new notice of availability when the amended version of the guidance was published has been mitigated.⁴⁰⁰ You were aware of the new version several weeks before you filed your first comments to the Draft Vancomycin BE Guidance in March 2009 (for which FDA granted an extension), and you since have taken multiple opportunities to opine on the contents of the revised draft.⁴⁰¹

³⁹² See, e.g. the guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*, at 8 (April 2003).

³⁹³ VP Mar. 25, 2010, Supp. at 20. Nor has FDA disclosed any protected information to any ANDA applicant regarding inactive ingredients in Vancocin. VP Mar. 25, 2010, Supp. at 30.

³⁹⁴ Compare Draft Vancomycin BE Guidance at 2, n.2-5, with VP Feb. 27, 2009, Supp., Attachment, Draft Guidance on Vancomycin Hydrochloride, at 2, n.2-5.

³⁹⁵ Specific Product BE Guidance at 1, n.2 (“[FDA] update[s] guidance documents periodically. To make sure you have the most recent version of product-specific bioequivalence study guidance, check the FDA Drugs guidance page”).

³⁹⁶ FDA drug guidance documents, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. (“**Note:** Draft guidances are undergoing finalization. Please contact the relevant division for the most up-to-date Agency perspective on an issue.”) (emphasis in original).

³⁹⁷ See VP Dec. 2, 2009, Supp., Exs. J (E-mail fr. E. Thakur, Program Management Officer, Office of Regulatory Policy, CDER, to M. Bigesby, FDA Legal Instruments Examiner, Division of Dockets Management re. “IMPORTANT changes needed to Posted Vanco Guidance” (Dec. 16, 2009) (“[t]he correct version [of the draft guidance] did not get posted ... It needs to be replaced on the web AS SOON AS POSSIBLE. ... Can this one be replaced quickly, also in FDMS and the docket? ... Please let me know if this needs to be sent to anyone else for these changes to be made.”)). See also See VP Dec. 2, 2009, Supp., Exs. K-L.

³⁹⁸ See VP Dec. 2, 2009, Supp. at 5, and 5 n.17.

³⁹⁹ VP Draft Guidance Resp. at 31.

⁴⁰⁰ *Novartis Pharm. Corp. v. Leavitt*, 435 F.3d at 349 (NDA holder’s request for notice and opportunity to comment in detail on issue moot as innovator already had received “every benefit that it could from a favorable judgment” on the issue).

⁴⁰¹ VP Feb. 27, 2009, Supp. to Vancomycin BE Draft Guidance Docket, at 1-3 (correspondence raising issue regarding Agency failure to republish revised vancomycin draft guidance).

Finally, you assert that FDA improperly made a “post hoc” effort to find legal authority for its decision to permit in vitro dissolution data to establish bioequivalence.⁴⁰² In support of this position you cite internal Agency documents that reflect ongoing discussions among OGD staff, FDA attorneys, and senior Agency officials on the appropriate methodology for demonstrating bioequivalence consistent with 21 CFR 320.24. You contend that such discussions demonstrate a “struggle” to find the legal authority to permit FDA to accept in vitro data.⁴⁰³ You also claim that internal Agency documents that do not mention a specific legal authority demonstrate that FDA did not believe it had the authority to permit in vitro data to demonstrate bioequivalence.⁴⁰⁴ Internal Agency discussions of the legal authority and compliance therewith, or the absence of citation to a legal authority in internal documents, do not indicate that FDA thought it lacked authority to take an action. Rather, these documents reflect the Agency’s internal discussion of the legal issues associated with bioequivalence determinations. As courts have concluded, these deliberations of legal and policy issues, like their scientific counterparts are a critical part of the agency’s pre-decision process.⁴⁰⁵ As set forth above, FDA has clear legal authority to determine appropriate bioequivalence methodology.⁴⁰⁶ Internal discussion (or lack thereof) of FDA’s legal authority by no means limits that authority.

(c) OGD Did Not Misrepresent to Senior FDA Officials the Process by Which the Agency Developed the 2008 Draft Vancomycin BE Guidance

Finally, you assert that OGD misrepresented to senior FDA officials the recommendation development process in order to hide the OGD decision making process from scrutiny.⁴⁰⁷ You base this charge largely on briefing materials that appear to have been prepared for internal FDA meetings that you received through FDA’s response to your FOIA request. As a preliminary matter, it is important to recognize that in addition to being pre-decisional, written background materials for oral briefings are summary in nature. They are not comprehensive, nor do they necessarily reflect the discussions that actually took place at any meeting or presentation, or the Agency’s final determination on any given issue. As a result, such materials are limited in their ability to illuminate what senior FDA officials did or did not know about the process by which generic vancomycin bioequivalence recommendations were developed. Notwithstanding these limitations, we address your arguments.

You first contend that OGD did not adequately represent to senior officials the history of the pre-2006 in vivo data requirement. Specifically, you claim that OGD failed to

⁴⁰² VP Mar. 25, 2010, Supp. at 23-26; VP Jan. 15, 2010 Supp. at 16-18.

⁴⁰³ VP Mar. 25, 2010, Supp. at 26.

⁴⁰⁴ *Id.* at 27.

⁴⁰⁵ *Wolfe v. Dep’t Health and Human Services*, 839 F.2d at 773 (“As stated in the legislative history, the purpose of [the deliberative process exemption] is to encourage the frank discussion of legal and policy issues”) (internal quotation and citation omitted); *Brinton v. Department of State*, 636 F.2d 600, 604 (D.C. Cir. 1980) (“There can be no doubt that such legal advice, given in the form of intra-agency memoranda prior to any agency decision on the issues involved, fits exactly within the deliberative process rationale.”).

⁴⁰⁶ See Section I.B., above.

⁴⁰⁷ VP Mar. 25, 2010, Supp. at 16-22.

reference several instances between 1996 and 2006 when FDA communicated to third parties the then-existing recommendation for in vivo studies.⁴⁰⁸ As the presentation materials you cite demonstrate, however, OGD accurately represented that it consistently had communicated the in vivo data recommendation up through 2006.⁴⁰⁹ These same presentations also reference historical events that led to the 2006 amendment, including the 2004 ACPS discussion on using in vitro dissolution data for locally acting GI products and the 2005 ANDA data submission that purported to demonstrate vancomycin's rapid dissolution rate.⁴¹⁰

You next assert that a briefing document on generic vancomycin dated April 2009 purportedly presented to then-FDA Deputy Commissioner Joshua Sharfstein was materially inaccurate in several respects with respect to the process by which the Q1/Q2 requirement was developed.⁴¹¹ The document indicates that OGD had discussed what ultimately became the 2008 amended recommendation (including the Q1/Q2 requirement) in earlier briefings with the relevant review division, the Director for the Center for Drug Evaluation and Research, the Deputy Commissioner and FDA Commissioner. You claim that this statement is inaccurate because there is no reference to Q1/Q2 inactive ingredient sameness in the briefing slides for these earlier meetings. As noted above, such slides are not the entire record of a meeting or presentation, and therefore, do not conclusively establish what actually was discussed at any meeting. In any event, your contention is inaccurate. For example, while "Q1/Q2" may not have been expressly referenced in some of these materials, product formulation, which includes active and inactive ingredients, is referenced.⁴¹²

You also claim that the statement in this briefing document that several ANDAs "would be approvable under the BE in vitro approach" at the time of the briefing could not have been accurate in light of the short time period between announcement of the revised standard (December 2008), which included the Q1/Q2 requirement for the first time, and the briefing (April 2009). You assert that this statement demonstrates that FDA had failed to adequately characterize Vancocin's inactive ingredients prior to permitting in vitro data because if it had, it would have not included the Q1/Q2 requirement due to the complexity of the inactive ingredients in Vancocin.⁴¹³ This series of inferences is unsupported.

Even if OGD had misrepresented the history of its development of the bioequivalence recommendation set forth in the Draft Vancomycin BE Guidance to Agency officials -- which it did not -- as detailed in this petition response, the Agency has considered the entire history of the bioequivalence recommendation, and the current scientific bases for

⁴⁰⁸ VP Jan. 15, 2010, Supp. at 3-6; VP Mar. 25, 2010, Supp. at 14.

⁴⁰⁹ See, e.g., VP Jan. 15, 2010, Supp., Ex. 46, Slide Presentation entitled "Establishing Bioequivalence of Vancomycin HCl Capsules: Commissioner Briefing" (Nov. 8, 2007), FDA-OC-02354-02356.

⁴¹⁰ See id.

⁴¹¹ VP Jan. Mar. 25, 2010, Supp. at 21; Ex. 53, Memo. re. Vancomycin Bioequivalence Issues, attached to e-mail fr. P. Pilsner to J. Woodcock et al. (April 15, 2009).

⁴¹² Id.

⁴¹³ VP Mar. 25, 2010, Supp. at 28-30.

the recommendation, and today endorses the bioequivalence recommendation for generic vancomycin capsules with full knowledge of the process by which it was developed.

III. CONCLUSION

For the foregoing reasons, FDA has determined that the recommendation in the Draft Vancomycin BE Guidance is scientifically sound, that FDA has clear legal authority to recommend in vitro dissolution data to demonstrate generic vancomycin bioequivalence, and that the process by which the Agency developed the current recommendation involved a robust, public consideration of the issues raised in this petition in accordance with the relevant legal authorities. FDA also has determined that Vancocin is not eligible for a 3-year exclusivity period because of the limitation on such exclusivity set forth in section 505(v) of the FD&C Act.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

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