March 21, 2006

Via U.S. Mail

Food and Drug Administration Staff
Division of Freedom of Information (DFOI)
5600 Fishers Lane, Parklawn (PKLN) Building
HFI-35, Room 6-30
Rockville, MD 20857

RE: Freedom of Information Act Request

Dear FOI Staff Officer:

Pursuant to the Freedom of Information Act, I request:

> A copy of the entire administrative record of the decision of the Office of Generic Drugs (OGD) (including, but not limited to, documents related to reference number: OGD #06-0200) that abbreviated new drug applications (ANDAs) or applications filed under 505(b)(2) for vancomycin hydrochloride capsules qualify for a waiver of *in vivo* bioequivalence and may demonstrate bioequivalence to the reference listed drug Vancocin® through *in vitro* dissolution testing.

I will gladly pay the charges for search time and photocopying. Search results should be sent to:

[personal information redacted]

Thank you for your consideration of this FOIA request.

Sincerely,

[personal information redacted]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

[personal information redacted]

03/27/2006

In Reply refer to:
2006-4517
Your reference:

Dear Requester:

The Food and Drug Administration (FDA) has received your Freedom of Information Act (FOIA) request for records regarding:

VANCOMYCIN HCL CAPS OGD #06-0200 - BIOEQUIVALENCE RECS

We will respond as soon as possible and may charge you a fee for processing your request. If you have any questions about your request, please call Shera S. Behram, Information Technician, at (301) 827-6552 or write to us at:

Food and Drug Administration
Division of Freedom of Information
5600 Fishers Lane, HFI-35
Rockville, MD 20857

If you call or write, use the reference number above which will help us to answer your questions more quickly.

Vancocin and the Office of Generic Drugs

Problem

There are three core measures of a good FDA decision. That it is based in good science, that there is a fair process in place to reach a decision, and that it is consistent with good public health. The current path that approval of a generic version of Vancocin is on violates all three of these measures. Absent intervention at the highest level at FDA, the Office of Generic Drugs (OGD) is on course to approve generic vancomycin without a fair process, absent the best available science, and without adequate consideration of public health.

Fair Process

- OGD dropped a requirement for vancomycin capsule generics to demonstrate bioequivalence through clinical trials without a public announcement, process, or opportunity for public review of the data or the argument
- Lack of transparency is particularly troubling in the case of vancomycin capsules – the only antibiotic treatment for life-threatening *clostridium difficile* infection
- The reversal in OGD's position only came to light when a Canadian stock analyst – who had received information from OGD – used the secret reversal in FDA's policy to downgrade the stock of Vancocin's maker, ViroPharma
- The lack of a fair and transparent process violates numerous laws, regulations and policies as detailed in a submission to FDA Docket No. 2006P-0124 (see attached)

Good Science

- Based on a secret process and without providing scientific support, OGD has determined that bioequivalence of generic forms of vancomycin capsules can be demonstrated by dissolution testing instead of clinical trials
- OGD has cited the Biopharmaceutics Classification System (BCS) as support but, by its own terms, the BCS Guidance does not apply to Vancocin – a locally acting drug that is neither highly permeable nor rapidly dissolving
- OGD's proposed *in vitro* dissolution test does not consider the *in vivo* conditions of patients who would be given the drug
- The lack of sufficient scientific support for OGD's policy reversal is detailed in a submission to FDA Docket No. 2006P-0124 (see attached)

Protect the Public Health

- Despite the widely-recognized public health threat from antibiotic resistance, OGD does not consider the impact of approvals of generic antibiotics on antibiotic resistance
- A subtherapeutic generic vancomycin capsule would exacerbate the problem of antibiotic resistance in a disease that already presents a serious treatment issue
- The low price of generic antibiotics, ordinarily viewed as good public policy, may trigger an increase in inappropriate use and antibiotic resistance, which threatens public health. This tension between public policy and public health must be carefully considered.
- Approval of life saving antibiotics, whether brand or generic, should include consideration of how to protect their long-term effectiveness.
- FDA requires sponsors of antibiotics used to treat animals to conduct a risk assessment regarding potential for drug approvals to increase resistant bacteria. It stands to reason that a similar risk assessment should be conducted for human antibiotics.

Remedy

First, to address the series of missteps described above and to avoid an indefensible decision by FDA, OGD should state that their previous policy of requiring clinical trials is reinstated. Second, FDA should announce that any change to this policy would only be undertaken through a public process based on the best available science including consideration of the broader public health issues raised by antibiotic resistance.

June 30, 2006

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA Docket Number 2006P-0124

On March 17, 2006, ViroPharma Incorporated filed a petition to FDA's Office of Generic Drugs (OGD) seeking to stay approval of any abbreviated new drug applications (ANDAs) that reference Vancocin® capsules (vancomycin hydrochloride capsules) based solely on *in vitro* bioequivalence testing.[1] Announcement of the new standard referenced within that petition and herein had occurred the day before, on March 16, 2006. Prior to that date, OGD's interpretation had been that different standard, *in vivo* clinical trials would be the basis for determining bioequivalence for generic vancomycin hydrochloride capsules.

In its petition, ViroPharma Incorporated indicated that it would subsequently file grounds establishing the bases for its disagreement with OGD's new bioequivalence test. On May 31, 2006, ViroPharma Incorporated submitted a supplement to that petition for stay of approval setting forth a number of legal bases demonstrating that OGD's new standard cannot, as a matter of law, be used in the review or approval of vancomycin hydrochloride capsule ANDAs.[2] This document is the second of those filings, and is intended to be incorporated by reference into the March 17, 2006 petition for stay of approval. It sets forth a number of scientific and clinical

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1 See Petition for Stay of Action. ViroPharma Incorporated (March 17, 2006). FDA Docket # 2006P-0124, PSA 1. Available at http://www.fda.gov/ohrms/dockets/dockets/06p0124/06p-0124-psa0001-01-vol1.pdf (last checked June 30, 2006). ViroPharma's petition also sought the same relief regarding applications filed under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act that reference Vancocin. References to "ANDAs" in this document should therefore be read also to refer to applications under section 505(b)(2).

2 See Supplement 1 to Petition for Stay of Approval. ViroPharma Incorporated (May, 31, 2006). FDA Docket # 2006P-0124, Sup 1. Available at http://www.fda.gov/ohrms/dockets/dockets/06p0124/06p-0124-sup1-index.htm (last checked June 30, 2006).

bases to demonstrate that OGD's new standard cannot, as a matter of sound science and prudent public health policy, properly be used in the review or approval of vancomycin hydrochloride capsule ANDAs.

1.0 OVERVIEW

Vancocin capsules are a unique, semi-solid filled gelatin capsule formulation of vancomycin hydrochloride, a complex, biologically derived peptide antibiotic, for oral administration. The OGD has proposed waiving *in vivo* studies in favor of using *in vitro* dissolution testing to establish the bioequivalence of a generic version of Vancocin capsules. OGD's proposal to modify the standard for determining bioequivalence and waive any requirement for human testing is concerning because Vancocin capsules are indicated for two potentially life-threatening infections of the gastrointestinal (GI) tract, antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile* and enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains). The United States is currently experiencing an epidemic of *C. difficile*-associated disease (CDAD) caused by a new strain that has been reported to result in significantly more morbidity and mortality than historically reported. Approval of a generic product that has not undergone rigorous human testing carries the risk that a potentially inferior product might be used to treat these life-threatening conditions.

ViroPharma Incorporated believes that the OGD has not fully considered all of the factors necessary to extrapolate an *in vitro* approach developed for rapidly dissolving, highly soluble and systemically absorbed drugs to a locally acting GI drug such as Vancocin capsules. As described in detail below, Vancocin capsules are not rapidly dissolving, and vancomycin, the active pharmaceutical ingredient is not well absorbed and cannot be considered highly soluble. As a result, Vancocin capsules do not fit the criteria of a candidate for a waiver of *in vivo* bioequivalence testing. In addition, the *in vitro* conditions of testing proposed by OGD are not representative of the *in vivo* environment of the GI tract in patients with CDAD or staphylococcal enterocolitis (SEC) to which the capsules will be exposed. There are several important pathophysiologic changes present in patients with CDAD compared to healthy individuals that make it even more difficult to extrapolate *in vitro* performance to the clinical situation. These changes in physiology include profound alterations in GI motility and pH along the GI tract, as well as abnormal constituents in the GI lumen that lead to conditions that are

difficult to reproduce in any *in vitro* media. It is not surprising that no *in vitro/in vivo* correlation (IVIVC) has been established for Vancocin capsules.

The OGD also seems to have overlooked that although Vancocin capsules are locally-acting in the GI tract, systemic absorption has been documented in patients with CDAD. The potential for enhanced systemic absorption and accumulation of vancomycin from a generic product is a significant safety concern as vancomycin can cause nephrotoxicity and ototoxicity. This can only be assessed by measuring serum concentrations in a clinical study.

As this supplement makes clear, OGD's proposal is neither supported by FDA guidance and precedent on establishing bioequivalence for locally acting GI drugs, the Advisory Committee for Pharmaceutical Sciences (ACPS) position on this issue, nor the clinical and scientific elements critical to consider a waiver of *in vivo* bioequivalence studies. The use of *in vitro* dissolution testing as the sole means of determining bioequivalence for any generic version of Vancocin capsules has an unacceptably high risk of approval of a suboptimally performing product and exposes patients to unnecessary risk of treatment failure and potential systemic toxicities.

2.0 BACKGROUND

On March 16, 2006, it became public knowledge that the FDA's OGD was modifying its bioequivalence standard for oral Vancocin capsules and would accept the submission of *in vitro* dissolution testing data as a surrogate measure of *in vivo* bioequivalence.[3] Until this point in time, the OGD had a long-standing policy requiring clinical studies as the basis to determine bioequivalence between any generic version of oral vancomycin hydrochloride capsules and oral Vancocin capsules. However, in a letter dated March 1, 2006 (Ref# OGD #06-0200) to Infinium Capital Corporation ("Infinium Letter"), Dr. Dale Conner (Director, Division of Bioequivalence, OGD) stated[4]:

"Vancomycin 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 abbreviated new drug applications (ANDAs), provided that the test product is rapidly dissolving at the

[3] Infinium Capital report on ViroPharma Incorporated, March 16, 2006.
[4] OGD letter to Infinium Capital. March 1, 2006.

conditions specified in the guidance *Waiver of in vivo BA and BE studies for IR solid oral dosage forms based on a biopharmaceutics classifications system (BCS Guidance)*. Dissolution data in various media on 12 dosage units each of test and reference products (for both strengths) should be provided 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
Sampling times:	5, 10, 15, 20, 25, 30, and 40 minutes or as needed for profile comparison"

This drastic and sudden change in policy by the OGD was implemented despite contrary views by the FDA's ACPS, without input from the Office of Antimicrobial Products (OAP), and without any public debate or dialogue with the innovator company, ViroPharma Incorporated.

OGD's new dissolution approach for Vancocin capsules is not supported by FDA regulations[5] or guidance. The biopharmaceutics classification system (BCS) that OGD relies on is expressly not intended to be applied to locally-acting GI drugs such as Vancocin capsules. The BCS, by its own terms, applies to drugs that are highly soluble, highly permeable, and rapidly dissolving (the so-called Class 1 drug products). As described in detail below, these are properties that do not apply to Vancocin capsules. Vancomycin is a large, biologically-derived antibiotic peptide, made up of multiple components, that possess complex solubility characteristics, and is a poorly absorbed, low permeability drug.

Vancocin capsules are indicated for the treatment of two serious infections that induce substantial pathophysiologic changes to the GI tract, CDAD and SEC. CDAD occurs almost

[5] See 21 C.F.R. § 320.22

exclusively in patients with recent antibiotic exposure. Clinical expression virtually always includes diarrhea as the most prominent feature; however, as with almost all enteric pathogens, severity is widely variable ranging from a few loose stools to a fulminant diarrhea associated with rapid dehydration. Common features include the findings of colitis with cramps, fever, fecal leukocytes, inflammation on colonic biopsy, and the presence of pseudomembranes (composed of a loose network of mucin, neutrophils, fibrin, and nuclear debris), that appear as adherent raised white and yellowish plaques on the colonic mucosa on endoscopy. The disease is nearly always restricted to the colon, and can result in a protein-losing enteropathy that is often associated with hypoalbuminemia.[6] Both CDAD and SEC result in significant changes in the physiology of the colon and small bowel including altered motility (ranging from ileus to hypermotility), pH and volume conditions, and the presence of various abnormal intraluminal constituents and inflammatory mediators. These changes in the GI tract physiology are difficult, if not impossible to simulate in an *in vitro* environment.

CDAD and SEC also most commonly occur in those greater than 65 years of age. Age is also associated with significant changes in the physiology of the GI tract that may impact the performance of an orally administered drug product in ways that can not be predicted from *in vitro* testing. To date, no correlation between *in vitro* performance and *in vivo* clinical outcomes for Vancocin capsules has been demonstrated; thus, the extrapolation of *in vitro* product performance to *in vivo* performance and clinical outcomes is associated with substantial risk.

One of the public health risks associated with the OGD's proposal is potentially allowing a bioINequivalent and poorly performing oral vancomycin product on the market at a time when the threat from CDAD is increasing. The incidence and severity of CDAD have increased so dramatically that several federal agencies, including the Centers for Disease Control and

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[6] Tedesco FJ, Barton RW, Alpers DH. Clindamycin-associated colitis. A prospective study. *Ann Intern Med.* 1974;81:429-33; Gerding DN. Disease associated with *Clostridium difficile* infection. *Ann Intern Med.* 1989;110:255-7; Fekety R, Shah AB. Diagnosis and treatment of *Clostridium difficile* colitis. *JAMA.* 1993;269:71-5; Kelly CP, Pothoulakis C, LaMont JT. *Clostridium difficile* colitis. *N Engl J Med.* 1994;330:257-62; Mogg GA, Keighley MR, Burdon DW, Alexander-Williams J, Youngs D, Johnson M, et al. Antibiotic-associated colitis: A review of 66 cases. *Br J Surg.* 1979;66:738-42; Bartlett JG, Taylor NS, Chang T, Dzink J. Clinical and laboratory observations in *Clostridium difficile* colitis. *Am J Clin Nutr.* 1980;33(Suppl 11):2521-6.

Prevention (CDC), the FDA, and the National Institutes of Health (NIH) held a joint conference on May 11, 2006 to begin to address this re-emerging and life-threatening infectious disease.[7]

Vancomycin is also a critically important antibacterial agent and the intravenous form is one of the preferred therapeutic options for methicillin-resistant staphylococcal infection. Not only does a potentially suboptimal performing generic version of Vancocin capsules being used in patients run the risk of having a negative impact with respect to decreased efficacy for CDAD, it may also result in an increase in the prevalence of organisms resistant to vancomycin including *Staphylococcus aureus* and *Enterococcus species*.

The OGD's decision to abandon the requirement for an *in vivo* demonstration of bioequivalence for generic versions of Vancocin capsules in favor of an inappropriately applied *in vitro* dissolution test is also unprecedented. To our knowledge, no first time generic has been approved for an RLD based solely on *in vitro* dissolution since the 1984 Hatch-Waxman amendment went into effect,[8] let alone for a drug used to treat potentially life-threatening infectious diseases.

3.0 VANCOCIN CAPSULES CONTAIN A COMPLEX, BIOLOGICALLY-DERIVED ANTIBIOTIC PEPTIDE IN A UNIQUE FORMULATION THAT ENSURES SAFETY AND EFFECTIVENESS

The active pharmaceutical ingredient (API) of Vancocin capsules is a complex, amorphous, tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* through a fermentation process. It has a molecular weight of approximately 1,486 Daltons.[9] Vancomycin is a polyfunctional amphoteric compound containing six functional groups in acid-base equillibria, with two basic and four acidic groups. Vancomycin forms a three-dimensional pocket shape as a result of bonds between aromatic amino acid residues and contains a number of chiral centers, which may create different diasteriomeric forms. At least 23 components have been identified

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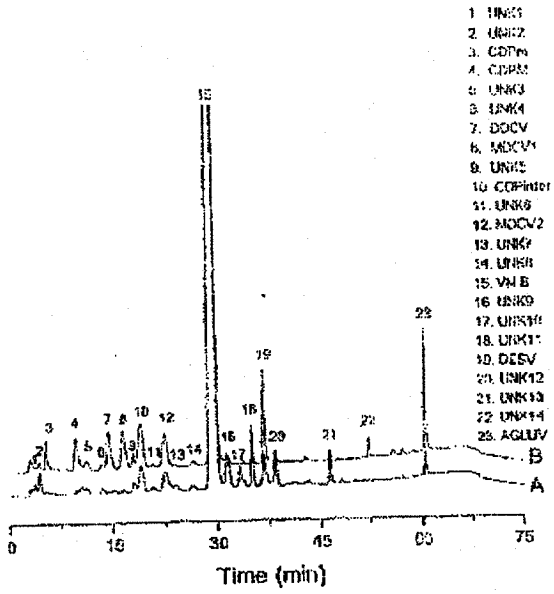
7 Public Workshop on Emerging Clostridial Diseases, May 11, 2006, http://www.fda.gov/cder/meeting/clostridia_disease.htm (accessed on June 30, 2006).

8 Ctr. for Drug Evaluation & Research, Guidance for Industry, Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (Aug. 2000).

9 Wilhelm MP, Estes L. Vancomycin. Symposium on antimicrobial agents -- Part XII. *Mayo Clin Proc.* 1999;74:928-35.

by high performance liquid chromatography (HPLC) that constitutes the raw drug material (Figure 1).[10]

Figure 1. Chromatogram of Vancomycin HCl Commercial Sample (A) and Purified Vancomycin HCl Sample (B)



The principal component, known as vancomycin 'B' (component #15 in Figure 1), accounts for most of the microbiological activity, but other components present are known to possess biological activity.

Vancomycin possesses activity against gram-positive bacteria that occurs as a result of rapid and irreversible binding to the cell walls of sensitive bacteria.[11] Vancomycin binds by its N-terminal end to the C-terminal D-alanine-D-alanine residues of the peptidoglycan precursor UDP-N-acetylmuramyl pentapeptide at the external surface of the cytoplasmic membrane of the bacteria. Vancomycin inhibits the addition of the peptidoglycan precursor to the growing peptidoglycan chain most likely due to steric hindrance. In addition, vancomycin inhibits transpeptidases and

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[10] Diana J et al. Development and validation of an improved method for the analysis of vancomycin by liquid chromatography selectivity of reversed-phase columns towards vancomycin components. *J Chromatogr A.* 2003;9;996(1-2):115-31.

[11] Sinha RK, Neuhas RC. Reversal of the vancomycin inhibition of peptidoglycan synthesis by cell walls. *J Bacteriol.* 1968;96:374-82.

carboxypeptidases that cross-link adjacent peptidoglycan chains with pentaglycine side chains.[12] The end result is the inhibition of synthesis of a normally rigid cell wall.[13] Vancomycin also alters bacterial cell membrane permeability and RNA synthesis,[14] but these functions are much less important than its actions on the cell wall.[15]

Vancocin capsules are the only FDA approved and marketed solid dosage form indicated for the treatment of two significant bacterial infections of the GI tract, antibiotic-associated pseudomembranous colitis caused by *C. difficile* and enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains). Vancocin capsules are poorly absorbed and act locally in the GI tract, specifically in the large intestinal mucosa in the case of CDAD and on both the small and large intestine in the case of SEC.

Vancocin capsules are a unique formulation of oral vancomycin consisting of a semi-solid matrix filled gelatin capsule utilizing a specific polyethylene glycol (PEG) 6000. Extensive testing has identified the particle size requirements of vancomycin necessary to formulate the capsule and the need for a strictly controlled environment during manufacture to ameliorate the hygroscopic nature of the API. The proprietary formulation processes, materials, and equipment used in the manufacture of Vancocin capsules have been shown sufficient to ensure adequate stability, consistency, and quality of the solid dosing form. As evidenced by clinical trials and greater than twenty-years of clinical use, Vancocin capsules are very effective in the treatment of CDAD and SEC.[16] It is postulated that the proprietary manufacturing process and resultant unique formulation are important for consistent delivery of vancomycin to the mucosal site of action within the GI tract and the subsequent excellent clinical results.

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[12] Nagarajan R. Antibacterial activities and modes of action of vancomycin and related glycopeptides. *Antimicrob Agents Chemother.* 1991;35(4):605-9.

[13] Id.; Barna JCJ, Williams DH. The structure and mode of action of glycopeptide antibiotics of the vancomycin group. *Annu Rev Microbiol.* 1984;38:339-57.

[14] Pfeiffer RR. Structural features of vancomycin. *Rev Infect Dis.* 1981;3 suppl:S205-9.

[15] Wilhelm MP, Estes L. Vancomycin. Symposium on antimicrobial agents - Part XII. *Mayo Clin Proc.* 1999;4:928-35.

[16] Davidson D. A phase 2 study of the toxin binding polymer tolevamer in patients with *C. difficile* associated diarrhea. European Society of Clinical Microbiology and Infectious Diseases, 2004, Prague, Czech Republic, abstract#902; Pullman J et al. Ramoplanin vs. vancomycin in the treatment of *Clostridium difficile* diarrhea: a phase 2 study. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2004, Washington D.C.

ViroPharma Incorporated has conducted extensive analyses of the physicochemical and pharmaceutic characteristics of vancomycin as well as the release characteristics of Vancocin capsules including dissolution and solubility of the API over a wide range of physiologically relevant pH's and volume conditions. ViroPharma Incorporated's data indicate that the API in Vancocin capsules (vancomycin HCl) exhibits complex, pH dependent solubility characteristics, and as described more fully in Section 4.4.2, although highly soluble at low pHs, its solubility is substantially reduced at pH values above 6.8. In addition, these studies have demonstrated that Vancocin capsules are not rapidly dissolving (defined in FDA Guidance as at least 85% dissolution within 30-minutes)[17] under *in vitro* dissolution testing conditions across a physiologically and pathophysiologically relevant pH range of 1.2 to pH 8.0 (data provided in Section 4.4.1). These findings are inconsistent with the recent OGD assertion in the Infinium Letter that a waiver of *in vivo* bioequivalence studies is appropriate for Vancocin capsules specifically because the API is highly soluble and the finished product is rapidly dissolving.

4.0 SCIENTIFIC AND CLINICAL EVIDENCE THAT INVALIDATES THE OGD'S APPROACH FOR A GENERIC PRODUCT TO DEMONSTRATE BIOEQUIVALENCE TO VANCOCIN CAPSULES

4.1 Vancocin Capsules Are Indicated for the Treatment of Serious, Often Life-Threatening Infectious Diseases. Waiving In Vivo Bioequivalence Testing for Vancocin Capsule Generics and the Consequent Risks to Individual Patients and the Public Health are not Defensible by Way of Science or Public Policy.

An important consideration in granting a biowaiver of *in vivo* bioequivalence studies is the disease(s) for which the RLD is indicated for use. Vancocin capsules are the only FDA approved and marketed solid dosage form indicated for the treatment of two significant, life-threatening bacterial infections of the lower gastrointestinal tract, antibiotic-associated pseudomembranous colitis caused by *C. difficile* and enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains). The benefit:risk assessment associated with improperly approving a bioINequivalent product based solely on *in vitro* dissolution testing is unacceptable for these disease states. Should a bioINequivalent generic vancomycin capsule be

[17] Ctr. for Drug Evaluation & Research, Guidance for Industry, Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (Aug. 2000).

approved for use, it would be very difficult to identify treatment failures in patients resulting from the use of a subtherapeutic formulation from those that would have proceeded to develop severe morbidity or death as a result of the infection regardless of drug formulation. The identification of a bioINequivalent oral vancomycin capsule would not occur until a large number of patients had experienced unnecessary suffering and/ or death. Only through an appropriately powered *in vivo* clinical trial can *in vitro* dissolution data be verified to reflect bioequivalence and clinical efficacy of a generic product prior to exposing and placing large numbers of seriously ill patients at risk.

Further, *in vitro* dissolution testing will not determine if a generic vancomycin capsule formulation is systemically absorbed to the same rate and extent as Vancocin capsules. If systemic absorption and accumulation occurs to a greater extent with a generic vancomycin capsule, patients will be placed at undue risk of developing systemic toxicities.

4.1.1 The United States is Experiencing an Emerging Clostridium difficile-Associated Disease Epidemic

Antibiotic-associated pseudomembranous colitis was first described to be caused by *C. difficile* in the 1970's.[18] Pseudomembranous colitis can occur when a patient's normal gastrointestinal tract flora becomes disrupted, typically following antibiotic exposure. In patients subsequently exposed to *C. difficile*, this disruption can result in colonization and overgrowth with *C. difficile*. Some strains of *C. difficile* produce toxins that result in an inflammatory reaction in the colonic mucosa. This results in the development of diarrhea that can be clinically significant, and in some patients cause hemodynamic instability.

CDAD is the most common cause of nosocomial-acquired antibiotic-associated diarrhea.[19] Although CDAD is not a nationally reportable disease, the CDC estimates that 500,000 patients are affected by CDAD annually.[20] Over the last several years, there has been an increase in the

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[18] Bartlett JG. Antibiotic-associated diarrhea. *N Eng J Med.* 2002;346:334-9.

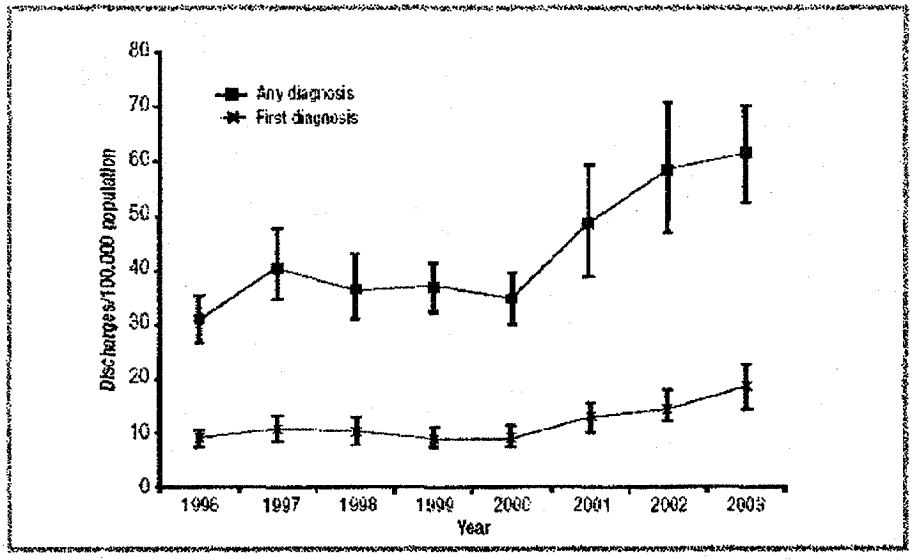
[19] Id.

[20] Centers for Disease Control and Prevention. http://www.cdc.gov/ncidod/dhqp/id_Cdiff.html. Accessed June 9, 2006.

number of cases of CDAD[21] and more descriptions of acute and severe disease associated with *C. difficile* have been reported.[22]

Data collected for the National Hospital Discharge Survey have been utilized to evaluate the increase of *C. difficile* in US hospitals.[23] The number of discharges for which CDAD was listed as the first diagnosis increased from 25,000 in 2000 to 54,000 in 2003 (P<0.001). Annual increases in the point estimates of these discharges over the precedent year were 43%, 18%, and 27% in 2001, 2002, and 2003, respectively. The estimated population-based rates of discharges with either a first-listed or any diagnosis of CDAD during this period are presented in Figure 2.[24] The upward trend in rates of CDAD both as first-listed (P=0.008) and as any (P=0.01) diagnosis were statistically significant between 2000 and 2003.

Figure 2. National Estimates of US Short-stay Hospital Discharges with *Clostridium difficile* Listed as Primary or as Any Diagnosis.



[21] McDonald LC et al. Increasing rates of Clostridium difficile infection among patients discharged from US short-stay hospitals, 1996-2003. *Emerg Infect Dis.* 2006;12(3):409-15; Chernak E. Severe *Clostridium difficile* associated Disease in populations previously at low risk -- four states, 2005. *MMWR.* 2005;54:1201-5.

[22] Pépin J et al. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. *CMAJ.* 2004;171(5):466-72; Loo VG et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med.* 2005;353:2442-9.

[23] McDonald LC et al. Increasing rates of Clostridium difficile infection among patients discharged from US short-stay hospitals, 1996-2003. *Emerg Infect Dis.* 2006;12(3):409-15.

[24] Id.

In 2005, Loo et al. identified a new strain of *C. difficile* that was associated with high rates of severe disease in several hospitals in Quebec. Over a 5-month period in 2004, they reported an incidence of 22.5 cases of CDAD per 1000 admissions, with an attributable mortality rate of 6.9% in 12 hospitals in Quebec.[25] This strain demonstrated high resistance to fluoroquinolones, the presence of binary toxin genes, and a partial deletion of the *tcdC* regulatory gene (that is believed to serve as a negative regulator of the production of toxins A and B). These mutations have been proposed to result in the increased virulence of this new strain of *C. difficile.*

In addition, the rate of colectomies related to CDAD has also been reported to have increased significantly.[26] In a report from the University of Pittsburgh, the number of colectomies increased from 3 in 1991 to 17 in 2000. This institution has also experienced the emergence of this new strain of *C. difficile* with increased virulence, antimicrobial resistance, or both.[27] The new strain of *C. difficile* belonging to the toxinotype III group has been identified in several reports[28] and been shown to produce 16 times more toxin A and 23 times more toxin B, (the primary virulence factors of *C. difficile),* than other *C. difficile* strains.[29]

Toxinotype III strains have been definitively identified in at least 21 states in the U.S., several hospitals in Canada, and Western Europe. Two surveys of clinicians have been conducted over the past 2-years to evaluate clinicians' perceptions regarding the number of patients they are treating with CDAD, the severity of cases of CDAD, and the frequency they encounter patients who have a relapse of disease. As shown in Figure 3, both surveys have noted an increase in the number of cases of CDAD, the number of cases of severe CDAD, and the number of cases of

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25 Loo VG et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med.* 2005;353:2442-9.

26 Dallal R M et al. Fulminant Clostridium difficile : An underappreciated and increasing cause of death and complications. *Ann Surg* 2002;235(3):363-72.

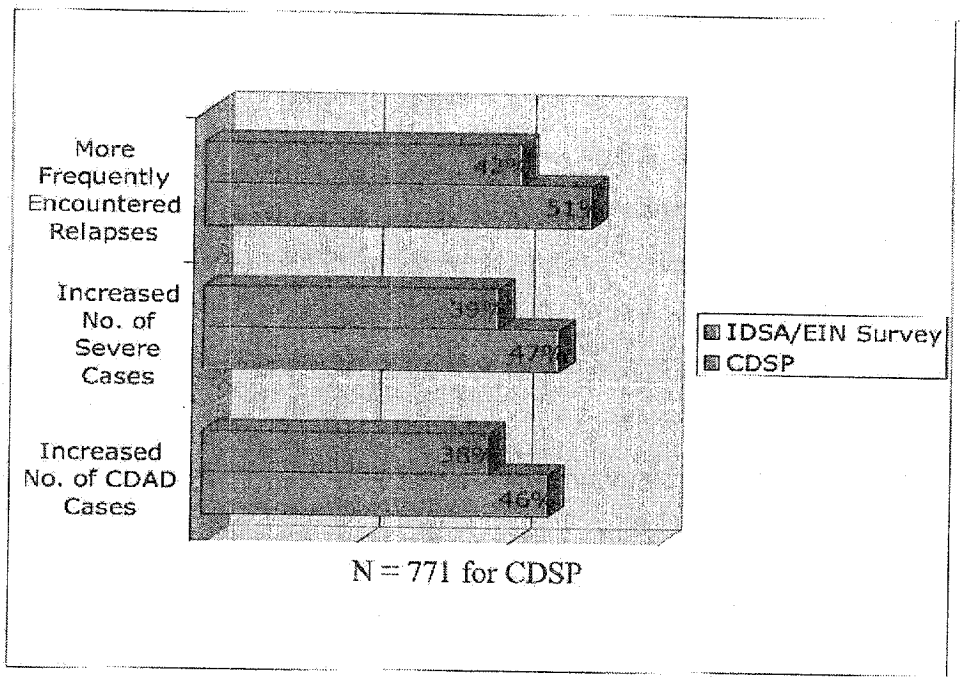
27 McDonald LC et al. An epidemic, toxin gene-variant strain of Clostridium difficile. *N Engl J Med.* 2005;353:2433-41.

28 Pépin J et al. Increasing risk of relapse after treatment of *Clostridium difficile* colitis in Quebec, Canada. *Clin Infect Dis.* 2005;40:1591-7; Muto CA et al. A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increase flouoroquinonlone use. *Infect Control Hosp Epidemiol.* 2005;26:273-80; Musher DM et al. Relatively poor outcome after treatment of *Clostridium difficile* colitis with metronidazole. *Clin Infect Dis.* 2005;40:1586-90.

29 Warny M et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. *Lancet.* 2005;366:1079-84.

CDAD that relapse, with the more recent and ongoing survey showing greater increases in all of these markers.[30]

Figure 3. Comparison of Infectious Diseases Society of America/ Emerging Infections Network (IDSA/EIN) and the *Clostridium difficile* Surveillance Project (CDSP) Results.



Further complicating matters, there have been recent reports of severe CDAD in individuals otherwise considered to be at low risk for contracting this disease. Specifically, the CDC has documented the occurrence of severe CDAD in Pennsylvania and three other states in otherwise healthy individuals living in the community who had minimal or no exposure to a health-care setting within the prior three months, and in peripartum women.[31] Moreover, 24% of the 33 patients investigated had not been exposed to antimicrobial agents within three months of the

[30] Gelone SP et al. Clostridium difficile Epidemiology: Results of an International Web-based Surveillance Project. SHEA Annual Meeting, Late-breaker presentation, April 2006.

[31] Chernak E. Severe *Clostridium difficile*-associated Disease in populations previously at low risk -- four states, 2005. *MMWR.* 2005;54:1201-5.

onset of CDAD.[32] Adding to the concern is that some of these cases were severe in nature and at least one resulted in death.

Additionally, Dial and colleagues have reported a dramatic increase in the occurrence of community-acquired CDAD in patients taking gastric acid suppressing proton-pump inhibitor drugs (e.g., Prilosec (omeprazole) or Nexium (esomeprazole)) in the U.K.[33] The authors reported a two- to three-fold increase in the risk of community-acquired CDAD in patients taking these drugs, and approximately 75% of CDAD cases in the "General Practice Research Database" were in patients who had not been hospitalized in the year prior to diagnosis. These findings led the investigators to postulate that the mechanism of increased CDAD risk is associated with the degree of gastric acid suppression, and noted that decreased gastric acidity is "a known risk factor for other infectious diarrheal illnesses such as travelers' diarrhea, salmonellosis, and cholera."[34]

4.1.2 The Availability of a Suboptimally Performing Generic Version of Vancocin Capsules May Enhance the Spread of Vancomycin-Resistant Organisms

The foregoing publications suggest that the occurrence of severe CDAD in populations previously considered to be at low risk may be related to the emergence of a more virulent strain of *C. difficile*, and that an increased risk of CDAD may be related to gastric acid suppression. As a result of the growing population affected by CDAD and the reports of poor response to metronidazole,[35] more clinicians may begin to use Vancocin capsules. Inappropriate or unwarranted use of any anti-infective agent may result in the selection and spread of resistant pathogens. Resistance to vancomycin in clinically important organisms was first described in the late-1980s in *Enterococcus species* and in 1997 in *Staphylococcus species*. As a result, recommendations to prevent the spread of vancomycin resistance and control vancomycin-intermediate and vancomycin-resistant *Staphylococcus aureus* (VISA/VRSA) were published by

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32 Chernak E. Severe *Clostridium difficile*-associated Disease in populations previously at low risk -- four states, 2005. *MMWR*. 2005;54:1201-5.

33 Dial S et al. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA*. 2005;294:2989-95.

34 Id.

35 Pépin J et al. Increasing risk of relapse after treatment of *Clostridium difficile* colitis in Quebec, Canada. *Clin Infect Dis*. 2005;40:1591-7; Musher DM et al. Relatively poor outcome after treatment of *Clostridium difficile* colitis with metronidazole. *Clin Infect Dis*. 2005;40:1586-90.

the CDC in 1995 and 1997,[36] respectively. These organisms have recently been identified by the Infectious Diseases Society of America (IDSA) as "problem pathogens."[37] The availability and use of a suboptimally performing generic version of Vancocin capsules may augment the spread of organisms resistant to vancomycin, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and VRSA. An increase in the prevalence of these pathogens will further challenge clinicians who have limited antimicrobial agents available that are effective in treating these organisms and will negatively impact public health.

4.1.3 Vancocin Capsules Are the Only FDA Approved Treatment for CDAD and Are Considered the Treatment of Choice for Patients with Severe CDAD by National Treatment Guidelines

Several national societies have published practice guidelines for the management of CDAD.[38] Although never approved by the FDA for the treatment of CDAD, metronidazole is recommended by these guidelines for the treatment of mild-to-moderate disease. This is based primarily on the results of two, prospective trials that compared oral vancomycin to oral metronidazole in patients with CDAD reporting no statistical difference between the two treatments with regard to initial clinical response or relapse.[39] Oral vancomycin has been recommended by these treatment guidelines for use in those who are pregnant, those allergic or intolerant to metronidazole, those requiring prolonged therapy, or those with severe or life-threatening disease.[40]

The development of more severe disease in patients with *C. difficile* infection presents significant clinical concerns. In particular, clinicians have noted a more rapid progression of disease from

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[36] Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR* 1995;44:RR-12. Interim guidelines for prevention and control Staphylococcal infections associated with reduced susceptibility to vancomycin. *MMWR* July 11, 1997, p. 626.

[37] Talbot G et al. Bad bugs need drugs: An update on the development pipeline from the antimicrobial availability task force of the Infectious Diseases Society of America. *Clin Infect Dis* 2006;42:657-68.

[38] Fekety R. *Amer J Gastroenterol.* 1997;92(5):739-50; Gerding DN et al. *Infect Control Hosp Epidemiol.* 1995;16(8):459-77; ASHP. *Am J Health-Sys Pharm.* 1998;55:1407-11; Guerrant RL et al. *Clin Infect Dis.* 2001;32:331-51.

[39] Teasley DG et al. Prospective randomized trial of metronidazole versus vancomycin for Clostridium difficile associated diarrhea and colitis. *Lancet.* 1983;Nov:1043-46; Wenisch C et al. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of Clostridium difficile-associated diarrhea. *Clin Infect Dis.* 1996;22:813-88.

[40] Fekety R. *Amer J Gastroenterol.* 1997;92(5):739-50; Gerding DN et al. *Infect Control Hosp Epidemiol.* 1995;16(8):459-77; ASHP. *Am J Health-Sys Pharm.* 1998;55:1407-11; Guerrant RL et al. *Clin Infect Dis.* 2001;32:331-51.

diarrhea to pseudomembranous colitis and hemodynamic instability, especially in patients infected with toxinotype III strains.[41] Of additional concern to clinicians is the increased number of colectomies performed as a result of this more aggressive disease[42] and the marked increase in mortality associated with toxinotype III infection.[43] It has been reported that response rates to metronidazole treatment, which typically is first-line therapy for CDAD,[44] have decreased from greater than 90%[45] to 60-70%[46] in centers affected by this strain. Available literature, however, continues to references a sustained response rate of greater than 90 percent with oral vancomycin during the timeframe when these strains have become more common.[47]

The consequences of a bioINequivalent and suboptimally performing product reaching the market could be devastating in terms of resulting patient morbidity and mortality. The new strain of *C. difficile* that produces significantly more toxin and has been reported to cause a clinical disease that rapidly progresses from mild to severe within a few days is being more commonly encountered by clinicians. As evidenced by accumulated clinical experience and recent reports, Vancocin capsules are a very effective treatment for CDAD.[48] In the absence of

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41 McDonald LC et al. An epidemic, toxin gene-variant strain of Clostridium difficile. *N Engl J Med.* 2005;353:2433-41; Loo VG et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med.* 2005;353:2442-9.

42 Dallal RM et al. Fulminant *Clostridium difficile*: an underappreciated and increasing cause of death and complications. *Ann Surg.* 2002;235:363-72.

43 Pépin J et al. Mortality attributable to nosocomial *Clostridium difficile*-associated disease during an epidemic caused by a hypervirulent strain in Quebec. *CMAJ.* 2005;173(9): online; Loo VG et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med.* 2005;353:2442-9.

44 Simor AE et al. SHEA Position Paper: *Clostridium difficile* in Long –Term Care Facilities for the Elderly. *Infect Control and Hosp Epidemiol.* 2002;23(11):696-703; Fekety R. Guidelines for the diagnosis and treatment of *Clostridium difficile*-associated diarrhea and colitis; American College of Gastroenterology, Practice Parameters Committee. 1997;92:739-750; Hospital Infection Control Practices Advisory Committee (HICPAC). Recommendations for preventing the spread of vancomycin resistance. *Infect Control Hosp Epidemiol.* 1995 16:105-113.

45 Teasley DG et al. Prospective randomised trial of metronidazole versus vancomycin for *Clostridium difficile*-associated diarrhea and colitis. *Lancet.* 1983;2:1043-6; Wenisch C et al. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea. *Clin Infect Dis.* 1996;22:813-8.

46 Pépin J et al. Increasing risk of relapse after treatment of *Clostridium difficile* colitis in Quebec, Canada. *Clin Infect Dis.* 2005;40:1591-7; Musher DM et al. Relatively poor outcome after treatment of *Clostridium difficile* colitis with metronidazole. *Clin Infect Dis.* 2005;40:1586-90.

47 Schroeder MS. Clostridium difficile-associated diarrhea. *Am Fam Physician.* 2005 Mar 1;71(5):921-8.

48 Davidson D. A phase 2 study of the toxin binding polymer tolevamer in patients with *C. difficile* associated diarrhea. European Society of Clinical Microbiology and Infectious Diseases May 2004, Prague, Czech Republic, abstract#902; Pullman J et al. Ramoplanin vs. vancomycin in the treatment of *Clostridium difficile* diarrhea: a phase 2 study. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2004, Washington D.C.

in vivo clinical studies that demonstrate bioequivalence, it will be very difficult to identify a suboptimally performing product due to the significant background morbidity and mortality associated with CDAD. The benefit:risk consideration and serious public health consequences associated with the potential approval of a bioINequivalent product must be considered and openly discussed.

4.1.4 Vancocin Capsules are a Locally Acting Agent But Have Been Documented to be Systemically Absorbed in Patients with CDAD. Clinical Assessment of Serum Concentrations is Essential to Ensure Patient Safety

As noted above, vancomycin hydrochloride is a large molecule (MW 1,486) and its systemic absorption after oral administration is limited in patients with normal GI tract physiology.[49] Although uncommon, systemic absorption of vancomycin after oral administration has been reported in patients with CDAD.[50] Accumulation appears to occur most commonly in patients with concomitant CDAD and renal insufficiency and the potential for this to occur is clearly documented in the product labeling for Vancocin capsules within the precautions section.[51]

There are important patient safety issues related to systemic absorption and accumulation of vancomycin. Most patients with CDAD are greater than 65 years of age.[52] The majority of these

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49 Lucas RA et al. Disposition of vancomycin in healthy volunteers from oral solution and semi-solid matrix capsules. *J Clin Pharm Ther.* 1987;12:27-31.

50 Thompson CM Jr et al. Absorption of oral vancomycin- possible associated toxicity. *Intern J Ped Nephrol.* 1983;4(1):1-4. Matzke GR et al. Systemic absorption or oral vancomycin in patients with renal insufficiency and antibiotic-associated colitis. *Amer J Kid Dis.* 1987;9(5):422-5. Armstrong CJ, Wilson TS. Systemic absorption of vancomycin. *J Clin Path.* 1995;48(7):689. Bergeron L, Boucher FD. Possible red-man syndrome associated with systemic absorption or oral vancomycin in a child with normal renal function. *Ann Pharmacother.* 1994;28(5):581-4. Hirata S et al. Elevated serum vancomycin concentrations after oral administration in a hemodialysis patient with pseudomembranous colitis. *Jap J Clin Pharmacol Ther.* 2003;34(3):87-90. Brouwer DM et al. Systemic absorption of low-dose oral vancomycin. *J Phar Practice Resear.* 2005;35(3):222-3. Barclay P, O'Connell P. Therapeutic serum levels achieved with oral vancomycin. *Austr J Hosp Phar.* 1994;24:125. Spitzer PG, Eliopoulus GM. Systemic absorption of enteral vancomycin in a patient with pseudomembranous colitis. *Ann Intern Med.* 1984;100:533-4. Tedesco F et al. Oral vancomycin for antibiotic-associated pseudo-membranous colitis. *Lancet.* 1978;2:226-228. Schaad UB et al. Clinical pharmacology and efficacy of vancomycin in pediatric patients. *J Ped.* 1980;96(1):119-26. Killian AD et al. Red man's syndrome after oral vancomycin. *Ann Intern Med.* 1991;115(5):410-11; Aradhyula S et al. Significant absorption of oral vancomycin in a patient with *Clostridium difficile* colitis and normal renal function. *South Med J* 2006;99(5):518-20.

51 Vancocin capsules. Product labeling. ViroPharma Incorporated, January 2005.

52 McDonald LC et al. Increasing rates of Clostridium difficile infection among patients discharged from US short-stay hospitals, 1996-2003. *Emerg Infect Dis.* 2006;12(3):409-15.

patients has some degree of renal insufficiency related to aging[53] or other concomitant disease state(s) and, therefore is at higher risk for systemic absorption and accumulation. Systemic accumulation of vancomycin is associated with a number of adverse effects including nephrotoxicity and ototoxicity[54] and serum trough concentrations in excess of 12 mcg/mL[55] have been associated with these toxicities. Several reports in the literature have documented serum concentrations after oral vancomycin administration to be in excess of 12 mcg/mL.[56] The product labeling states in the precautions section "Clinically significant serum concentrations have been reported in some patients who have taken multiple oral doses of vancomycin for active *C. difficile*-induced pseudomembranous colitis; therefore, monitoring of serum concentrations may be appropriate in some instances, e.g., in patients with renal insufficiency and/or colitis. Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of vancomycin and, therefore, may be at risk for the development of adverse reactions associated with the parenteral administration of vancomycin (see package insert accompanying the intravenous preparation). The risk is greater if renal impairment is present. It should be noted that the total systemic and renal clearances of vancomycin are reduced in the elderly. Ototoxicity has occurred in patients receiving vancomycin. It may be transient or permanent. It has been reported mostly in patients who have been given excessive intravenous doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity. When patients with underlying renal

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53 Lamy PP. Comparative pharmacokinetic changes and drug therapy in an older population. *J Am Geriatr Soc.* 1982;30(11 Suppl):S11-9; Hanmerlein A et al. Pharmacokinetic changes in the elderly. Clinical implications. *Clin Pharmacokinet.* 1998;35(1):49-64.

54 Levine DP. Vancomycin: A history. *Clin Infect Dis.* 2006;42:S5-12.

55 Rybak MJ et al. Nephrotoxicity of vancomycin, alone and with an aminoglycoside. *J Antimicrob Chemother.* 1990;25(4):679-87.

56 Thompson CM Jr et al. Absorption of oral vancomycin- possible associated toxicity. *Intern J Pediatr Nephrol.* 1983;4(1):1-4; Bergeron L, Boucher FD. Possible red-man syndrome associated with systemic absorption or oral vancomycin in a child with normal renal function. *Ann Pharmacother.* 1994;28(5):581-4; Hirata S et al. Elevated serum vancomycin concentrations after oral administration in a hemodialysis patient with pseudomembranous colitis. *Jap J Clin Pharmacol Ther.* 2003;34(3):87-90; Brouwer DM et al. Systemic absorption of low-dose oral vancomycin. *J Phar Practice Resear.* 2005;35(3):222-3; Spitzer PG, Eliopoulus GM. Systemic absorption of enteral vancomycin in a patient with pseudomembranous colitis. *Ann Intern Med.* 1984;100:533-4.

dysfunction or those receiving concomitant therapy with an aminoglycoside are being treated, serial monitoring of renal function should be performed."[57]

Additionally, parenteral administration of vancomycin has been associated with a systemic pseudoallergic reaction called Red Man Syndrome.[58] This is most commonly caused by rapid administration of parenteral vancomycin and manifests as itching, rash (usually restricted to the torso and neck), shortness of breath, and tachycardia.[59] This has also been documented in patients after receiving oral vancomycin therapy.[60] In one report in a child, a 1-hour post oral dose serum level was documented to be 28.7 mcg/mL and the child experienced Red Man Syndrome.[61]

ViroPharma Incorporated is requiring assessment of systemic absorption of orally administered Vancocin capsules in all clinical studies it has sponsored or supported to ensure patient safety and further characterize the potential systemic exposure to vancomycin.

Comparison between oral Vancocin capsules and any generic oral vancomycin product with regard to systemic exposure and accumulation is critical to patient safety. The potential for enhanced absorption and subsequent accumulation clearly exists. Importantly, alterations in the formulation of oral vancomycin have been shown to enhance the systemic bioavailability of vancomycin and can potentially result in systemic exposure that is unsafe.[62] Although the unique formulation process and resultant product, Vancocin capsules, have resulted in systemic absorption in patients with CDAD, no cases of nephrotoxicity or ototoxicity have been reported to occur as a result. Dissolution testing is neither designed to nor able to predict the rate and

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57 Vancocin capsules. Product labeling. ViroPharma Incorporated, January 2005.

58 Levine DP. Vancomycin: A history. *Clin Infect Dis.* 2006;42:S5-12. Healy DR et al. Vancomycin-induced histamine release and "Red Man Syndrome": Comparison of 1- and 2-hour infusions. *Antimicrob Agents Chemother.* 1990;34(4):550-4.

59 Garrelts JC, Peterie JD. Vancomycin and the "Red Man's Syndrome". *N Engl J Med.* 1985;312:245; Davis RL et al. The "red man's syndrome" and slow infusion of vancomycin. *Ann Intern Med.* 1986;104(2):285-6.

60 Bergeron L, Boucher FD. Possible red-man syndrome associated with systemic absorption of oral vancomycin in a child with normal renal function. *Ann Pharmacother.* 1994;28(5):581-4; Killian AD et al. Red man's syndrome after oral vancomycin. *Ann Intern Med.* 1991;115(5):410-11.

61 Bergeron L, Boucher FD. Possible red-man syndrome associated with systemic absorption of oral vancomycin in a child with normal renal function. *Ann Pharmacother.* 1994;28(5):581-4.

62 Kajita M et al. Enhanced enteral bioavailability of vancomycin using water-in-oil-in-water multiple emulsion incorporating highly purified unsaturated fatty acid. *Journal of Pharmaceutical Sciences.* 2000;89(10):1243-52; Shively ML, Thompson DC. Oral bioavailability of vancomycin solid-state emulsions. *International Journal of Pharmaceutics.* 1995;117(1):119-22.

extent to which a generic formulation of oral vancomycin will be absorbed. This can only be accomplished through assessment in clinical trials. Given the potential severity of both nephrotoxicity and ototoxicity, it is clearly in the best interest of patient safety to evaluate systemic exposure *in vivo* to ensure no unanticipated exposure and accumulation of vancomycin occurs.

4.2 The OGD Has Not Considered the Pathophysiology of CDAD in Recommending an In Vitro Approach to Evaluate the Bioequivalence of Vancocin Capsules. Any In Vitro Approach to Determine Bioequivalence Must Be Correlated to In Vivo Outcomes and Be Conducted Under "Bio-relevant" Conditions.

As stated in the dissolution testing guidance, "The value of dissolution as a quality control tool for predicting *in vivo* performance of a drug product is significantly enhanced if an *in vitro-in vivo* relationship (correlation or association) (IVIVC) is established...."[63] It is also stated that "For highly water soluble (BCS classes I and III) immediate release products using currently available excipients and manufacturing technology, an IVIVC may not be possible."[64] In contrast, the dissolution method proposed by the OGD is one that has been proposed to simulate product performance in the gastrointestinal tract of *healthy* subjects and assumes *normal* gastric emptying and gastrointestinal motility.

4.2.1 Establishing In Vitro-In Vivo Correlations (IVIVC) is Extremely Difficult and Has Never Been Established for Vancocin Capsules

Dr. Lawrence Yu (Director for Science, OGD) described the difficulties in establishing IVIVC at the May 2005 FDA ACPS meeting as follows: "FDA has lots and lots of dissolution data. We have a lot of products approved that have required dissolution data. Yet, when we look at dissolution data and try to transfer those dissolution data into knowledge, unfortunately we almost get nothing because every single drug, every single product has used similar or different dissolution media. It has been difficult for us to get some kind of *in vivo/in vitro* correlation even though we have lots, and lots, and lots of data because the difference among *in vitro* dissolution tests almost cannot be translated *in vivo*. That is the difficulty. You really need a lot of laughing, sunshine, and good luck to get IVIVC, and even if you get it today it may not exist

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[63] Cntr. for Drug Evaluation & Research, Guidance for Industry, Dissolution testing of immediate release solid oral dosage forms at p. 7. (August 1997).

[64] Id. at p. 7.

tomorrow if you change the formulation a bit. That is why the famous words of [Dr.] Ajaz [Hussain, Deputy Director, Office of Pharmaceutical Science (at the time of the meeting)] is that IVIVC is formulation specific."[65]

For Vancocin capsules, an IVIVC has not been established. It has been suggested that local (i.e., intraluminal) concentrations of vancomycin must be in excess of the minimum inhibitory concentration ("MIC") (1–8 µg/mL) for *C. difficile.*[66] Oral administration of standard doses of Vancocin capsules results in sufficient concentrations to be effective against these bacteria, as evidenced by the fecal recovery of 3,100±400 µg/g wet weight of vancomycin in patients who were successfully treated for pseudomembranous colitis.[67] Of importance, however, there are no validated correlations between the foregoing MIC and fecal recovery concentrations with concentrations achieved at the site of action, effectiveness, and safety of Vancocin capsules. FDA has determined that it is not feasible to use fecal recovery of drugs as an approach to evaluate bioequivalence[68] In the absence of such a relationship or any other validated IVIVC, a trial with clinical endpoints must be the method of determining bioequivalence.

Of note, there have been difficulties associated with applying *in vitro* dissolution testing to drugs used to treat GI-related disorders. A well documented example of this in FDA's background document presented at the FDA ACPS meeting in October 2004 included the following data, which provided an example of comparative dissolution for several mesalamine formulations in different media (Figure 4).[69]

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65 Transcript of FDA Pharmaceutical Science Advisory Committee, at, May 3, 2005, *available at* http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4137T1.pdf, accessed June 14, 2006.

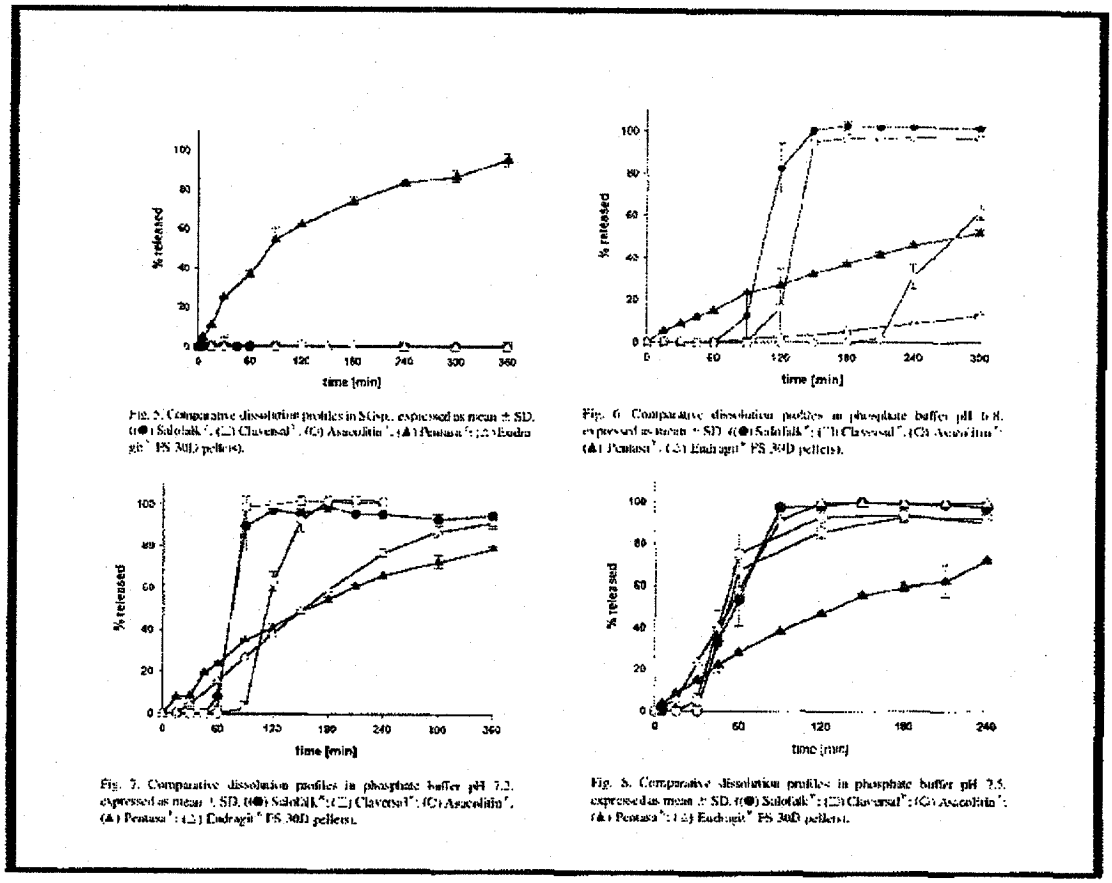
66 Lucas, R.A., et al. 1987. Disposition of vancomycin in healthy volunteers from oral solution and semi-solid matrix capsules. *J Clin Pharm Ther* 12:27-31.

67 Tedesco, F., et al. 1978. Oral vancomycin for antibiotic-associated pseudomembranous colitis. *Lancet* 2:226-8.

68 OGD letter to Mintz Levin (OGD #05-1400), March 7, 2006.

69 M. W. Rudolph, S. Klein, T. E. Beckert, H. Petereit, and J. B. Dressman. A new 5-aminosalicylic acid multi-unit dosage form for the therapy of ulcerative colitis. *Eur J Pharm Biopharm.* 2001 May;51(3):183–190.

Figure 4. Comparative *In Vitro* Dissolution Profiles of Various Mesalamine Formulations.



Importantly, as opposed to demonstrating the ability of this approach to establish the bioequivalence of different mesalamine formulations, the foregoing data suggest these formulations are biolNequivalent even though they appear to have comparative clinical safety and efficacy. Dr. Robert Lionberger (an FDA official) confirmed in a presentation that clinical studies have not demonstrated significant differences between existing mesalamine formulations.[70] Dr. Gordon Amidon (a Professor at the University of Michigan) commented that it was a surprise to development scientists that the mesalamine products dissolved at different rates at pH 6.8, and that he did "not think they would be bioequivalent in the gastrointestinal

[70] Sandborn WJ. Rational Selection or oral 5-aminosalicylate formulations and prodrugs for the treatment of ulcerative colitis. *Am J Gastroenterol.* 2002 Dec;97(12):2939; Hanauer et al. An Oral Preparation of Mesalamine as Long-term Maintenance Therapy for Ulcerative Colitis, A Randomized Placebo Controlled Trial. *Ann Int Med.* 1996;124:204-211.

tract even if they were bioequivalent *in vivo*."[71] Dr. Amidon explained that the products have similar dissolution profiles at pH 7.8 "because they all dissolve rapidly above the pH of the enteric coating[,] ... but at the critical pH where dissolution is occurring, they would be different."[72] In addition, the OGD had originally recommended pharmacokinetic studies for orally administered mesalamine, but after consultation with the new drug review division appears to have abandoned this approach. Subsequently, OGD is still attempting to formulate the best approach to establish bioequivalence for this orally administered, locally-acting product.

Additionally, the experience with propanthaline bromide, a drug that affects GI motility and acid secretion, found that even though *in vitro* testing showed generic versions to be bioequivalent, subsequent *in vivo* testing demonstrated this not to be the case. As outlined in the Center for Drug Evaluation and Research's Office of Compliance Annual Report for 1996,[73] "A well-controlled *in vivo* bioequivalence study submitted to OGD by the holder of the approved NDA for Pro-Banthine revealed that an approved generic version of the drug, which met the *in vitro* determination of bioequivalence, did not meet the agency's *in vivo* bioequivalence criteria.... OGD examined the study and, in 1995, requested an inspection of the NDA holder's manufacturing facilities and the clinical study records of the contract laboratory. The audits conducted by the division verified the results of the study. The generic tablets did not perform within required limits...."

Although the study proved neither bioequivalence nor bioINequivalence, it did raise significant concerns regarding the agency's original decision to classify the tablets as lacking actual or potential bioequivalence problems, and to waive an *in vivo* bioequivalence study to support the approval of generic versions. As a result, pending and new ANDAs for this drug require performance of an *in vivo* bioequivalence study rather than *in vitro* studies alone."

With respect to *in vitro* dissolution testing and binding assays, FDA's background document stated that "for GI acting drugs we should focus more attention on dissolution testing for demonstrating bioequivalence," but noted that "[t]he main concern is, of course, how well *in*

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71 Transcript of FDA Pharmaceutical Science Advisory Committee, at 288 (Oct. 20, 2004) *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf.

72 Id.

73 Food and Drug Administration, Center for Drug Evaluation and Research. Annual report, 1996, pp.114-5.

vitro dissolution reflects *in vivo* dissolution."[74] Although Dr. Amidon suggested that comparative dissolution testing at different pH could demonstrate that test and reference products are targeting the same region of the GI tract, he acknowledged that establishing the connection between *in vitro* dissolution methodology and the *in vivo* dissolution process is "where there is a big gap in our knowledge today, not just for GI drugs, for all drugs."[75] For example, Dr. Amidon commented that it is an "open question" as to whether this type of testing could be done using normal dissolution apparatus, and generally noted that "we are not there yet" on a dissolution testing approach.[76]

The concept of biorelevant media and appropriate testing conditions was raised in the broad context of better simulation and understanding of the *in vivo* conditions of the normal GI tract. To date, little if any information of the appropriate conditions for simulation of the GI system in a patient receiving Vancocin capsules for CDAD has been made available by OGD or in the published literature. Current discussions between OGD and the ACPS continue to focus on the need for better simulation of *in vivo* conditions and questions regarding the sufficiency and appropriateness of the current limited set of *in vitro* testing conditions. Nonetheless, the OGD inexplicably has reached a determination that these same *in vitro* testing conditions are appropriate and sufficient to establish bioequivalence for generic copies of Vancocin capsules while apparently also failing to consider the impact of the pathophysiologic changes associated with the GI tract of patients who would be receiving the drug. The often extreme deviations from normal GI physiological conditions (discussed more fully below) found in these patients represents a discreet set of conditions that need to be identified and considered prior to the development of an appropriate and specific testing apparatus, the physical environment, and the relevant values for media composition, volume, and pH.

Numerous variables and uncertainties exist with OGD's proposed *in vitro* methodology. Importantly, this method has been developed to predict product performance in patients with normal GI physiology. Extrapolation of these conditions by OGD to those present in patients

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[74] Food & Drug Admin., Background Information for Advisory Committee for Pharmaceutical Science: Bioequivalence Testing of Locally Acting Gastrointestinal Drugs (Oct. 20, 2004) *available at* http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4078b1.htm.

[75] Transcript of FDA Pharmaceutical Science Advisory Committee, at 282 (Oct. 20, 2004) *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf.

[76] Id. at 296, 300.

with CDAD or *Staphylococcus aureus* enterocolitis has not been validated and no IVIVC exists. Application of these principles by OGD is scientifically unsupportable and puts patients with these potentially life-threatening diseases at unwarranted risk.

4.2.2 Pathological Changes and Variability in Gastrointestinal Motility Associated with CDAD Negate the Assumptions of Normal and Predictable GI Physiology Upon Which the BCS Rational for a Waiver of In Vivo Bioequivalence is Based

The normal physiologic movement of a drug within the GI tract depends on whether the alimentary canal contains recently digested food or is in the fasted or interdigestive state. Anatomically, an orally administered drug rapidly reaches the stomach. Eventually, the stomach empties its contents into the small intestine. A number of factors affect gastric emptying time, including the volume ingested, the presence of a meal and the specific type of meal, osmotic pressure, the physical state of the gastric contents, concomitant disease states or administered drugs, body position, emotional state, and exercise. In healthy subjects in a fasted state the gastric half emptying time for liquids is approximately 15 to 30-minutes.[77] Once emptied, normal peristaltic movements mix the contents of the duodenum, bringing drug particles into intimate contact with the intestinal mucosal cells.

CDAD and SEC are both infections of the GI tract. They cause a spectrum of disease that includes diarrhea, ranging from mild to profuse with numerous (> 6 stools/ day) liquid stools. In more severe cases, paradoxically, there may be no GI motility (ileus) and an absence of diarrhea. As a result, GI physiology and motility is profoundly abnormal.[78] GI motility can range from hypermotility (associated with profuse diarrhea) to GI luminal stasis or ileus, with pooling of intestinal contents. The consequences are that the location of *in vivo* dissolution of a solid dosing form is highly variable in patients with CDAD or SEC and may take place anywhere along the GI tract under a wide range of luminal conditions that involve exposure to a wide range of pH's, fluid volume and abnormal intestinal contents. Importantly, in those with hypermotility, the drug may have a very brief residence time in the GI tract which may not allow for dissolution to occur in the stomach or even further down in the GI tract. Indeed, partially disintegrated solid

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[77] Feldman M et al. Gastric emptying of solid radiopaque markers: studies in healthy subjects and diabetic patients. *Gastroenterology*. 1984;87(4):895-902.

[78] Thielman NM and Wilson KH. Antibiotic-Associated Colitis. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases.*, Elsevier, Philadelphia, 6th ed. Ch 92 pp. 1111-26.

dosage forms, including Vancocin capsules, have been identified in the stool of patients with CDAD.[79] The presence of more severe disease with ileus does not equate to the controlled conditions and perturbation of the fluid environment in an *in vitro* dissolution test. Under these highly variable pathophysiologic conditions Vancocin capsules cannot be assumed to undergo dissolution in the stomach. Therefore one of the critical elements for having confidence in waiving *in vivo* bioequivalence that a rapidly dissolving formulation behaves as an oral solution in the stomach is certainly not applicable to the patient population suffering from these diseases. Indeed, the location of dissolution of a solid dosing form is likely to be highly variable, therefore no single set of *in vitro* conditions are likely to be predictive of the *in vivo* dissolution environment in a patient with CDAD or SEC. As a result, and as more fully described below, dissolution testing of generic versions of Vancocin capsules cannot be used to confirm the rate and extent to which the generic product becomes available at the site of action.[80]

4.2.3 The In Vitro Media Recommended for Dissolution Testing Does Not Adequately Simulate That of the Gastrointestinal Contents of Patients with CDAD

The use of biorelevant media to conduct dissolution testing is based upon assumptions developed to predict product performance in patients with normal GI tract physiology. The contents of the GI tract in patients with CDAD are highly abnormal and differ significantly from the simple, buffered fluid suggested for use by OGD in its guidance for *in vitro* dissolution testing.[81] The relevance of these solutions for predicting *in vivo* performance of a solid dosing form in a normal GI tract is often questioned; further, to extrapolate findings from studies performed under these *in vitro* conditions to patients with CDAD is not scientifically valid. The GI contents of patients with CDAD include many components not present in those with normal GI tract physiology and consist of exudates, protein, inflammatory mediators, cellular debris, blood, and other biologic components[82] that are very difficult if not impossible to simulate in an in *vitro* medium. The influence of any of these factors on the availability of vancomycin at the site of action will not be

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79 See, e.g., Vancocin pulvules. Annual Report submitted to the FDA. May 1987, pp. 149, 209.

80 USC 355 (j)(8)(B)(i); 21 C.F.R. 320.1(e).

81 Ctr. for Drug Evaluation & Research, Guidance for Industry, Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (Aug. 2000).

82 Thielman NM. Antibiotic-Associated Colitis. In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases.* 5th ed. Ch 84 pp. 1111-26.

predicted by the proposed *in vitro* testing. These serious limitations of *in vitro* dissolution testing clearly indicate that the altered GI physiology of patients with CDAD has not been considered by the OGD and that these conditions are clearly outside of the scope of the *in vitro* model which was developed to be predictive for rapidly dissolving, highly permeable, systemically absorbed drugs in subjects with a normal GI tract.

These concerns are consistent with remarks delivered by Dr. Yu at the May 2006 American Association of Pharmaceutical Scientists (AAPS) Workshop on dissolution testing where he commented that the *in vivo* environment is very complicated and that there were questions regarding variability in pH and the concept of the 900 mL vessel used for *in vitro* dissolution testing.[83] He also expressed the need for use of biorelevent media to provide a more consistent and better correlate to *in vivo* conditions. One would expect that if the OGD is uncertain about the appropriateness of the current *in vitro* dissolution testing paradigm for BCS drugs, they would have a heightened awareness when considering a potential waiver of *in vivo* bioequivalence testing for a unique class of drugs such as locally acting GI antimicrobials including Vancocin capsules.

4.2.4 The Intra-Gastric pH of the Patient Population with CDAD is Higher Than Healthy Subjects and Vancocin Capsules Are Not Rapidly Dissolving Under These Conditions. Vancocin Capsules Cannot Be Considered Eligible for Consideration of a Waiver of In Vivo Bioequivalence.

The pH levels of 1.2, 4.5, and 6.8 selected for dissolution testing were chosen as representative of the gastric and small bowel pH of an individual with normal GI physiology, under the assumption that a drug is highly permeable and therefore absorbed in the upper GI tract. The fasting pH of the stomach in normal individuals is usually acidic but can range from 2 to 6.[84] In the immediate post-prandial period stomach pH is buffered by food and fluid intake, but in the healthy individual, the stomach pH may subsequently be as low as 1.5 to 2.0 due to food mediated secretion of hydrochloric acid by the parietal cells of the stomach. Stomach acid secretion is stimulated by the release of gastrin and histamine. Gastrin release from G cells in the antral mucosa and the duodenum is regulated by stomach distention from food and the

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[83] Yu LX. AAPS Dissolution Workshop. May 2006, slides 11,12,31.

[84] Feldman M et al. Fasting gastric pH and its relationship to true hypochlorhydria in humans. *Dig Dis Sci.* 1991;36(7):866-69.

presence of peptides and amino acids. The duodenal pH is about 6 – 6.5 because of the active secretion of bicarbonate ions that neutralizes the acidic chyme emptied from the normal stomach. This pH is optimum for enzymatic digestion of protein and peptide food. Other substances including the enzymes trypsin, chymotrypsin, carboxypeptidase, amylase, and lipase make up the remainder of the complex fluid medium found in the duodenum. The majority of small molecule drugs are absorbed in the jejunum, the area between the duodenum and the ileum. The proximal ileum has a pH of about 7, while the pH in the distal portion may be as high as 8. The colon is lined with mucin and has a pH that is usually between 5.5 (caecal region) and greater than 7.0 in the distal colon.

The physiology and pH of the gastrointestinal tract of patients most susceptible to CDAD differs significantly from that of healthy individuals upon whom the proposed *in vitro* environment for dissolution testing was based. First, the majority of patients with CDAD are greater than 65 years of age.[85] It is well documented that aging is associated with reduced acidity in the stomach, either as a result of reduced parietal cell volume or due to the increased incidence of atrophic gastritis (which occurs in 25% of those older than 50 years).[86] A high proportion of elderly patients are infected with *H. pylori*, which is also a causative factor in the development of antral gastritis and hypochlorhydria.[87] Many patients who develop CDAD are receiving a proton pump inhibitor (PPI), an identified risk-factor for CDAD,[88] or other acid suppressing therapy such as an H2 blocker or antacid. In addition, most patients are anorexic and/or nauseated due to their illness with minimal food intake to stimulate any gastric acid secretion. Consequently there may be reduced secretion of gastric acid (hypochlorhydria) or potentially no secretion of gastric acid (achlorhydria) in this population, particularly in the fasted state, where pH may be 7.0 or greater due to either underlying pathology or therapeutic intervention, or both causes.

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85 McDonald LC et al. Increasing rates of Clostridium difficile infection among patients discharged from US short-stay hospitals, 1996-2003. *Emerg Infect Dis.* 2006;12(3):409-15.

86 Geokas M, Haverback BJ. The aging gastrointestinal tract. *Am J Surg.* 1969;117(6):881-92.; Hammerlein A et al. Pharmacokinetic changes in the elderly. Clinical implications. *Clin Pharmacokinet.* 1998;35(1):49-64.

87 Majumdar APN and Basson MD. Effect of aging on the gastrointestinal tract. In: Johnson LR, Barrett KE, Ghishan FK, Merchant JL, Said HM, Wood JD, eds. *Physiology of the Gastrointestinal Tract.* 4th ed., London, Elsevier; 2006, pp. 405-33.

88 Dial S et al. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA.* 2005;294:2989-95.

The pH for dissolution testing recommended by OGD is fixed at 1.2, 4.5, and 6.8. The choice of the low pH of 1.2 represents an extreme that may be subphysiologic, but perhaps acceptable for dissolution testing of drugs for which dissolution and subsequent absorption occur in an acidic stomach and upper small bowel of a normal GI tract, respectively. However, the choice is inappropriate for a typical patient who suffers from CDAD, for whom the relevance of dissolution data at the lower pHs of 1.2 and 4.5 is questionable, and even the choice of 6.8 may be sub-optimal.

Testing recommendations give no consideration to the possibility that dissolution occurs at pH values greater than 6.8, which is representative of the luminal pH in the distal small bowel or colon. Dissolution may occur at these distal locations in patients with rapid GI transit, such as those with CDAD and severe diarrhea, or at similarly high pH's in the stomach as described above secondary to hypochlorhydria or PPI use.

In addition, the pH of the GI contents in patients who have developed ileus has not been studied. The pH range recommended for *in vitro* dissolution testing does not include the elevated pH likely to be present in many patients with CDAD. Dissolution testing at a pH above 6.8 must be considered relevant to the clinical situation. This deficiency clearly identifies that OGD has not considered the pathophysiology of the relevant disease state in attempting to extrapolate *in vitro* dissolution to *in vivo* product performance.

4.2.5 FDA Has Determined That In Vivo Data Have Failed To Demonstrate That Oral Vancomycin Solution Is Bioequivalent to Vancocin Capsules

The entire scientific premise to waive the requirement for *in vivo* bioequivalence testing is that if a drug is considered highly soluble and rapidly dissolving it will be in the form of a solution in the stomach before gastric emptying occurs. Because solutions are considered bioequivalent, two similarly rapid dissolving formulations might be considered to be in the solution form in the stomach and bioequivalence can be inferred. As described more fully in Section 4.4.1, Vancocin capsules can not be considered rapidly dissolving, and therefore, it cannot be assumed that the API, vancomycin, is in solution in the stomach.

Although Vancocin capsules have been demonstrated to be very effective in the treatment of CDAD in randomized, controlled clinical trials,[89] Vancocin capsules have not been considered by the FDA to be bioequivalent to the oral solution. Eli Lilly and Company conducted a clinical pharmacology study comparing Vancocin capsules to the oral solution of Vancocin.[90] The results of this study were submitted to the FDA and in July 1985, FDA determined that bioequivalence was not established between the oral solution and Vancocin capsules.[91] Based on these data, FDA required Lilly to remove language from the product labeling, which stated "In comparative bioavailability of the pulvule (capsule) to the oral solution, there were no significant differences in serum or fecal concentrations." As such, the oral solution has not been deemed equivalent to the oral capsule formulation and such a relationship can not be used to infer bioequivalence between oral Vancocin capsules and any generic formulation.

4.2.6 Another Oral Glycopeptide Solution Has Not Been Shown to be Bioequivalent to an Oral Solid Dosage Form in Clinical Studies in CDAD

Clinical data that also question the assumption that bioequivalence is likely to be observed for the oral solution and capsule forms of vancomycin come from the development experience of teicoplanin. Teicoplanin is also a poorly-absorbed glycopeptide antibiotic that is structurally similar to vancomycin and has been shown to have clinical activity in the treatment of CDAD when dosed as a solution at 100 mg BID for 10 days with a reported response rate of > 90%.[92] However, a clinical study of oral teicoplanin in patients with CDAD using a 50 mg capsule formulation of teicoplanin dosed at 100 mg twice daily did not result in such favorable results

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89 Wenisch C et al. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea. *Clin Infect Dis.* 1996;22:813-8; Davidson D. A phase 2 study of the toxin binding polymer tolevamer in patients with *C. difficile* associated diarrhea. European Society of Clinical Microbiology and Infectious Diseases May 2004, Prague, Czech Republic, abstract#902; Pullman J et al. Ramoplanin vs. vancomycin in the treatment of *Clostridium difficile* diarrhea: a phase 2 study. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2004, Washington D.C.

90 Lucas RA et al. Disposition of vancomycin in healthy volunteers from oral solution and semi-solid matrix capsules. *J Clin Pharm Ther* 1987;12:27-31.

91 Data on file. ViroPharma Incorporated.

92 Wenisch C et al. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea. *Clin Infect Dis.* 1996;22:813-8; De Lalla F et al. Prospective study of oral teicoplanin versus oral vancomycin for therapy of pseudomembranous colitis and Clostridium difficile-associated diarrhea. *Antimicrob Agents Chemother* 1992;36:1292-96.

and reported a response rate of 70%. The trial was stopped early due to lower than expected efficacy of the capsule formulation.[93]

Although the number of patients studied was relatively small, the authors speculate that differences in the pharmacokinetics and dosing regimen between the capsule and solution, as well as the contribution of rapid GI transit times and frequent loose stools, may have contributed to the lower response rate and higher relapse rate observed with the capsule compared to the oral solution formulation of teicoplanin.

Vancomycin and teicoplanin are glycopeptide antimicrobial agents. This class of antibiotics is made up of large molecular weight compounds, each a complex mixture of biologically-derived peptides. Based on the clinical experience with both compounds, it cannot be assumed that glycopeptides behave like small molecules and there is no data supporting the comparability of an oral solution to a solid dosage form, especially in those with hypermotility associated with diarrhea and CDAD. The clinical evidence suggests that for this class of antibiotics there needs to be a greater understanding of the key factors that impact *in vivo* performance prior to the development of recommendations for *in vitro* dissolution testing capable of discriminating between formulations at pathophysiologically relevant conditions. Absent this understanding, the application of a waiver of *in vivo* bioequivalence testing for Vancocin capsules is not scientifically justifiable and creates unacceptable and unnecessary risk for patients.

4.3 In Vitro Dissolution Testing and Its Potential as a Surrogate for In Vivo Product Performance

4.3.1 Overview of Dissolution Testing

Dissolution is the process by which a solid drug substance becomes dissolved in a solvent. Solubility is the mass of solute that dissolves in a specific mass or volume of solvent at a given temperature. Solubility is a static property, whereas dissolution is a dynamic property. In biologic systems, drug dissolution in an aqueous medium is an important prior condition for systemic absorption. The rate at which drugs with poor solubility dissolve from an intact or

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[93] Wistrom J et al. Treatment of *Clostridium difficile* associated diarrhea and colitis with an oral preparation of teicoplanin: A dose finding study. *Scan J Infect Dis.* 1994;26:309-16.

disintegrated solid dosage form in the gastrointestinal tract often controls the rate of systemic absorption of the drug.

Dissolution testing has evolved to be an important quality assurance method used to evaluate lot-to-lot variability in the manufacturing process of solid dosage forms. *In vitro* dissolution testing standards are published by the United States Pharmacopoeia (USP) and /or may be dictated by the FDA where there is no published USP method. This testing is required for all US FDA-approved solid dosage form products and other selected dosage forms and is used to (1) assess the lot-to-lot quality of a drug product; (2) guide development of new formulations; and (3) ensure continuing product quality and performance after certain changes, such as changes in the formulation, the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process. *In vitro* dissolution data are generally obtained from batches that have been used in pivotal clinical and/or bioavailability studies and from other human studies conducted during product development.

4.3.2 The Variability Associated with Dissolution Testing Complicates Extrapolation To In Vivo Product Performance

Although *in vitro* dissolution testing has been utilized as a quality control tool to assess lot-to-lot variability, it is important to identify that this methodology has many variables that can affect the data generated. At least six major parameters of USP Apparatus 1 or 2 needs to be calibrated before each use. In the U.S., a calibration tablet is used to aid in quality control of the device as well. Using the basket method, the range for passing for the calibration tablet is currently set at 51 – 81%.[94] At the May 2005 ACPS meeting Dr. Lucinda Buhse (Director of Pharmaceutical Analysis, FDA) stated that "It does have quite a bit of variability associated with it and some stability issues so they would like to see if they can find something else.... We have an internal calibration tablet that we use now that we characterized ourselves in our lab that has lower variability. We stopped using this one (the USP calibration tablet) probably the end of last year."[95] In addition, inter-laboratory variability is also quite large. Dr. Buhse summarized the variability associated with dissolution testing at the May 2005 ACPS as follows: "For dissolution

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[94] Transcript of FDA Pharmaceutical Science Advisory Committee, at p. 56, May 3, 2005, *available at* http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4137T1.pdf, accessed June 14, 2006.

[95] Buhse C. FDA Pharmaceutical Sciences Advisory Committee meeting, May 3, 2005 at p. 77. *available at* http://www.fda.gov/ohrms/dockets/as/05/slides/2005-4137S1_Buhse_files/frame.htm, accessed 5/25/2006.

the variability inherent to the test method can be quite large, especially if you don't understand how all the different parameters can affect your product."[96]

The ACPS Chair, Arthur Kibbe, Ph.D., noted that a dissolution testing approach could present problems if "two products that have slightly different excipient compositions who appear, in a dissolution apparatus, to dissolve equivalently, but that aren't presenting the same amount of drug to the surface of the membrane for one reason or another."[97] Similarly, ACPS member Kenneth Morris, Ph.D. stated that "[t]here is still a lot of work to do in terms of dissolution testing. As [Dr. Amidon] said, redesigning the dissolution test is no [deed] for the faint hearted. I mean that is something that is going to really take some serious scientific and engineering work."[98] Likewise, Ajaz Hussain, Ph.D., Deputy Director, Office of Pharmaceutical Science (at the time of the meeting), suggested in his concluding remarks that the use of dissolution testing presents known challenges.[99]

Importantly, examples of when dissolution testing has not been predictive of *in vivo* performance have been reported both in the literature and by the FDA. These include mesalamine, mebendazole, and propantheline bromide.[100] The variability associated with the *in vitro* dissolution testing methodology further complicates the attempt to associate *in vitro* and *in vivo* performance and produces an unacceptable level of risk and uncertainty if it be used as a substitute for a clinical determination of bioequivalence for any generic copy of Vancocin capsules.

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96 Buhse C. FDA Pharmaceutical Sciences Advisory Committee meeting, May 3, 2005 at p. 77. *available at* http://www.fda.gov/ohrms/dockets/as/05/slides/2005-4137S1_Buhse_files/frame.htm, accessed 5/25/2006.

97 Transcript of FDA Pharmaceutical Sciences Advisory Committee, at 297 (Oct. 20, 2004) available at http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf.

98 Id. at 333.

99 Id. at 348-349.

100 Swanepoel et al. *Eur J Pharm Biopharm.* 2003;55:345-9; Sandborn WJ. Rational Selection or oral 5-aminosalicylate formulations and prodrugs for the treatment of ulcerative colitis. *Am J Gastroenterol.* 2002 Dec;97(12):2939; Hanauer et al. An Oral Preparation of Mesalamine as Long-term Maintenance Therapy for Ulcerative Colitis, A Randomized Placebo Controlled Trial. *Ann Int Med.* 1996;124:204-211; Food and Drug Administration, Center for Drug Evaluation and Research. Annual report, 1996, pp.114-5.

4.4 The Guidance For Waivers of In Vivo Bioequivalence Testing Addresses Immediate Release, Orally Administered Drug Products That Are Systemically Absorbed. Vancocin Capsules are Poorly Absorbed and Locally-Acting in the GI Tract. No Specific BE Guidance For Locally-Acting GI Drugs Is Currently Available From The FDA.

An approach to waiving the requirement for an *in vivo* demonstration of the bioequivalence of immediate release solid oral dosage form products has been the subject of a long, open, data-driven debate, including FDA ACPS meetings in 2004 and 2005. Based on the BCS originally proposed by Amidon et al in 1995,[101] the BCS categorizes drug products based on solubility and permeability as follows:

Class I: High solubility and high permeability

Class II: Low solubility and high permeability

Class III: High solubility and low permeability

Class IV: Low solubility and low permeability

The waiver of *in vivo* bioequivalence testing guidance provides recommendations for sponsors of investigational new drug applications (INDs), new drug applications (NDAs), ANDAs, and supplements to these applications who wish to request a waiver of *in vivo* bioavailability (BA) and/or bioequivalence (BE) studies for immediate release (IR) solid oral dosage forms. This guidance explains when biowaivers can be requested for IR solid oral dosage forms based on the BCS. The approach outlined in this guidance can be used to justify biowaivers for *highly soluble* and *highly permeable* drug substances (i.e., Class 1) in IR solid oral dosage forms that exhibit *rapid in vitro dissolution* using the recommended test methods (21 CFR 320.22(e)).

The three major criteria for consideration of a biowaiver as stated in the guidance are as follows: (1) Solubility: 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; (2) Permeability: In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is

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[101] Amidon G et al. A theoretical basis for a biopharmaceutic drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharmaceutical Research*. 1995;12(3):413-20; Yu LX et al. Biopharmaceutics Classification System: The scientific basis for biowaiver extensions. *Pharmaceutical Research*. 2002;19(7):921-25.

considered to be *highly permeable* 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; and (3) Dissolution: 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 I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 mL or less in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

It is noteworthy that the most appropriate definition for rapid dissolution for low permeability drugs has been in question. Work conducted by OGD investigators identified that the current rapid release criterion (i.e., >85% dissolved in less than 30 minutes in 0.1N HCl, pH 4.5, and pH 6.8 buffers) may ensure the bioequivalence of solid dosage forms containing highly soluble and highly permeable drugs, but not highly soluble and poorly permeable drugs. These investigators recommend for products that have poor permeability (such as Vancocin capsules), the appropriate *in vitro* release requirements should be that 90% dissolution occurs in 30 minutes.[102]

If a drug product possesses all three of these criteria, FDA postulates that systemic bioavailability of a drug will not be limited by dissolution and performance in an *in vitro* dissolution test may be predictive of absorption and pharmacokinetic performance in a healthy subject. For BCS Class I drugs, the rate limiting step for drug absorption is likely to be gastric emptying. In the healthy individual, following an overnight fast, the gastric fluid half-emptying time (the time taken for half the fluid content of the stomach to pass into the duodenum) is estimated to be 15 - 30 minutes.[103] Consequently it is assumed that a solid dosage form that is rapidly dissolving would be expected to be mostly dissolved by the time it leaves the stomach and can be considered likely to have the pharmacokinetic performance of a solution and therefore bioequivalence can be inferred.

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[102] Yu LX et al. Influence of drug release properties of conventional solid dosage forms on the systemic exposure of highly soluble drugs. *AAPS Pharm Sci.* 2001;3(3):E24.

[103] Cntr. for Drug Evaluation & Research, Guidance for Industry, Dissolution testing of immediate release solid oral dosage forms at p. 3. (August 1997); Minami H, McCallum RW. The physiology and pathophysiology of gastric emptying in humans. *Gastroenterology.* 1984;86(6):1592-610.

4.4.1 Vancocin Capsules Are Not Rapidly Dissolving as Asserted by the OGD and the Application of a Waiver of In Vivo Bioequivalence Testing Is Therefore Not Applicable

As noted above, the scientific basis for extending a waiver of *in vivo* bioequivalence studies and acceptance of *in vitro* dissolution testing as a means to determine bioequivalence is that some drugs (BCS Class I) are highly soluble, highly permeable, and rapidly dissolving. It is clear from correspondence to third parties that OGD considers Vancocin capsules to be rapidly dissolving and therefore potentially eligible for consideration of a biowaiver.

ViroPharma Incorporated has conducted studies to evaluate the release characteristics of vancomycin from Vancocin capsules. The appropriate USP methods (those recommended by the OGD to potential ANDA applicants) have been used to evaluate dissolution of Vancocin capsules across a pathophysiologic pH range, including those specified in the OGD letter. Data from the 250 mg dosage strength are presented in Table 1.

Table 1. Dissolution of 250 mg Vancocin Capsules Performed Using the USP Apparatus I @ 100 rpm.

pH	Time (minutes)	Mean % Dissolved (Range)	Relative Standard Deviation (%)
1.2	30	89.6 (81.2 – 94.2)	4.4
4.5	30	66.0 (59.7 – 77.3)	6.5
6.8	30	67.6 (60.7 – 78.4)	4.1
8.0	30	77.9 (67.4 – 86.9)	5.5

Based on these studies, 250 mg Vancocin capsules are not 85% dissolved within 30 minutes across the pH range relevant to patients with CDAD and therefore do not meet the OGD's definition of a rapidly dissolving, immediate release solid dosage form. Preliminary analysis of the lower strength 125 mg capsules across a similar pH range indicate that dissolution occurs more rapidly compared to the 250 mg capsules. The mean percentage dissolution of the 125 mg capsules at 30 minutes is greater than 85%, however due to the variability of the data, the range and relative standard deviation traverse this value, and the data are therefore inconclusive. Work is ongoing to further characterize the dissolution profile of both the 125 mg and 250 mg capsules, including the relationship to time following product manufacture.

Given the results for the 125 mg and 250 mg capsule dissolution, including the variability of the data, one can not consider Vancocin capsules rapidly dissolving. As such they should not be considered for a waiver of *in vivo* bioequivalence studies, as they are neither rapidly dissolving nor highly permeable.

It is important to consider that the BCS model was developed as a way to approach orally administered drugs that are well absorbed systemically. In fact, the original academic paper on which the waiver guidance is based explicitly states that the BCS does not apply to locally-acting drugs such as Vancocin capsules:

> "Drug dissolution is a prerequisite to drug absorption and clinical response for almost all drugs given orally. Exceptions to this general requirement such as "GI" drugs, e.g., resins, antidiarrheals, adsorbants, some laxatives, etc. are not considered in this report."[104]

Accumulated experience with dissolution testing of BCS class I drugs and *in vivo* correlation with pharmacokinetic performance are supportive of this concept in many cases. This model, however, was not intended to be extrapolated to drugs products that are not rapidly dissolving, poorly absorbed and locally acting in the GI tract such as Vancocin capsules. Even for BCS Class I drugs, a waiver of the requirement for *in vivo* bioequivalence testing for certain pending ANDAs, has to the best of our knowledge, seldom if ever, been granted.

4.4.2 Vancomycin Cannot Be Considered Highly Soluble in the GI Luminal Environment of Patients with CDAD. Classification of Vancocin Capsules Solubility Should Not Be Conducted Using 250 mL.

Vancomycin is highly soluble at low pH but solubility is pH dependent. As pH increases there is a reduction in solubility from approximately 10 mg/mL at pH of 6.8 to 2 mg/mL at pH of 8.0 (Figure 5). These pH levels are physiologically relevant for the gastrointestinal tract of patients with CDAD, as described above in Section 4.2.

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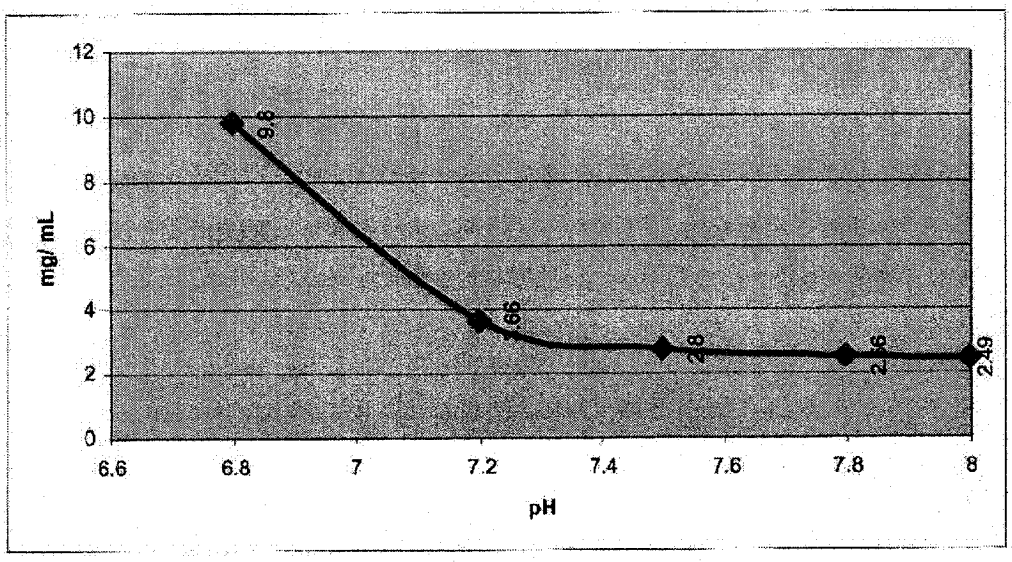
[104] Amidon G et al. A theoretical basis for a biopharmaceutic drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharmaceutical Research*. 1995;12(3):413-20.

Figure 5 **Solubility of Vancomycin Hydrochloride As Determined By The Shake Flask Method at 37°C.**



From the perspective of the BCS criteria 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 volume estimate of 250 mL is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.

This definition of high solubility is not relevant in the context of patients with CDAD. Many patients complain of severe abdominal pain, nausea, vomiting, and a decreased desire for oral intake.[105] Many of these patients are dehydrated, requiring intravenous fluids and will only take enough liquid orally to swallow the capsule. Consequently the volume of gastric fluid present to dissolve Vancocin capsules may be significantly less than 250 mL, even as low as the normal residual fasting volume of 20 to 30 mL. Administration of a 250 mg capsule (or two 250 mg capsules to achieve a commonly prescribed dose of 500 mg) into such a low volume may greatly exceed the solubility of vancomycin, particularly in the presence of elevated intra-gastric pH observed in many patients with CDAD. Solubility may also be an issue throughout the rest of the GI tract where pH ranges up to 8.0 are present, particularly in the terminal ileum and colon.

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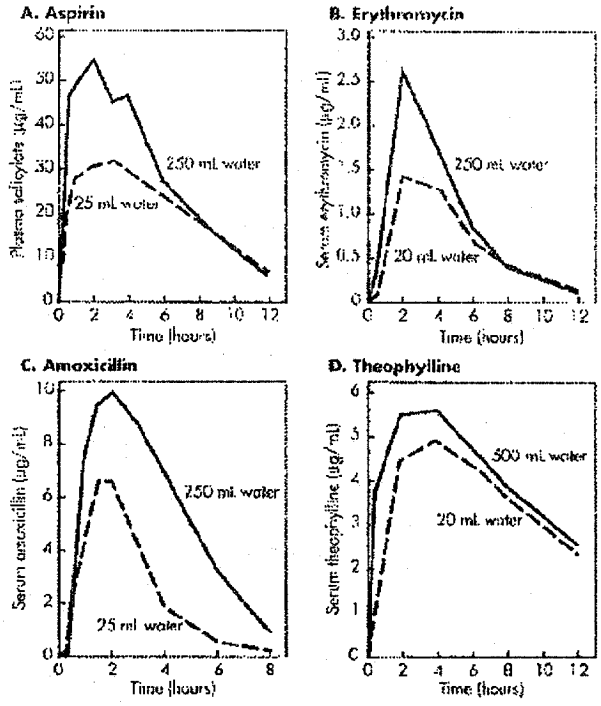
[105] Thielman NM. Antibiotic-Associated Colitis In: Mandell G, Bennett J, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 5th edition. Ch 84 pp. 1111-26.

Vancomycin is a large, complex, biologically-derived antibiotic peptide and its behavior in the GI tract of patients with CDAD is not well characterized. Extrapolation of *in vitro* performance of a solid dosing form to an *in vivo* pathological state is inherently difficult and several noteworthy examples of altered drug availability associated with decreased oral liquid intake resulting in decreased drug product solubility have been reported in the literature, as shown in Figure 6.[106]

Figure 6. **Mean Plasma or Serum Concentrations in Healthy, Fasting Volunteers Receiving Single Oral Doses of Aspirin, Erythromycin Stearate, Amoxicillin, and Theophylline With Large and Small Accompanying Volumes of Water.**



Moreover, and in addition to the dissolution data presented by ViroPharma Incorporated in Section 4.4.1, these findings further question the assertion that Vancocin capsules are highly soluble under pathophysiologic conditions.

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[106] Welling PG. Drug bioavailability and its clinical significance. In: Bridges KW, Chasseaud LF, eds. *Progress in Drug Metabolism.* Vol. 4. London, Wiley; 1980, chap 3.

5.0 BIOEQUIVALENCE REQUIREMENTS FOR LOCALLY-ACTING DRUGS AND PRECEDENT FOR APPROVAL OF LOCALLY-ACTING GI DRUGS ARE NOT CONSISTENT WITH OGD'S PROPOSAL FOR VANCOCIN CAPSULES

5.1 Statute and Regulation Requires A Scientifically Reasonable And Adequate Demonstration of Biocquivalence

The Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Act") amended the Federal Food, Drug and Cosmetic Act ("FFDCA") to permit the approval and marketing of generic drugs by relying in certain circumstances upon the relevant safety and effectiveness data developed by the pioneer drug company.[107] To receive approval of an ANDA, a sponsor must establish that its generic product is pharmaceutically equivalent (e.g., same active ingredient, dosage form, route of administration) and bioequivalent to a RLD.[108] Together, the pharmaceutical equivalence and bioequivalence requirements are meant to ensure that the generic applicant adequately demonstrates that it is appropriate to rely on the data developed by the innovator company for the RLD.[109]

A generic drug is considered to be bioequivalent to a RLD 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."[110] A primary objective of establishing bioequivalence is to assure interchangeability between pioneer and generic formulations. Accordingly, a finding of biocquivalence for a generic drug proclaims that such a drug will produce an effect in patients' equivalent to that produced by the listed drug upon which the ANDA relies. FDA has stated that bioequivalence correlates to both clinical safety and

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[107] Pub. L. No. 98-417 (codified at 21 U.S.C. § 355(j)). The House Report concerning the Hatch-Waxman amendments to the FFDCA emphasizes that generic copies of drugs may only be approved if the generic is the same as the pioneer drug, or so similar that FDA has determined that the differences do not require safety and effectiveness testing. H.R. Rep. No. 98-857, pt. 1, at 14-15 (1984).

[108] 21 U.S.C. § 355(j)(2)(A). See also 21 C.F.R. § 314.94(a)(7). FDA requires that ANDAs contain completed bioequivalence studies, and not just bioequivalence study protocols. Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17951, 17959 (Apr. 28, 1992).

[109] Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research to Douglas L. Sporn, Director, Office of Generic Drugs (May 5, 1997) (Approvability of a Synthetic Generic Version of Premarin).

[110] 21 U.S.C. § 355(j)(8)(B)(i). See also, 21 C.F.R. 320.1(e) (A drug shall be considered to be bioequivalent to a listed drug if the rate and extent to which its active ingredient or active moiety becomes available at the site of drug action is not significantly different than that of the listed drug, when administered at the same molar dose of therapeutic moiety under similar conditions).

clinical efficacy,[111] and views "bioequivalent" drugs as possessing the same efficacy.[112] FDA must use reasonable and scientifically supported criteria to reach a finding of bioequivalence, and must impose a specific bioequivalence requirement on all generic drugs.[113] Importantly, "FDA concedes that the burden of showing bioequivalence may sometimes be comparable to, or perhaps even greater than, the pioneer's burden of showing bioavailability."[114]

The statutory burden for establishing the pharmaceutical equivalence and bioequivalence of a generic product, such that they may be considered interchangeable, lies exclusively with the ANDA sponsor.[115] Neither a pioneer drug company nor the public has any responsibility to demonstrate lack of equivalence, and FDA has no authority to shift the burden of proving equivalence to anyone other than the ANDA sponsor.[116]

5.2 FDA's ACPS Consider Comparative Clinical Trials to be the Only Adequate Approach to Demonstrate Bioequivalence For Locally-Acting Drugs

Compared to the regulatory and FDA guidance recommendations for pharmacokinetic bioequivalence studies, there is relatively little information about the bioequivalence requirements for locally-acting drugs. Accordingly, and in recognition of the challenging bioequivalence issues presented by locally-acting drugs, FDA's ACPS has considered appropriate scientific approaches several times over the last few years.

At the Committee's March 12, 2003 meeting, Dena Hixon, M.D., Associate Director for Medical Affairs in the OGD, made a presentation titled "Clinical Endpoint Bioequivalence Studies for Locally Acting Drugs" that clearly articulated the Agency's position on the bioequivalence requirements for locally-acting drugs. Of interest, Dr. Hixon identified oral vancomycin for pseudomembranous colitis as a locally-acting GI drug, but her slides and comments did not otherwise focus on Vancocin capsules.

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111 Response to Petition of Marian Merrell Dow, Inc., Docket No. 93P-0450 (Sept. 12, 1995).

112 Schering Corp. v. Food and Drug Administration, 51 F.3d 390, 393 (3d Cir. 1995). Additionally, former FDA Commissioner Jane E. Henney, M.D. has stated that if FDA declares a generic drug to be therapeutically equivalent to an innovator drug, the two products must provide the same intended clinical effect. Henney, Review of Generic Bioequivalence Studies, *JAMA*. 1999;282(21):1995.

113 Schering Corporation v. Sullivan, 782 F. Supp. 645, 651 (D.D.C. 1992).

114 Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17975 (Apr. 28, 1992).

115 Id. ("The burden of showing that a new product is bioavailable or bioequivalent rests with the applicant").

116 21 U.S.C. § 355(j)(2)(A)(ii).

Dr. Hixon stated that pharmacokinetic studies are not adequate to establish the bioequivalence of locally-acting drugs, and most locally-acting drugs require clinical endpoint studies to demonstrate bioequivalence.[117] More specifically, Dr. Hixon explained that FDA typically requires the following type of clinical endpoint study to demonstrate the bioequivalence of locally-acting drugs:

- Three-arm comparative trial of the generic product versus reference listed drug ("RLD") versus placebo;
- Treatment of an approved indication for the RLD in a patient population according to the labeled dosing;
- Trial design and endpoints similar to a New Drug Application ("NDA");
- Both the generic product and RLD must be statistically superior to placebo ($p<0.05$) in order to assure that the study is sensitive enough to show a difference between the products;
- Clinical endpoints must meet the established bioequivalence limits (i.e., studies with dichotomous endpoints need to fall within plus or minus 20 percent in terms of the difference between the test product and RLD, and studies with variable endpoints must fall between 80 and 125 percent [90 percent confidence interval]);
- May require several hundred patients;
- Study duration may be several weeks depending on approved RLD labeling; and
- Some products require multiple studies.[118]

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[117] Dena R. Hixon, M.D., Associate Director of Medical Affairs, Office of Generic Drugs, Clinical Endpoint Bioequivalence Studies for Locally Acting Drugs (Mar. 12, 2003) *available at* http://www.fda.gov/ohrms/dockets/ac/03/slides/3926s1.htm; Transcript of FDA Pharmaceutical Science Advisory Committee, at 189-205 (Mar. 12, 2003) *available at* http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3926T1.pdf.

[118] Transcript of FDA Pharmaceutical Science Advisory Committee, at 189-205 (Mar. 12, 2003) *available at* http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3926T1.pdf.

Apart from these general parameters, Dr. Hixon clarified that FDA does not have a specific required study design, and that one of the primary challenges is to make sure that the patient population and endpoints are appropriate.[119] Dr. Hixon acknowledged that these challenges are significant when the Agency is considering the first generic product, as the Agency will endeavor to review the scientific research and labeling for the RLD, and OGD generally will consult with the review division to arrive at a joint decision about the appropriateness of a proposed study design.[120]

Consequently, while the ACPS had a comprehensive discussion about and explored technological options for assessing the bioequivalence of locally-acting GI drugs at its October 2004 meeting, the ACPS did not recommend deviating from Dr. Hixon's 2003 clinical study recommendations. In fact, the ACPS expressed reservations about alternative approaches such as dissolution testing, and fully acknowledged that extensive scientific and engineering work must be completed before a dissolution testing approach can truly be evaluated. FDA's background document for this meeting acknowledged that "[f]or drugs whose site of action is the GI tract, determination of bioequivalence is more complicated as local drug concentrations cannot be measured directly."[121]

5.3 FDA Guidance on Bioequivalence Requirements for Locally-Acting Drugs Fully Supports the Use of Comparative Clinical Trials to Demonstrate the Bioequivalence of Such Generic Products

While there is relatively little specific FDA guidance concerning the bioequivalence requirements for locally-acting GI drugs, the guidance that is available recommends the use of comparative clinical trials. FDA's guidance on bioavailability and bioequivalence studies for orally-administered drug products states that, for orally administered drugs that produce their effects by local action in the gastrointestinal tract:

> documentation of bioequivalence for ANDAs ... can be achieved using BE studies with clinical efficacy and safety endpoints and/or suitably designed and validated *in vitro*

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[119] Transcript of FDA Pharmaceutical Science Advisory Committee, at 189-205 (Mar. 12, 2003) *available at* http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3926T1.pdf.

[120] Id. at 198.

[121] Food & Drug Admin., Background Information for Advisory Committee for Pharmaceutical Science; Bioequivalence Testing of Locally Acting Gastrointestinal Drugs (Oct. 20, 2004) *available at* http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4078b1.htm.

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. To ensure comparable safety, additional studies with and without food may help to understand the degree of systemic exposure that occurs following administration of a drug product intended for local action in the gastrointestinal tract.[122]

This guidance states that "[i]n some instances, it may be useful to admit patients into BE studies for whom a drug is intended,"[123] as opposed to a study in healthy subjects.

In the 1990s, the Agency required significant clinical studies to establish the bioequivalence of generic versions of sucralfate, which is a locally-acting GI drug used to treat ulcers. Sucralfate, which is not absorbed by the GI tract, adheres to damaged ulcer tissue and protects against acid and enzymes so healing can occur. The approval summary for Teva's ANDA for sucralfate (70-848), reveals that FDA required the following clinical study to establish bioequivalence:

- Multicenter, double-blind, placebo-controlled, randomized, parallel design clinical study comparing generic sucralfate, the RLD (Carafate), and placebo in the treatment of duodenal ulcer disease;

- Enrollment of over 230 patients to ensure 75 patients in each treatment group (273 patients were randomized in the study, with 241 evaluated with respect to the primary efficacy endpoint);

- Inclusion criteria included patients with an active duodenal ulcer of at least 0.3 cm in diameter and not exceeding 0.5 cm, as diagnosed by endoscopy;

- Primary efficacy parameter was the percent of patients whose duodenal ulcers have healed at four weeks, with a positive response requiring endoscopic evidence of completed healing;

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[122] Ctr. for Drug Evaluation & Research, Guidance for Industry, BA and BE Studies for Orally Administered Drug Products – General Considerations, at 20 (Mar. 2003).

[123] Id. at 8.

- Secondary efficacy parameters including average weekly frequency and intensity of day and night pain and the amount of antacids taken during the study; and

- Safety evaluation of serum aluminum (measured at baseline, two weeks, and termination).[124]

FDA also required RatioPharm to conduct a clinical study to establish the bioequivalence of its generic sucralfate (ANDA 74-415). While the RatioPharm approval summary does not include details about the clinical study, the Agency's bioequivalence and division review summaries reveal that the company conducted a clinical study comparing its generic product to the RLD (Carafate), and that these products were compared in terms of the treatment of active duodenal ulcers.[125] It is also known that OGD was originally approached with an *in vitro* testing protocol for sucralfate which was dismissed by the agency as inadequate to establish bioequivalence.

6.0 COMPARATIVE CLINICAL TRIALS ARE NECESSARY TO ESTABLISH THE BIOEQUIVALENCE OF GENERIC VERSIONS OF VANCOCIN CAPSULES

The FFDCA requires that a generic drug be bioequivalent to an RLD, and that FDA use reasonable and scientifically-supported criteria to make bioequivalence determinations. Accordingly, in recognition of the fact that pharmacokinetic and pharmacodynamic approaches generally are inadequate to establish the bioequivalence of locally-acting drugs, FDA's regulations state that comparative clinical studies are an accurate approach to establish the bioequivalence of dosage forms intended to deliver the active moiety locally, including oral dosage forms not intended to be absorbed.[126] Relatedly, FDA's regulations require the Agency to consider specific factors that may reveal bioINequivalent generic drugs, including active drugs that are poorly absorbed (less than 50% compared to intravenous dose) or absorbed from a localized site in the gastrointestinal tract.[127]

Available FDA guidance and Agency pronouncements before the ACPS also strongly support the use of comparative clinical studies to establish the bioequivalence to locally-acting drugs.

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[124] ANDA 70-848, Study Summary of Comparative Clinical Trial Conducted by Biocraft (Jan. 24, 1996).
[125] ANDA 74-451, Review of In Vitro (Disintegration) Data (Oct. 20, 1993).
[126] 21 C.F.R. § 320.24(b)(4).
[127] 21 C.F.R. § 320.33(f).

Consistent with more specific Agency guidance, such as that provided for bioequivalence studies of topical and vaginal antifungal drugs, the Agency's position is that pharmacokinetic studies are not adequate to establish the bioequivalence of locally-acting drugs, and most necessitate the conduct of rigorous clinical endpoint studies.[128] While the Committee and FDA have begun to explore other bioequivalence approaches for such products, such as dissolution testing, FDA has also acknowledged that these approaches are imprecise and, thus far, have been unusable. Moreover, FDA and its experts have agreed that significant scientific and engineering work must be completed before these approaches can even be evaluated, and any *in vitro* approach ultimately would need to be correlated to and validated against a clinical standard. In the meantime, FDA has consistently required that the bioequivalence of locally-acting non solution drugs be established on the basis of comparative clinical studies, such as the rigorous clinical studies required for the approval of generic versions of sucralfate, tretinoin, topical antifungals and ammonium lactate. At the October 2004 Committee meeting, Jurgen Venitz, M.D., Ph.D., the only physician on the Committee, offered the following perspective:

> "I was just going to speak and for being a former clinician, in favor of clinical studies. I mean everybody here is mentioning a true statement. They are not very sensitive to formulation effects, but on the other hand, they are the ultimate relevant test. I mean they make what we are doing clinically relevant."[129]

As established in this paper, the safety and effectiveness of Vancocin capsules in treating antibiotic-associated pseudomembranous colitis caused by *C. difficile* and enterocolitis caused by *S. aureus* (including methicillin-resistant strains) depends on adequate vancomycin concentrations at the site of action in the small and/or large intestinal mucosa, where these pathogens reside and cause disease.[130] Moreover, not only are Vancocin capsules poorly absorbed, but systemic concentrations of vancomycin are not correlated to the clinical efficacy of

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[128] Dena R. Hixon, M.D., Associate Director of Medical Affairs, Office of Generic Drugs, Clinical Endpoint Bioequivalence Studies for Locally Acting Drugs (Mar. 12, 2003) *available at* http://www.fda.gov/ohrms/dockets/ac/03/slides/3926s1.htm; Transcript of FDA Pharmaceutical Science Advisory Committee, at 189-205 (Mar. 12, 2003) *available at* http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3926T1.pdf.

[129] Transcript of FDA Pharmaceutical Science Advisory Committee, at 335-337 (Oct. 20, 2004) *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf.

[130] Lucas RA et al. Disposition of vancomycin in healthy volunteers from oral solution and semi-solid matrix capsules. *J Clin Pharm Ther*. 1987;12:27-31. Tedesco F et al. Oral vancomycin for antibiotic-associated pseudomembranous colitis. *Lancet*. 1978;2:226-8.

Vancocin capsules for treating these conditions.[131] More importantly, systemic concentrations of vancomycin may produce adverse reactions, such as seen with intravenous vancomycin, including nephrotoxicity and ototoxicity.[132] Because of the potential for serious adverse events associated with systemic absorption, the impact of formulation differences on the comparative rate and extent of absorption are essential to assure the generic formulation is not absorbed to a greater extent than that of the innovator product.

Vancocin capsules are a bioproblem drug due to their poor absorption from a localized site in the gastrointestinal tract. There is no available validated pharmacodynamic or *in vitro* testing approach that has been correlated with the local action or clinical safety and effectiveness of Vancocin capsules. Moreover, Vancocin capsules are ineligible for a waiver of *in vivo* bioequivalence studies because they do not satisfy either the regulatory or guidance waiver criteria. As described in detail above, orally-administered, locally-acting GI drugs are not one of the dosage forms for which bioequivalence may be considered self evident,[133] and FDA has explicitly stated that the bioequivalence of oral dosage forms not intended to be absorbed are not considered self-evident.[134] Vancocin capsules are also not eligible for a waiver of *in vivo* bioequivalence studies because they are neither systemically absorbed nor rapidly dissolving."[135]

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131 Thompson CM Jr et al. Absorption of oral vancomycin- possible associated toxicity. *Intern J Ped Nephrol.* 1983;4(1):1-4. Matzke GR et al. Systemic absorption or oral vancomycin in patients with renal insufficiency and antibiotic-associated colitis. *Amer J Kid Dis.* 1987;9(5):422-5. Armstrong CJ, Wilson TS. Systemic absorption of vancomycin. *J Clin Path.* 1995;48(7):689. Bergeron L, Boucher FD. Possible red-man syndrome associated with systemic absorption or oral vancomycin in a child with normal renal function. *Ann Pharmacother.* 1994;28(5):581-4. Hirata S et al. Elevated serum vancomycin concentrations after oral administration in a hemodialysis patient with pseudomembranous colitis. *Jap J Clin Pharmacol Ther.* 2003;34(3):87-90. Brouwer DM et al. Systemic absorption of low-dose oral vancomycin. *J Phar Practice Resear.* 2005;35(3):222-3. Barclay P, O'Connell P. Therapeutic serum levels achieved with oral vancomycin. *Austr J Hosp Phar.* 1994;24:125. Spitzer PG, Eliopoulus GM. Systemic absorption of enteral vancomycin in a patient with pseudomembranous colitis. *Ann Intern Med.* 1984;100:533-4. Tedesco F et al. Oral vancomycin for antibiotic-associated pseudo-membranous colitis. *Lancet.* 1978;2:226-228. Schaad UB et al. Clinical pharmacology and efficacy of vancomycin in pediatric patients. *J Ped.* 1980;96(1):119-26. Killian AD et al. Red man's syndrome after oral vancomycin. *Ann Intern Med.* 1991;115(5):410-11.

132 Levine DP. Vancomycin: A history. *Clin Infect Dis.* 2006;42:S5-12.

133 21 C.F.R. § 320.22(b).

134 Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17975 (Apr. 28, 1992).

135 Lucas RA et al. Disposition of vancomycin in healthy volunteers from oral solution and semi-solid matrix capsules. *J Clin Pharm Ther.* 1987;12:27-31. Dr. Amidon commented at the October 19-20, 2004 Pharmaceutical Science Advisory Committee meeting that most locally GI have low permeability.

7.0 THE CLINICAL STUDY DESIGN FOR GENERIC VERSIONS OF VANCOCIN SHOULD BE CONSISTENT WITH REQUIREMENTS OF THE COMPARATIVE CLINICAL STUDY MODEL ADVANCED BY FDA'S DR. DENA HIXON

The parameters of a clinical study to establish the bioequivalence of generic versions of Vancocin capsules generally should mirror the study requirements articulated in 2003 at the ACPS by Dr. Hixon for locally-acting GI drugs.[136] Given the life-threatening nature of the conditions Vancocin is used to treat, and in particular antibiotic-associated pseudomembranous colitis caused by *C. difficile*, careful attention must be given to the design of the comparative clinical trial used to establish the bioequivalence of generic products. The clinical study design must assure that any differences between Vancocin and generic formulations do not result in decreased safety and effectiveness for patients with one of the most severe forms of CDAD. The conduct of such a trial has been demonstrated to be feasible as evidenced by the ongoing clinical trial programs of tolevamer, ramoplanin, rifaximin, and PAR-101, compounds currently under evaluation in randomized, controlled clinical trials for the treatment of CDAD.

To assure that generic products have an equivalent safety profile, the clinical study must include an evaluation and quantification of the systemic absorption of vancomycin using standard *in vivo* pharmacokinetic test methodology, to ensure that generic versions have a rate and extent of absorption of vancomycin that is no greater than that of Vancocin capsules. As noted, systemic concentrations of vancomycin present potential safety concerns including nephrotoxicity and ototoxicity, and the patient population is already complicated with severe CDAD and likely other serious conditions. Of note, this proposal is consistent with the safety evaluation of serum aluminum as measured in Teva's generic sucralfate clinical study.[137]

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[136] Dena R. Hixon, M.D., Associate Director of Medical Affairs, Office of Generic Drugs, Clinical Endpoint Bioequivalence Studies for Locally Acting Drugs (Mar. 12, 2003) *available at* http://www.fda.gov/ohrms/dockets/ac/03/slides/3926s1.htm; Transcript of FDA Pharmaceutical Science Advisory Committee, at 189-205 (Mar. 12, 2003) *available at* http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3926T1.pdf.

[137] ANDA 70-848, Study Summary of Comparative Clinical Trial Conducted by Biocraft (Jan. 24, 1996).

7.1 Proposed Elements of a Clinical Study to Evaluate Generic Versions of Vancocin Capsules

- The objective of the study is to compare the safety and efficacy of a generic capsule of vancomycin hydrochloride with that of Vancocin capsules in the treatment of *Clostridium difficile* associated disease (CDAD).
- The study design should be a prospective, randomized, double-blind, multi-center, comparative trial.
- The patient population should be hospitalized adults patients with documented CDAD who have not been treated for CDAD within the past 90-days.
- The sample size estimate must consider a non-inferiority design, an anticipated response rate for the RLD, adequate power, and an appropriate delta.
- Methods should include 1) stratification of patients based on whether they continue concomitant antibiotic therapy; 2) Diagnosis of CDAD defined as patients with diarrhea (≥ 3 loose stools per day) AND a positive EIS toxin assay or a positive culture for *C. difficile*;
- Endpoints and analysis should include:

  1) Use of an intent-to-treat analysis;

  2) The primary endpoint of clinical success defined as:

  a) Patient is alive;

  b) No complications develop (surgery, ICU admission);

  c) Diarrhea resolves;

  d) No relapse within 2-weeks of completion of therapy.

3) Secondary endpoints should include:

a) Serial measurement of serum vancomycin concentration assessed at baseline, during therapy, and at the end of therapy;

b) Time to resolution of symptoms as reported by the patient (as outlined in: "Draft Guidance for Industry: Patient-reported outcome measures: Use in medical product development to support labeling claims, February 2006);

c) Relapse rate within 30-days of completion of therapy;

d) Comparison of efficacy based on organism typing (toxinotype III versus others).

8.0 CONCLUSION

This document raises serious concerns regarding the scientific validity, the clinical and patho-physiologic rationale and the potential health risks associated with an apparent decision by OGD to modify the position held prior to March of 2006 that required a clinical demonstration of bioequivalence to approve a generic version of the oral formulation of the antibiotic vancomycin (Vancocin capsules).

OGD has stated that generic copies of Vancocin capsules may be approved based solely on a set of *in vitro* dissolution data and without any clinical or pharmacokinetic data from humans. The proposed set of *in vitro* tests are those for consideration of waiving *in vivo* testing for a wholly separate class of small molecule drugs (BCS Class I), that are both highly soluble and highly permeable in addition to being rapidly dissolving. To our knowledge, *in vitro* dissolution testing has not been used after 1984 as the sole method for approval of generic versions of these relatively simple and predictably behaving drugs, even when considering drugs used to treat non-life-threatening or even self-limiting conditions.

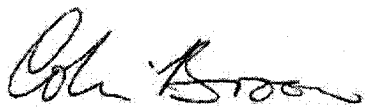
Based on the information provided in this document, Vancocin capsules cannot be considered rapidly dissolving, and the pharmaceutically active ingredient vancomycin is a large, complex, biologically-derived antibiotic peptide, that is poorly absorbed. The scientific basis for

extrapolating *in vitro* test results to predict how generic forms of Vancocin capsules would perform therapeutically has not been validated and it is unknown whether clinically relevant differences in performance can be discerned through *in vitro* testing. Further, the impact of the proprietary Vancocin capsule formulation on delivery of vancomycin to the site of infection is not fully characterized. Accumulated experience and clinical data confirms its effectiveness even in the face of the current worsening epidemic of CDAD.

ViroPharma Incorporated requests that the OGD reverse its proposal to waive *in vivo* studies to determine bioequivalence for Vancocin capsules and reinstate the requirement for clinical studies that evaluate both safety and efficacy. Since Vancocin capsules are used to treat life-threatening diseases, the risk associated with approving any generic product without robust bioequivalence data places patients at unnecessary risk of treatment failure and potential systemic toxicities.

The undersigned submits this supplement to the petition requesting that the Commissioner of Food and Drugs stay the effective date of the foregoing matter.

Respectfully submitted,



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