March 18, 2009

Submitted Electronically

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Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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RE: Docket Nos. FDA-2008-D-0626 & FDA-2006-P-0007

Dear Sir or Madam,

Thank you for the opportunity to comment on the Draft Guidance for Industry on Bioequivalence Recommendation for Vancomycin HCL (FDA-2008-D-0626). We regard the safety of the patient as the highest priority.

Detailed comments are provided in the attached document. As the Draft Guidance for Industry on Bioequivalence Recommendation for Vancomycin HCL follows several years of filings to ViroPharma's related petition (Docket No. FDA-2006-P-0007[1]), ViroPharma is filing the attached document to both dockets. Additionally, ViroPharma will shortly file to Docket No. FDA-2008-D-0626 all previous filings posted to Docket No. FDA-2006-P-0007.

Regards,

Thomas F. Doyle
Vice President, Strategic Initiatives
ViroPharma Incorporated

Enclosure

[1] This petition was originally assigned Docket No. 2006P-0124 but the number was changed to FDA-2006-P-0007 following FDA's transition to a new docketing system (Regulations.gov) in January 2008.

Vancocin and the "Rising Tide of Skepticism About Generic Drugs"

Secret Science & the Mistakes it Enabled Should Disqualify FDA's Office of Generic Drugs from Further Leadership of Vancocin Bioequivalence Method Development

ViroPharma Incorporated Comments on

OGD's Flawed Draft Bioequivalence Guidance on Vancomycin Hydrochloride

Docket No. FDA-2008-D-0626
March 18, 2009

Administrative agencies that hide from the public they serve no longer serve that public, but themselves. "Trust me", from unelected officials working in secret, is rarely allowed in our democracy, and never a permissible response from FDA's Office of Generic Drugs.

-- ViroPharma, May 31, 2006

There is a rising tide of skepticism about generic drugs.

-- Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA
October 29, 2008

Executive Summary

Until early 2006, drug companies seeking FDA approval to sell generic copies of Vancocin® (vancomycin hydrochloride) capsules needed to prove their drugs would be safe and effective by conducting clinical trials in patients. This approach was consistent with settled FDA policy that for locally acting drugs, like Vancocin, clinical studies are typically the only method by which generic products can be shown to be "bioequivalent".

On March 16, 2006, a Canadian stock analyst broke the news that FDA's Office of Generic Drugs (OGD) was recommending a novel, in vitro bioequivalence (BE) method for generic copies of Vancocin that required no testing in humans. Vancocin is approved for the treatment of two serious infections of the gastrointestinal (GI) tract, *Staphylococcus aureus*-induced enterocolitis (SAE), and *Clostridium difficile* Infection (CDI), a serious colonic disease which in its current epidemic form can kill patients within days.

It is disquieting that it took a Canadian stock analyst to protect patients suffering from CDI and SAE. By making OGD's secret new method public, the analyst ignited a firestorm of criticism from all quarters: infectious disease specialists, scientists, consumers, Vancocin's manufacturer ViroPharma, and patients themselves. Of concern to all was that OGD had, in secret, made a significant change that seemed to be an untested hypothesis rather than validated science. This gave OGD pause, preventing critically ill patients from receiving generic copies of Vancocin based on OGD's new method.

Thankfully for patients, OGD did not approve generics based on its new method, as OGD has now conceded the critics' concerns were justified. According to OGD's reasoning in the 12/08 Draft Guidance on Vancomycin Hydrochloride, the 2006 method failed to "ensure that differences [between Vancocin and generic versions] will not affect the safety and effectiveness of generic vancomycin HCl oral capsules." As a result, in December 2008 OGD abandoned the method.

OGD, of course, represents its new method differently. OGD claims that its December 2008 Draft Guidance on Vancomycin Hydrochloride merely "further clarifies" OGD's 2006 BE method for generic copies of Vancocin. As with much that OGD has said about Vancocin capsules over the past three years, this claim is, in a manner of speaking, difficult to swallow.

OGD's 2008 Draft Guidance is a Fundamental Change, Not a Mere "Clarification"

The 12/08 Draft Guidance represents a fundamental change in both OGD's scientific understanding of Vancocin and its recommended BE method for generic copies of the drug, as well as the abandonment of OGD's original scientific basis for in vitro dissolution BE testing for generics versions of Vancocin.

Rapid dissolution was critical to OGD's 2006 dissolution method. In 2006 OGD declared Vancocin was "rapidly dissolving." In December 2008, FDA confirmed that OGD's statement was false. The 12/08 Draft Guidance thus announces a fundamental change in OGD's understanding of a basic physical chemical property of this drug.

When it became clear Vancocin is not rapidly dissolving, OGD lost the ability to cite (albeit tenuously, as Vancocin is not a systemic drug) the behavior of rapidly dissolving systemic drugs as evidence that its 2006 method was valid. This left OGD with no choice but to abandon the 2006 method. OGD now seeks an alternate justification for the assumption, key to its original model, that the drug would be "solution-like" when it reached the site of action (defined by OGD as the colon).

To accomplish this, OGD selectively picks values for relevant GI parameters from the healthy GI literature, ignores the uncertainty and range of variability associated with these values, and asserts (without data) that even though there is no well-characterized understanding of the diseased GI tract of Vancocin patients, there is no reason to assume the drug will not be dissolved before reaching the colon. As such, OGD's basis for in vitro dissolution BE for Vancocin has shifted from relying on a database of rapidly dissolving systemic drugs (always a suspect position) to a hypothesis which relies on assumptions unsupported by any data describing the environment where Vancocin actually will be used: the diseased GI tract.

The 12/08 Draft Guidance is not a clarification. Nor is it an evidence-based BE method. Rather, the 12/08 Draft Guidance is a poorly done risk-assessment based on assumptions drawn from a selective and incomplete review of healthy GI literature whose applicability to Vancocin OGD has not established. OGD is asking patients to rely on this "close enough" approach to bioequivalence for a drug where the consequences of getting it wrong can be major surgery (colectomy) or death. After OGD's March 2006 BE recommendation turned out not to be supported by the science, OGD is proposing another apparently untested hypothesis to approve generic drugs for this critically ill patient population.

OGD's 2008 Draft Guidance is Flawed and an Insufficient Basis for Approval of Generic Copies of Vancocin

In addition to the fact that OGD's "rapid dissolution" premise for dissolution-based BE is no longer valid and OGD's new approach is based on the healthy GI tract, not the diseased GI tract of Vancocin patients, the 12/08 Draft Guidance suffers from many additional flaws, including:

- **FDA Advisory Committees do not support OGD's 12/08 Draft Guidance method**

As noted above, OGD needs to justify its assumption that Vancocin is "solution-like" in order to continue its commitment to dissolution-based BE for Vancocin in the absence

of additional data. However, FDA has disavowed the fundamental premise underlying OGD's 2006 dissolution method: Vancocin is not rapidly dissolving. Faced with data that flatly contradicts its original premise, OGD responds with inapposite healthy GI data (see above) and contorts a 2004 FDA Advisory Committee discussion into a "conclusion" that OGD's dissolution method is appropriate even if Vancocin is not rapidly dissolving. The meeting transcript in fact reveals the Committee's discussions were exploratory and open-ended. The Committee did not address drugs that are not rapidly dissolving, and the Committee neither took votes nor adopted "conclusions."

- **Initial findings in patients substantiate the inapplicability of OGD's healthy GI data**

Initial data from work sponsored by ViroPharma at Temple University substantiate that CDI patients do not exhibit the healthy GI physiology asserted by OGD. This is the first study to begin to scientifically characterize the in vivo environment of CDI patients. Although the study is not complete, initial numbers seen in CDI patients fall outside of the ranges which OGD claims, based on healthy GI literature, describe the in vivo environment of patients who will receive generic copies of Vancocin. Thus the only available data underscore that OGD's new method is a hypothesis that has yet to be measured against the physiologic reality of Vancocin patients. Therefore OGD's proposed comparable dissolution method is not suitable for approving generic drugs destined for these critically ill people.

- **OGD ignores a labeled safety issue**

OGD ignores a safety issue identified at the July 2008 meeting of FDA's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS), the potential for systemic absorption of clinically significant levels of drug and the need for pharmacokinetic (PK) testing to address that safety concern. Instead, OGD once again turns away from CDI and SAE patients and toward healthy volunteer data to conclude that PK testing is unnecessary as the drug is not absorbed in the GI tract of healthy subjects. To do so OGD must also ignore the fact that this safety issue is prominently described in Vancocin's labeling. Furthermore, OGD did not intervene when a generic applicant misinformed the July 2008 ACPS panel that systemic absorption is not a concern with Vancocin. Because the 12/08 Draft Guidance does not acknowledge or address this risk, it cannot be finalized without an opportunity for the ACPS and the general public to discuss and consider this important safety issue.

- **The 12/08 Draft Guidance does not account for an additional labeled indication**

OGD argues that its proposed method is conducted under conditions that assure generic products will be in solution before they reach the colon. By exclusively focusing on the lower GI tract ("[v]ancomycin acts locally in the lower gastrointestinal tract"), the 12/08 Draft Guidance fails to account for *Staphylococcus aureus*, which can affect the upper GI tract. Any method that is to rely on "solution-like" behavior at the site of action

would need to substantiate that the drug was in solution in the upper GI tract as this is a site of *S. aureus* infection.

- **OGD's Q1Q2 sameness standard is flawed and incomplete**

OGD acknowledges that inactive ingredients may affect product performance, and that the state of knowledge in this area is underdeveloped. The 12/08 Draft Guidance therefore permits in vitro dissolution BE testing only for generic products that are Q1 (same inactive ingredients) and Q2 (in the same quantities) to Vancocin. Nonetheless, OGD also proposes that generics can circumvent this Q1Q2 sameness requirement by providing "evidence" that the variation in the generic formulation will not affect the product's safety or efficacy. This approach is flawed for a number of reasons, including:

- FDA's regulations only authorize reliance on the Q1Q2 standard for certain drugs, e.g. solutions, but not for drugs like Vancocin.

- Even if FDA's Q1Q2 regulations did apply to Vancocin, those regulations also would require generics to show they have no "other change in formulation" that could affect BE, but the 12/08 Draft Guidance makes no mention of this requirement.

- If OGD is permitted to use a Q1Q2 standard, then it must require exact Q1Q2 sameness. OGD has not advanced any data regarding whether any, and if so how much, Q1 or Q2 variability could be allowed without affecting the equivalence of generic formulations. Nor has OGD proposed standards detailing how "evidence" purporting to show generics are within acceptable tolerance limits will be evaluated, or by whom. Unless and until such tolerances and standards can be properly developed, exact Q1Q2 sameness is the only option.

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- The "same" inactive ingredients from different sources may not be the same. For example, ViroPharma tested 6 manufacturers' versions of a key Vancocin inactive ingredient, and the data show they were not all the same. In the absence of fully considered tolerance limits and standards, as noted above, the 12/08 Draft Guidance cannot be finalized unless FDA develops appropriate means to ensure ostensibly identical inactive ingredients are in fact the same.

- **The 12/08 Draft Guidance Does Not Consider Patient Risk of BioINequivalence**

The World Health Organization and FDA both endorse consideration of patient risk of bioinequivalence as part of the development of new bioequivalence methods, but OGD fails to do this in the 12/08 Draft Guidance. In light of the acute, life-threatening disease Vancocin treats as well as OGD's past mistakes in Vancocin BE method development, the 12/08 Draft Guidance cannot be finalized without public

consideration of the risk to patients who will receive inequivalent generics if, once again, OGD has proposed a mistaken BE method for generic copies of Vancocin.

Generic Copies of Vancocin are Not Currently Approvable

While these and the other flaws described in this document prevent use of the new in vitro BE method proposed in the 12/08 Draft Guidance, this document also explains how even if the new method were perfectly valid, generic copies of Vancocin are not presently approvable:

- **Trade secret inactive ingredient prevents generics from being Q1Q2 to Vancocin**

The in vitro BE method proposed in the 12/08 Draft Guidance requires generics to have the same inactive ingredients in the same quantity as Vancocin. It also cautions against variations in Q1Q2 that may affect the safety or efficacy of the generic product. To comply, generic applicants therefore need to know Vancocin's inactive ingredients, and their quantities. One Vancocin inactive ingredient linked to the drug's potency, however, is a trade secret. Thus, even if the 12/08 Draft Guidance were valid (which it is not), generics cannot presently avail themselves of it. Having just learned in December 2008 that Q1Q2 is the only path to using in vitro dissolution to demonstrate BE to Vancocin, generics would have had little reason previously to investigate the detail particulars of Vancocin's inactive ingredient profile. Further, even if generics now could somehow divine Vancocin's trade secret inactive ingredient without violating trade secret law, it is unlikely they are already Q1Q2 with respect to it, so they would need to reformulate in order to become approvable under the 12/08 Draft Guidance's in vitro method.

- **Existing generic applications that relied on OGD's abandoned 2006 BE method are now unapprovable by law**

OGD's 2006 BE method required generic copies of Vancocin to be rapidly dissolving. Thus, any generic applicant who relied on OGD's 2006 method would have submitted an application purporting to show its drug was rapidly dissolving. OGD, however, has now abandoned the 2006 method because FDA generated data showing vancomycin capsules are not rapidly dissolving. Given these data, each generic applicant's claim to show rapid dissolution is a false statement of material fact, which under the Federal Food, Drug, and Cosmetic Act requires disapproval of the application. Consequently, while applications for generic copies of Vancocin based on OGD's 12/08 Draft Guidance (assuming its myriad flaws are overcome) may someday receive approval, existing applications, to the extent they claimed to meet OGD's previous rapid dissolution test, are unapprovable.

ViroPharma also notes that it would be highly unlikely that an applicant for a generic product that was formulated to meet OGD's 2006 rapid dissolution standard could now

suddenly claim that same product – with no formulation changes – is not rapidly dissolving. It is difficult to postulate how without a reformulation a product's dissolution characteristics could change in such a significant fashion.

- **Existing applicants' data showing rapid dissolution are suspect and must be audited**

How generic applicants could have shown their vancomycin capsules were rapidly dissolving when FDA's own data demonstrate the contrary is worthy of further investigation by FDA. It seems that generic applicants either uniformly generated bad data, or their applications were made in bad faith. Generic products should not be approved under either scenario. Moreover, given the history of OGD's attempts to impose a dissolution-based method for determining the bioequivalence of generic copies of Vancocin, FDA should require that generic applicants submit ***all*** of their dissolution data for review by the Agency.

OGD Has Demonstrated Bad Faith in the Vancocin Bioequivalence Method Development Effort

It is incumbent upon FDA to ensure that OGD's actions seeking to establish a new BE method for Vancocin are corrected and do not reflect a systemic problem within the Office. Until there is clarity around the Vancocin issue, serious questions remain regarding OGD's ability to appropriately regulate. OGD's conduct speaks for itself:

- OGD began in bad faith by making no public announcement about its March 2006 change from clinical testing to a dissolution based BE method for generic copies of Vancocin.
- In May 2006 OGD's Director of Science publicly stated that OGD had "science" and "evidence" supporting its March 2006 method. By that time (the Canadian stock analyst incident was nearly 2 months old) he knew or should have known that there was no good faith basis to make this claim.
- OGD also apparently reassigned its reviewer who initially endorsed the March 2006 method, which presumably reflects OGD's understanding the method was flawed. Nonetheless, OGD made no public effort to disavow the method.
- FDA ultimately generated data showing OGD's "rapid dissolution" conclusion, key to OGD's "solution-like" premise and the extrapolation of the BCS-based waiver for its dissolution BE approach, was false, and still OGD did not disavow the method. These data were withheld from the public for at least 10 months, and likely longer.
- In January 2008, one month before FDA's dissolution study report was officially signed, FDA met with ViroPharma, professing the principle of transparency. The dissolution data and results, pivotal to a meaningful discussion of the scientific rationale being advanced by OGD at the time, were withheld from ViroPharma.
- At the July 2008 ACPS meeting, FDA professed "commitment to transparency and public process." Nonetheless, OGD's Director of Science again failed to

disclose OGD's findings that Vancocin is not rapidly dissolving and that OGD's thinking had changed, even when a generic applicant presented graphs to the Committee implying that Vancocin is rapidly dissolving.

- The transcript from the July 2008 ACPS meeting strongly suggests that at least one generic company knew about OGD's 12/08 comparative dissolution method and Q1Q2 sameness requirement months before OGD made that method public in December 2008.
- Yet another stock market analyst spoke with a member of the ACPS about Vancocin BE methods in the week preceding the July 2008 ACPS meeting, leading to yet another research report and a downgrade of ViroPharma's stock similar to the 2006 Canadian stock analyst incident.
- To this day, OGD still refuses to disclose the data on which its 2006 method was based.

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OGD's data-free, behind-closed doors approach to Vancocin contributes to the Rising Tide of Skepticism About Generic Drugs identified by FDA officials, including the Director of OGD. Perhaps the Infectious Diseases Society of America said it best when it wrote FDA that "our faith waivers when the Agency makes its decisions behind closed doors rather than through an open data-driven process." The recent revelations about OGD's performance presumably will only redouble the concern of IDSA and others that OGD's secret actions on Vancocin "could lay the groundwork for future such decision-making on other locally acting anti-infective agents".

Unfortunately, FDA management is in the unenviable position of not being able to rely on the information and conclusions presented to it by OGD. OGD's conduct and lack of rigor in this instance warrant its divestiture of a leading role in the development of bioequivalence methods for this important antibiotic. If FDA hopes to counter the "Rising Tide of Skepticism About Generic Drugs" identified by FDA, closer management and oversight of OGD will be needed. ViroPharma respectfully requests that FDA shoulder this responsibility, step in, and bring science back to the regulation of generic drugs.

FDA can begin to help the public regain trust in OGD's science by making OGD fully document, explain, and publicly discuss its thinking around BE methods for generic copies of Vancocin. A critical antibiotic used for infections that can kill within days, Vancocin should not be the test case for novel BE methods developed in secret by an FDA Office with a track record with respect to this effort of getting it wrong and covering up.

FDA should also rescind the 12/08 Draft Guidance and consult with outside experts regarding proposed new BE method(s) for Vancocin, including FDA Anti-Infective Drugs Advisory Committee and Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, as well as relevant experts from the Centers for Diseases Control and Prevention. This should include a public process, with all data on the table, and must

ensure that any such method is validated to correlate with clinical outcomes in the very sick patients who rely on this drug.

Furthermore, FDA should refuse to approve generic vancomycin capsule applications that unwisely claimed to meet OGD's 2006 "rapid dissolution" test, audit their data and investigate their sponsors.

Finally, although FDA has yet to take up the offer, ViroPharma reiterates its willingness to assist FDA in any way it can in the development of a rigorous bioequivalence method that will ensure the approval of safe and effective generic versions of Vancocin, including a pledge of unrestricted financial support for that effort.

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Introduction

Some three years ago FDA's Office of Generic Drugs ("OGD") changed bioequivalence ("BE") methods for generic versions of ViroPharma's product Vancocin® (vancomycin hydrochloride) capsules ("Vancocin"). Without public process, OGD abandoned the established method of demonstrating BE through clinical studies with an efficacy endpoint, and replaced it with an in vitro method based on rapid dissolution.

Upon learning of this change, ViroPharma petitioned FDA to drop the rapid dissolution method and contended that only through a valid public process could OGD abandon clinical endpoint BE.[1] In December 2008 OGD issued the Draft Guidance for Industry on Bioequivalence Recommendation for Vancomycin HCl ("12/08 Draft Guidance") which is the subject of these comments by ViroPharma. In the 12/08 Draft Guidance OGD has now dropped the rapid dissolution method, and agreed, at least in some cases, on the need for clinical endpoint BE studies for generic versions of Vancocin.

ViroPharma is heartened that our petition has prevented approval of ostensibly bioequivalent generic copies of Vancocin utilizing a method now abandoned. However, we remain concerned as the 12/08 Draft Guidance proposes a new in vitro dissolution methodology ("12/08 comparative dissolution method") for products that are deemed qualitatively and quantitatively the same as Vancocin ("Q1Q2 sameness") as an exception to the requirement for clinical endpoint BE studies. As described further below, neither the 12/08 comparative dissolution method nor the framework for evaluating Q1Q2 sameness are sufficiently developed for OGD to propose or finalize as an appropriate BE method for Vancocin.

The 12/08 Draft Guidance also has implications beyond the new Vancocin BE method it proposes. As described further below, the 12/08 Draft Guidance discloses data that confirm existing generic applications for Vancocin are not approvable. The 12/08 Draft Guidance also confirms that OGD's actions on Vancocin BE continue to undermine confidence in generic copies of Vancocin, exemplifying what FDA officials have identified as a "Rising Tide of Skepticism about Generic Drugs."[2]

Finally, although FDA has yet to accept the offer, ViroPharma reiterates its willingness to work with FDA to address these issues in a transparent, data-driven manner. To ensure patients only receive truly bioequivalent generic versions of Vancocin, ViroPharma also takes this opportunity to offer unrestricted funding to develop a scientifically rigorous

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[1] As the 12/08 Draft Guidance follows several years of filings to the docket for ViroPharma's related Petition for Stay of Approval ("PSA"), ViroPharma henceforth is filing this document to both dockets and is filing to Docket No. FDA-2008-D-0626, all previous filings posted to Docket No. FDA-2006-P-0007. The PSA was originally assigned Docket No. 2006P-0124 but the number was changed to FDA-2006-P-0007 following FDA's transition to a new docketing system (Regulations.gov) in January 2008.

[2] Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA; Helen Winkle, Director Office of Pharmaceutical Science, CDER, FDA; Gary Buehler, Director, Office of Generic Drugs, CDER, FDA, Generic Pharmaceutical Industry Fall Technical Conference, October 29-30, 2008.

bioequivalence method to ensure the approval of safe and effective generic copies of Vancocin.

I. Background[3]

As acknowledged in the 12/08 Draft Guidance, OGD's established policy for generic applicants to demonstrate BE to Vancocin was a BE study with clinical endpoints.[4] This flowed from Vancocin's status as a locally acting drug, as BE for most locally acting drugs can only be established through clinical endpoint studies.[5]

In early 2006 certain private individuals began to receive controlled correspondence from OGD (letters known to ViroPharma are dated early March 2006) indicating that clinical endpoint BE would no longer be necessary for Vancocin generics.[6] Instead, OGD stated that generics could be approved "provided that the [generic] is rapidly dissolving at the conditions specified in the guidance *Waiver of in vivo BA and BE studies for IR solid oral dosage forms based on a biopharmaceutics classification system (BCS Guidance)*."[7] Neither ViroPharma nor the general public was notified of these changes.

The BCS is a scientific model that permits waiver of the requirement of in vivo BE studies in favor of in vitro dissolution studies for drugs meeting a set of very specific criteria. The BCS model was developed through numerous publications and scientific meetings during the 1990s and categorizes orally administered systemically absorbed drugs into four classes. FDA's BCS Guidance recommends use of in vitro dissolution to demonstrate BE for the first class (BCS I drugs), those which are highly soluble and highly permeable, as long as they are also rapidly dissolving.[8] Additional publications and scientific meetings have sought to lay the groundwork for FDA also to approve drug applications, including abbreviated new drug applications ("ANDAs"), based only on in

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[3] To the extent this document encompasses material previously filed by ViroPharma with FDA, ViroPharma makes every effort to cite previous filings rather than repeating previous material in full.

[4] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 3 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

[5] See, e.g., OGD, Critical Path Opportunities for Generic Drugs, May 1, 2007, at 4 (identifying "current" BE method for locally acting drugs as "comparative clinical trials"), *available at* http://www.fda.gov/oc/initiatives/criticalpath/reports/generic.html.

[6] For a more detailed background of these events, see, e.g., ViroPharma Inc., Supplemental Filing to Petition for Stay of Approval, 2-6, May 31, 2006, Docket No. FDA-2006-P-0007 [hereinafter *May 31, 2006 Filing to PSA*].

[7] E.g., Letter from Dale Conner, Director of the Division of Bioequivalence, OGD to Bernadine Leung, Infinium Capital Corp., 1 (Mar. 1, 2006), *attached as* Tab 1 of *May 31, 2006 Filing to PSA, supra* note 6.

[8] FDA, Center for Drug Evaluation and 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, 2, 12 (Aug. 2000) [hereinafter *BCS Guidance*], *available at* http://www.fda.gov/CDER/GUIDANCE/3618fnl.pdf.

vitro dissolution BE for other BCS drug classes, but to date those efforts have not been brought to a successful conclusion.[9]

OGD's March 2006 letters stating that Vancocin generics could be approved if they rapidly dissolve under BCS conditions did not mention that the BCS was explicitly developed for systemically acting, orally administered, immediate-release solid-dosage forms, and specifically states that the model has not been validated for locally-acting GI drugs such as Vancocin.[10] Also, of the three key parameters for application of the BCS Guidance – high solubility, high permeability, rapid dissolution – OGD's March 2006 letters did not mention permeability, but stated only that "Vancomycin is a highly soluble drug and [Vancocin] is rapidly dissolving."[11] It is well established that Vancocin is ***not*** highly permeable, and as ViroPharma discusses further below, OGD later concluded that vancomycin also is ***not*** rapidly dissolving.

OGD did not conduct any public process when developing its rapid dissolution method for Vancocin BE, and subsequently refused to explain itself when asked by ViroPharma (who learned of OGD's method change when it was announced by the Canadian stock analyst, one of the private parties to whom OGD selectively and privately disclosed the new method).[12] ViroPharma, clinicians and the general public were left to speculate as to OGD's rationale and underlying data. This led ViroPharma to file a petition with FDA asking that any approvals of generic copies of Vancocin under the new rapid dissolution method be stayed until these problems were remedied.[13] OGD's ongoing failure to explain itself has led ViroPharma to make several supplemental petition filings over the past three years.[14] Numerous other parties have also filed comments regarding OGD's rapid dissolution method for determining BE for Vancocin, all but one in support of

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[9] See, e.g., Yu LX et. al. Biopharmaceutics Classification System: The Scientific Basis for Biowaiver Extensions, *Pharm Res.* 19: 921-925 (2002); Hussain A, "An Update on the BCS Guidance: Waiver of In Vivo Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" (Nov. 16, 2000), *available at* http://www.fda.gov/ohrms/dockets/ac/00/slides/3657s2.htm.

[10] It has been clear from the outset of the development of the BCS model that it was not designed to apply to locally acting GI agents like Vancocin. See, e.g., Amidon GL et. al. A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of *in Vitro* Drug Product Dissolution and *in Vivo* Bioavailability, *Pharm Res.* 12: 413-420 (1995).

[11] See, e.g., Letter from Dale Conner, Director of the Division of Bioequivalence, OGD to Bernadine Leung, Infinium Capital Corp., 1 (Mar. 1, 2006), *attached as* Tab 1 of *May 31, 2006 Filing to PSA, supra* note 6.

[12] The Director of OGD, when reached by ViroPharma's Chief Scientific Officer, refused to furnish OGD's new BE recommendations to ViroPharma, claiming that they were confidential.

[13] ViroPharma Inc., Petition for Stay of Action, Mar. 17, 2006, Docket No. FDA-2006-P-0007; Petition for Stay of Action (Amended), Mar. 30, 2006, Docket No. FDA-2006-P-0007.

[14] See *May 31, 2006 Filing to PSA, supra* note 6; ViroPharma Inc., Supplemental Filing to Petition for Stay of Approval, June 30, 2006, Docket No. FDA-2006-P-0007 [hereinafter *June 30, 2006 Filing to PSA*]; ViroPharma Inc., Supplemental Filing to Petition for Stay of Approval, May 17, 2007, Docket No. FDA-2006-P-0007 [hereinafter *May 17, 2007 Filing to PSA*]; ViroPharma Inc., Supplemental Filing to Petition for Stay of Approval, Dec. 30, 2007, Docket No. FDA-2006-P-0007 [hereinafter *Dec. 30, 2007 Filing to PSA*]; ViroPharma Inc., Supplemental Filing to Petition for Stay of Approval, Jan. 11, 2008, Docket No. FDA-2006-P-0007 [hereinafter *Jan. 11, 2008 Filing to PSA*]; ViroPharma Inc., Supplemental Filing to Petition for Stay of Approval, July 25, 2008, Docket No. FDA-2006-P-0007 [hereinafter *July 25, 2008 Filing to PSA*].

ViroPharma's position that FDA should conduct a public, data-driven public process before using in vitro dissolution BE to approve potentially inequivalent generic copies of Vancocin.[15] The lone commenter to support OGD's rapid dissolution BE method was a firm seeking approval of a Vancocin generic, albeit with a modified version of OGD's March 2006 BCS dissolution method.[16]

ViroPharma also filed a FOIA request in March 2006 asking for the administrative record of FDA's adoption of the rapid dissolution BE method for Vancocin generics.[17] After FDA did not meet the 20-day FOIA deadline (FDA has not responded to the FOIA request for nearly three years), ViroPharma brought suit in December 2008 to enforce its FOIA request.[18] FDA has asked the Court to postpone fulfillment of ViroPharma's FOIA request until the request "reaches, in the normal course of business, the front of the processing queue to which it is assigned".[19] FDA then asked ViroPharma to agree to this postponement in exchange for FDA delivering documents to ViroPharma in thirteen months. After having been refused access to documents to which it is legally entitled for almost three years, ViroPharma nonetheless, in a show of good faith, proposed to accept a targeted list of information relating to the 2006 bioequivalence recommendation in exchange for agreeing to a stay in the FOIA suit. This proposal was rejected by FDA. Thus, ViroPharma has been forced to continue to seek access to the full administrative record in the courts.

At a scientific meeting in May 2006 OGD's Director of Science Dr. Lawrence Yu gave a talk entitled "Challenges in Dissolution Testing: An FDA Perspective". As the title of his presentation implies, Dr. Yu's general message was that dissolution is challenging. However, Dr. Yu also inserted in his presentation (i.e., without reference on the slides themselves) the statement that:

> [V]ery often, based on science, we do recommend dissolution for some specific products, for example vancomycin, to replace in vivo clinical studies, because there is evidence, science tells us, that in vitro dissolution is sufficient to ensure the performance of product in vivo.[20]

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[15] See Docket No. FDA-2006-P-0007.

[16] Mylan Pharmaceuticals Inc. Comment Filing to Petition for Stay of Approval, June 13, 2008, Docket No. FDA-2006-P-0007. Mylan did not use the USP apparatus specified in OGD's March 2006 letters. Another commenter filed a non-serious submission, styled as an opposition to ViroPharma's petition, that consisted of three cryptic and unexplained sentences. Dave Lowe Comment Filing to Petition for Stay of Approval, Oct. 18, 2006, Docket No. FDA-2006-P-0007.

[17] Letter from ViroPharma Inc. to FDA Division of Freedom of Information (Mar. 21, 2006), *attached as* Tab 4 of *May 31, 2006 Filing to PSA, supra* note 6.

[18] Complaint, ViroPharma Inc. v. U.S. Dep't. of Health and Human Services, No. 08-CV-02189-PLF (D.D.C filed Dec. 16, 2008).

[19] Defendant Answer at 8, ViroPharma Inc. v. U.S. Dep't. of Health and Human Services, No. 08-CV-02189-PLF (D.D.C filed Jan. 16, 2009).

[20] Transcribed statement of Lawrence X. Yu, Ph.D., Director for Science, Office of Generic Drugs, Food and Drug Administration, in his presentation: "Challenges in Dissolution Testing: An FDA Perspective", Dissolution Testing AAPS Workshop, Hyatt Regency Crystal City, Virginia (May 2, 2006).

Dr. Yu did not indicate what "evidence" or "science" he was referring to in this statement.

In January 2008, ViroPharma met with FDA. One issue raised by ViroPharma was to critique how OGD apparently does not consider the risk to patients of bioinequivalent generics, despite FDA's commitment to do so and this being the approach of the World Health Organization (WHO).[21] Because Vancocin treats acute, life-threatening infections, ViroPharma believes consideration of patient risk from bioinequivalent generics is justified. OGD's Director of Science responded that OGD's science is appropriate such that ***consideration of patient risk is unnecessary***, and stated that the WHO examples cited by ViroPharma were BCS III drugs, for which OGD does not permit waivers of in vivo testing.[22] At this meeting FDA also "reaffirmed the Agency's commitment to transparency and public process" and "indicated that sound science is the principle that OGD uses to establish bioequivalence methodologies".[23]

Two internal FDA study reports dated February 5, 2008 were made public for the first time with the 12/08 Draft Guidance. One of the reports concludes that Vancocin is highly soluble.[24] The other concludes, based on nineteen separate dissolution studies, that Vancocin and certain generic vancomycin capsules are not rapidly dissolving.[25] This statement directly contradicts OGD's controlled correspondence in March 2006 which state that Vancocin is "rapidly dissolving".

In July 2008 FDA's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology ("ACPS") considered, among other issues, BE for low solubility gastro-intestinal ("GI") drugs. Two presentations were made discussing vancomycin bioequivalence, but FDA did not bring up its new data showing vancomycin is not rapidly dissolving. Dr. Abu Alam from generic firm Akorn Inc. ("Akorn"), which has an application pending for a generic version of Vancocin, discussed vancomycin during a slide presentation that included graphs implying rapid dissolution of Vancocin.[26] Present at the meeting were certain of the FDA personnel listed on FDA's February 2008 study report concluding that Vancocin and generic versions were <u>not</u> rapidly dissolving. FDA's data also show that as pH rises dissolution slows, but Akorn's graphs indicated

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[21] ViroPharma Inc., "Vancocin® Bioequivalence (BE): Appropriate Method Development" at 16-19, 24, 27 (Jan. 7, 2008), *available at* http://www.viropharma.com/About%20Us/~/media/Files/ViropharmaFDAmeeting10708final.ashx.

[22] See Letter from Thomas Doyle, ViroPharma Inc., to Helen Winkle, Director, Office of Pharmaceutical Science, FDA, 2-3 (Jan. 30, 2008) (subsequently posted to Docket No. FDA-2006-P-0007 by FDA) available as document FDA-2006-P-0007-0020 at Docket No. FDA-2006-P-0007.

[23] Minutes of Meeting, FDA/ViroPharma Regarding Vancomycin Hydrochloride, Jan. 7, 2008, at 3.

[24] FDA, *Report to Office of Generic Drugs: Vancomycin Solubility Study* (Feb. 5, 2008), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510att1.pdf.

[25] FDA, *Report to Office of Generic Drugs: Vancomycin Dissolution Study* (Feb. 5, 2008), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510att2.pdf.

[26] See Alam A, Akorn presentation at July 22-23, 2009 FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, at 6-8, 10-11 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4370s2-04-OPH-Alam_files/frame.htm; Transcript of FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology at 91-101 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/cder08.html#PharmScience.

identical dissolution rates regardless of pH[27], an apparently impossible result.[28] None of the FDA personnel present mentioned to the Committee that FDA had generated data for vancomycin which contradicted Akorn's results. The Committee did not question or discuss Akorn's presentation.

Although they reached different conclusions, both FDA and Akorn used the three pHs specified in the BCS Guidance (1.2, 4.5, 6.8). The BCS model specifies these pHs based on years of research into the conditions of the healthy human GI tract.[29] In support of the BCS Guidance, FDA emphasizes that there can be a high level of confidence that BCS-based dissolution testing will accurately substitute for in vivo studies because, among other things (e.g., rapid dissolution), there is a substantial body of data demonstrating that the pH levels and other parameters recommended in the BCS guidance accurately reflect the in vivo conditions of the healthy human GI tract.[30] However, as discussed below, there are no data that describe the GI tract of patients with *Clostridium difficile* Infection (CDI) or *Staphylococcus aureus* induced enterocolitis (SAE) sufficiently to provide confidence that dissolution testing will predict in vivo performance.

Unlike the drugs for which the BCS model was designed, Vancocin is only prescribed to patients with diseased GI tracts, including CDI, a serious and potentially life-threatening infection of the lower GI tract.[31] This point was made at the July 2008 ACPS meeting by a leading expert, Dr. Dale Gerding of the Loyola School of Medicine/Hines VA Medical Center. Dr. Gerding presented case studies and autopsy evidence of the severely deranged GI tracts of patients with CDI. He stated that the structural, functional, and biochemical changes in the GI tract of CDI patients are poorly understood, and that currently no in vitro model of the diseased GI tracts of CDI patients has been

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[27] A bullet in Akorn's presentation also stated that "[d]issolution is pH independent". Alam A, Akorn presentation at July 22-23, 2009 FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, at 10 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4370s2-04-OPH-Alam_files/frame.htm.

[28] Akorn's presenter, Dr. Abu Alam, recently reiterated and stood by the data he presented at the July 2008 ACPS meeting. Letter from Akorn, Inc. to Division of Dockets Management regarding Docket No. FDA-2008-D-0626, 2-3 (Jan. 22, 2009). Presumably these data were also filed to Akorn's application to market generic vancomycin capsules, as Akorn has also said publicly that it met OGD's now-abandoned rapid dissolution BE test for generic copies of Vancocin. See, e.g., Thomson StreetEvents, Conference Call Transcript AKRX - Q4 2007 Akorn, Inc. Earnings Conference Call, at 3 (Mar. 11, 2008, 5:00pm ET) (attached at Tab 1) ("[O]ur ANDA clearly demonstrates equivalency to the reference listed drug based on published FDA guidance and our CMC and stability results.") Thus, it seems unlikely that Akorn believes its data are in error. If however that becomes Akorn's position, the implications of presenting incorrect and misleading data to an FDA Advisory Committee, then re-presenting the same data months later, as well as FDA's failure to notice the data discrepancy or mention it to the Advisory Committee, are grave.

[29] See, e.g., Yu LX et. al. Biopharmaceutics Classification System: The Scientific Basis for Biowaiver Extensions, *Pharm Res.* 19: 921-925 (2002); Hussain A, "An Update on the BCS Guidance: Waiver of In Vivo Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" (Nov. 16, 2000), *available at* http://www.fda.gov/ohrms/dockets/ac/00/slides/3657s2.htm.

[30] Id.

[31] ViroPharma has described CDI and the increased morbidity and mortality associated with the current epidemic strain of *Clostridium difficile* in previous filings. See, e.g., *May 31, 2006 Filing to PSA, supra* note 6, at 2; *June 30, 2006 Filing to PSA*, *supra* note 14, at 2, 5-6, 10-14.

developed.[32] Accordingly, Dr. Gerding concluded by asking for human testing before patients are exposed to generic copies of Vancocin, and asked FDA to openly discuss the uncertainties associated with proposed BE methods for Vancocin as well as the risks to patients of inequivalent generic formulations.[33]

The 12/08 Draft Guidance does not address Dr. Gerding's concern that no in vitro model of the diseased GI tract of Vancocin patients exists. Instead 12/08 Draft Guidance cites publications describing the GI tract of healthy subjects including pH ranges, fluid volumes and transit times to support the conclusion that "vancomycin is expected to be in solution long (e.g., hours) before it reaches the site of action in the lower GI tract."[34] OGD asserts its "expectation" based on transit time data generated from the GI tracts of healthy subjects, and the demonstration by generic applicants of dissolution profiles similar to Vancocin over a range of pH values also generated in the GI tracts of healthy subjects, will account for any variability that the diseased GI environment of patients with CDI or SAE may have in GI pH or transit times.[35] OGD does not address whether the 12/08 Draft Guidance accounts for other deranged aspects of the in vivo environment of patients with CDI or SAE, such as altered motility patterns, low volume of gastric or intestinal contents, inflamed mucosa, and abnormal intraluminal constituents. OGD also makes no representations like those FDA made for the BCS, i.e., that there can be a high level of confidence in OGD's in vitro model because there is a large body of data demonstrating that it accurately mimics in vivo conditions.

The 12/08 Draft Guidance also abandons another BCS parameter – rapid dissolution. Presumably this is because OGD's own data demonstrate Vancocin and the other generic formulations it tested do not rapidly dissolve. Thus, while the 12/08 Draft Guidance claims merely to "further clarif[y]" OGD's March 2006 method which relied on the BCS Guidance, it is based on only one of the three BCS Guidance parameters – high solubility. OGD has not sought to explain or justify the elimination of the other two parameters (high permeability, rapid dissolution). Nor has OGD proposed any other model in support of the 12/08 Draft Guidance, presumably because, as Dr. Gerding stated, none exists.

Vancocin's labeling states that in some patients, toxic systemic levels of vancomycin have been observed, and cautions clinicians to monitor accordingly. FDA's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS) also, at its July 2008 meeting, focused on the idea that if any active ingredient from a locally acting GI drug enters systemic circulation, blood sampling should be done for safety reasons.

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[32] Gerding D, "*Clostridium difficile* Infection (CDI): Increasingly Severe and Rapidly Fatal Disease Requires High Certainty of Treatment Efficacy" at 14-15 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4370s2-05-OPH-Gerding_files/frame.htm.

[33] Id. at 15.

[34] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

[35] See id. at 2-3.

The 12/08 Draft Guidance ignores both Vancocin's labeling as well as the recommendation of the advisory committee.

Because the 12/08 Draft Guidance proposes an in vitro BE method, under FDA's regulations the method must meet the criteria for waiver of the requirement of in vivo evidence of bioequivalence.[36] However, unlike most draft guidances, the 12/08 Draft Guidance does not cite any legal authority.

Finally, at a bioequivalence conference in London in October 2008, FDA's Dr. Mehul Mehta, Director of the Division of Clinical Pharmacology I within CDER's Office of Clinical Pharmacology, was asked whether he thought that in vitro dissolution testing alone would be acceptable for a drug like Vancocin – a locally acting GI product which is systemically absorbed at clinically relevant levels in some patients. Dr. Mehta did not see how in vitro testing would be appropriate in such an instance. Dr. Mehta co-chairs FDA's BCS-BE methods development committee along with OGD's Dr. Yu. Given Dr. Mehta's role, it is surprising that OGD would not have discussed oral vancomycin capsule BE with him, as OGD's BE approach to Vancocin has been unequivocally based on the BCS model, to the point of in 2006 proposing for Vancocin the waiver developed exclusively for rapidly dissolving BCS-1 drugs.

II. Multiple Flaws Prevent Finalization of the 12/08 Draft Guidance

A. OGD Has Not Met its Burden to Correlate the BE Method Proposed in the 12/08 Draft Guidance with In Vivo Data

By law FDA must ensure that generic drug applications contain information showing the generic is bioequivalent to the brand drug they seek to copy. Federal Food, Drug, and Cosmetic Act (FFDCA) § 505(j)(4)(F). Such information must be obtained in vivo, unless specified waiver criteria are met. 21 CFR 320.21-22.[37] The waiver permitting in vitro BE testing requires that the in vitro test be correlated with in vivo data. 21 CFR 320.22(d)(3).[38] Rigorous science also requires that OGD correlate in vitro methods it proposes with what actually happens in patients; otherwise there can be little confidence that generic drugs will be the same as the brands for which they are substituted.[39]

As described above, FDA sought to meet this burden when developing the BCS model by participating in a decade-long process of meetings, publications, and FDA advisory committee meetings. The end result was a significant body of scientific evidence on the conditions of the GI tract in healthy subjects upon which FDA could claim correlated dissolution testing for rapidly dissolving BCS I drugs with the in vivo environment of

[36] 21 C.F.R. 320.21-22.
[37] See also *July 25, 2008 Filing to PSA, supra* note 14, at 1-12.
[38] As ViroPharma has explained in previous filings, OGD's occasional assertions to the contrary do not withstand scrutiny. See id.; *May 31, 2006 Filing to PSA*, supra note 6, at 16-22.
[39] See *July 25, 2008 Filing to PSA, supra* note 14, at 12-13.

patients who would receive those drugs. Accordingly Ajaz Hussein, FDA's then Acting Director of the Office of Testing Research and the Chair of the BCS Working Group Biopharmaceutics Coordinating Committee, stated that this minimized the risk that use of the BCS Guidance would result in the marketing of bioinequivalent drugs.[40] For oral vancomycin, however, OGD has not conducted a similar, rigorous approach.

1. OGD's Assumptions that Vancocin Patients Have Healthy GI Tracts and that Differences with Diseased Patients Do Not Inform Development of an In Vitro Model Lack a Scientific Basis

Unlike FDA's development of the BCS, OGD has made no effort to meet its burden to correlate the 12/08 comparative dissolution method with the in vivo environment of patients taking Vancocin. Rather than a substantial body of data on the in vivo environment of the GI tract of patients with CDI or SAE, OGD cites none. Instead, OGD either asserts, without data, that it knows how Vancocin behaves in vivo, or it selectively cites data derived from healthy subjects.

Among OGD's data-free assertions is the claim that "[a]fter oral administration, a vancomycin capsule releases the drug in the stomach and upper GI tract, the released drug is completely solubilized in GI fluids, and is transported to its site of action in the lower GI tract."[41] OGD also asserts without data that the pH conditions and dissolution media it selected for the 12/08 comparative dissolution method are "physiologically relevant" to Vancocin patients.[42] To make these statements with any degree of certainty, OGD would need data defining the GI parameters of patients with CDI or SAE, including GI fluids and range of motility parameters in this patient population.

Recall, however, that Dr. Gerding, who has spent over 30 years conducting research and providing direct patient care to patients with CDI and SAE, told an FDA Advisory Committee that the profound structural, functional and biochemical changes in the GI tract of CDI patients are poorly understood, such that currently there is no in vitro model of this deranged physiology. Other infectious disease specialists have written FDA expressing the same concerns.[43] OGD thus claims physiologic knowledge of CDI and SAE patients that the experts say does not exist. In the absence of data, OGD's statements are hypothetical, and are therefore no basis for an in vitro model of an in vivo environment, which necessarily is based on in vivo data.

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[40] Hussain A, "An Update on the BCS Guidance: Waiver of In Vivo Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" (Nov. 16, 2000), *available at* http://www.fda.gov/ohrms/dockets/ac/00/slides/3657s2.htm.

[41] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

[42] Id. at 2.

[43] See, e.g., Dr. William Bishai, Health Professional, Comment Filing to Petition for Stay of Approval, Aug. 30, 2006, Docket No. 2006P-0124 (now FDA-2006-0007); Letter from Dr. Joseph Bertino, FCCP, Scientific Director, Ordway Research Institute Drug Development Center, Comment Filing to Petition for Stay of Approval, Sept. 1, 2006, Docket No. 2006P-0124 (now FDA-2006-0007).

Notably, prior to development of the BCS model, FDA officials made statements similar to those found in the 12/08 Draft Guidance about why rapidly dissolving oral formulations might be considered solution-like and therefore eligible for biowaivers[44]. FDA, however, never sought to approve drugs based solely on such speculation. Rather, FDA spent a decade generating the data for the BCS model before it even considered proposing its use in regulatory approvals of drug products.[45]

Moreover, it is clearly the consensus view of the pharmaceutical science experts on which FDA relies that before developing an in vitro dissolution BE test for Vancocin OGD should first have gained an understanding of the in vivo environment of patients with CDI and SAE. Thus, for example, at an ACPS meeting in 2004, Dr. Gordon Amidon stated that "[f]or locally acting drugs, in vivo dissolution is the key determinant. So, for the in vitro dissolution test, we should cover the range of in vivo variables."[46] Similarly, at the July 2008 ACPS meeting, Professor James Polli observed that "there is no universal dissolution media"[47] and stated that dissolution media should "mimic the gastrointestinal luminal conditions, based on things like composition, physical chemical properties, things of that sort."[48]

Likewise, in a publication cited by OGD in the 12/08 Guidance, Dressman et al. state that "the dissolution test selected for a given product should be validated in terms of its ability to discriminate adequately between dosage forms that are not bioequivalent, as well as to exhibit similar release profiles for products that are bioequivalent."[49] Apparently, there was much in this Dressman publication that OGD found troubling. As discussed below, OGD went so far as to delete reference to this article in a second, unannounced version of the 12/08 Draft Guidance.

At the 2004 ACPS meeting Dr. Gordon Amidon specifically highlighted the need for evidence demonstrating the biorelevance of dissolution media:

> Often now today, we have what we call biorelevant dissolution media or biorelevant dissolution. I think we need to use that term carefully because,

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[44] For example, at a 1986 meeting on bioequivalence, FDA's Bob Temple said "[i]t certainly seems sensible to think that swallowing something that turns into a solution rapidly would be difficult to lead to differences from one product to the next. But in part, that's a data question." Transcript of Proceedings of the Food and Drug Administration: Bioequivalence Hearing, at 72 (Sept. 29-30, Oct. 1, 1986), Docket No. 86N-0251.

[45] Hussain A, "An Update on the BCS Guidance: Waiver of In Vivo Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System", at 2 (Nov. 16, 2000), *available at* http://www.fda.gov/ohrms/dockets/ac/00/slides/3657s2.htm.

[46] Transcript of FDA Advisory Committee for Pharmaceutical Science at 284-285 (Oct. 20, 2004), *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf.

[47] Transcript of FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology at 58 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4370t2-part1.pdf.

[48] Id. at 56.

[49] Dressman JB et al. Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms. *Pharm Res.*15: 11-22, 20 (1998). OGD's unannounced revision of the 12/08 Draft Guidance is discussed further below.

> you know, to take some natural surfactants and a little bit of phospholipid and put it in water and shake, you either have a drug delivery company or you call it biorelevant dissolution media, but what is it? There is no evidence that it is relevant to the in vivo dissolution process.[50]

In the 12/08 Draft Guidance OGD fails to meet Dr. Amidon's challenge to carefully justify the dissolution media used. OGD should follow the advice of its expert and demonstrate the relevance of the dissolution media specified in the 12/08 Draft Guidance to the in vivo dissolution process as it occurs in patients.

Even a generic drug company thinks OGD's method does not specify appropriate dissolution media. In comments on the 12/08 Draft Guidance, APP Pharmaceutical Products ("APP") says OGD should permit use of Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluids (SIF) (both of which seek to simulate the GI conditions in healthy subjects) in addition to the BCS-based dissolution media already provided for in the 12/08 Draft Guidance. In support, APP cites pharmaceutical science experts for the proposition that "including gastrointestinal enzymes in the dissolution medium may better simulate the physiological conditions than an orally administered capsule would come in contact with on its way to the lower gastrointestinal (GI) tract."[51] ViroPharma applauds APP's recognition that OGD's 12/08 method should better simulate the physiological conditions that vancomycin capsules will actually encounter, although we disagree that SGF and SIF have been shown to accurately simulate the diseased GI tracts of patients with CDI and SAE.

Nonetheless, undeterred by its failure to correlate its suggested dissolution media and pH values with the GI pathophysiology of CDI or SAE patients, OGD utilized them to conduct a dissolution study of Vancocin and certain unidentified generic versions of the drug.[52] This study is curious for many reasons, as discussed elsewhere in this document. For purposes of this discussion regarding whether OGD met its burden to correlate the 12/08 comparative dissolution method with in vivo data in patients with CDI and SAE, it is clear OGD's dissolution study does not meet the burden. Because the conditions under which it was conducted have not been shown to mimic the physiological conditions or relevant parameters of patients with CDI and SAE, the study's results cannot be relied on to show how Vancocin dissolves in patients with CDI and SAE. OGD's dissolution study merely shows how Vancocin dissolves under OGD's uncorrelated conditions.

OGD's 12/08 Draft Guidance is also inconsistent with the Vancomycin Solubility Study Report OGD cites in support of that method. The highest pH the 12/08 Draft Guidance requires for testing of generic vancomycin capsules is 6.8. However, OGD's solubility study sets the relevant value for this parameter substantially higher, at pH 7.5. Moreover,

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

[51] APP Pharmaceutical Products, LLC Comment Filing to 12/08 Draft Guidance, Feb. 11, 2009, Docket No. FDA-2008-D-0626, 2.

[52] FDA, *Report to Office of Generic Drugs: Vancomycin Dissolution Study* (Feb. 5, 2008), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510att2.pdf.

the Vancomycin Solubility Study Report states that even pH 7.5 is only "with-in the extremes of the normal physiological pH of the human gastrointestinal tract".[53] Thus OGD's 12/08 dissolution method does not even cover the relevant pH range of the healthy human GI tract as defined by OGD itself.

2. OGD Cites Publications Which Studied the Healthy GI Tract and Acknowledge Disease Can Modify Their Findings

For the past three years, OGD has chosen not to discuss or acknowledge any of the uncertainties associated with its underlying approach but has instead attempted to avoid a full disclosure of its thinking or the limitations to its supporting data. This is made clear in the 12/08 Draft Guidance where scientific rationale is selectively culled from the literature and values presented in a way that misleads the audience with respect to the intended use and variability around the numbers.[54]

Rather than seek to show that its in vitro method accurately mimics the diseased in vivo environment of patients with CDI or SAE, the only in vivo data OGD does cite are from publications which studied the GI tract of healthy subjects. Without explaining how, OGD asserts that these fluid volume, pH, and transit time conditions derived from healthy subjects accurately describe the diseased GI tract of patients who receive Vancocin.[55]

In fact, the publications OGD cites reinforce the need for additional characterization of the GI tracts of patients with CDI or SAE before an in vitro dissolution BE method like that in the 12/08 Draft Guidance will be appropriate for use in approval of generic versions of Vancocin. Several areas of concern are presented below:

Fluid Volume in the Upper GI Tract of Patients with CDI

Fluid volume in the upper GI tract of patients with CDI is likely to be substantially lower than the volumes cited by OGD in support of its in vitro dissolution method. OGD cites Dressman and Reppas[56] as the basis for its assertion that that the relevant estimate of

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[53] FDA, *Report to Office of Generic Drugs: Vancomycin Solubility Study*, 3 (Feb. 5, 2008), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510att1.pdf.

[54] The absence of any scientific "fair balance" in OGD's approach is troubling, and does not bode well for the scientific rigor that should apply to all such deliberations by OGD. Failure to do so risks major adverse impact on patient safety and mortality.

[55] "Given that vancomycin is highly soluble at pH conditions encountered in the GI tract[3] and the dosage form is expected to be in contact with a relatively large fluid volume,[4] vancomycin is expected to be in solution long (e.g., hours) before it reaches the site of action in the lower GI tract.[5]" OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf. As discussed in this section, the footnote cites in this quotation reference three publications that report results from investigations seeking to characterize the healthy human GI tract.

[56] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 n. 4 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf (citing Dressman J and Reppas C. *Eur J Pharm Sci*. 11: S73-S80 (2000)).

physiological fluid volume of the small intestine in this patient population is in the range of 500 mL – 1000 mL or more. It is worth noting that the authors proposed these values based on a survey of published reports as representative of normal, healthy gut conditions for use in a standard USP paddle apparatus within a discussion of parameters affecting the dissolution of Class II drugs.[57, 58] In this paper, the authors set out to model in vitro the limiting factor to drug absorption and pointed out that, in order to achieve correlation with in vivo performance, the volume of the contents of the GI lumen, among other things, must be accurately simulated. Importantly, Dressman and Reppas stressed that these volumes are dependent on a number of factors including disease state(s) and associated pathophysiological changes.[59]

OGD has seemingly ignored this explicit limitation by the authors and has yet to present any data specific to the fluid volumes of the small intestine of a CDI patient. Nor, for that matter, has OGD presented any data to support a claim that the pathological changes present in the GI of the average CDI patient do not modify the fluid volume of the small intestine relative to those of the healthy individual identified by Dressman and Reppas in the publication cited by OGD.

An appreciation of the clinical condition of CDI patients underscores the cautionary comments of Dressman and Reppas. These patients are often anorexic, cannot tolerate food or fluids, (i.e., they are fasting), and often require intravenous fluid administration to maintain hydration. The stomach of a healthy fasted individual has fluid volume of only 20 to 30ml, which may be reduced further by the use of anti-secretory agents such as proton pump inhibitors and H2 receptor blockers which are known to cause profound reduction in volume of secretion and acidity. Such agents are commonly used in patients with CDI to such an extent that evidence links their use to an increased incidence of

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[57] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 n. 4 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf (stating "The physiological fluid volume of the small intestine varies from 500 mL (fasting conditions) to approximately 1000mL or more (fed conditions)"). In fact, what the Dressman and Reppas article states is that these "volumes can be used to approximate the volumes available in the upper GI tract". Dressman J and Reppas C. In Vitro—In Vivo Correlations for Lipophilic, Poorly Water-Soluble Drugs. *Eur J Pharm Sci.*11:S73-S80, S75 (2000). Of further note, the Dressman and Reppas article underscores that "[c]orrelation of in vivo results with dissolution tests is likely to be best for Class II drugs [and t]he other case where in vitro/in vivo correlations (IVIVCs) are often obtained is when a Class I drug is formulated as an extended release product". Id. at S74. Thus, the authors of the article OGD cited explicitly acknowledge limitations on their work which OGD does not address.

[58] However, it is also interesting to note that in the second version of the 12/08 Draft Guidance, OGD removed any reference to the Dressman et al. journal article published two years earlier which had in fact mentioned that the volume of fluid of the stomach might be as little as 20-30 mL and could be as low as 120 mL in the jejunum and ileum. Dressman JB et al. Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms. *Pharm Res.*15: 11-22, 15 (1998) (stating "The volume of the stomach in the fasted state may be as little as 20-30 mL . . . [and] the volume of fluid in the jejunum and ileum varies from 120-350 mL"). OGD's unannounced revision of the 12/08 Draft Guidance is discussed further below.

[59] Dressman J and Reppas C. In Vitro—In Vivo Correlations for Lipophilic, Poorly Water-Soluble Drugs. *Eur J Pharm Sci.*11:S73-S80, S74 (2000).

developing CDI.[60] Consequently it cannot be assumed that the volume of fluid in the upper GI tract of a CDI patient is likely to be the same as in a healthy non-fasted individual, indeed it is likely to be substantially less. The additional assumption that a capsule of Vancocin will be swallowed with 240ml of water is erroneous. Due to the factors outlined above, fluid intake by these patients is minimal. Even OGD's own data on vancomycin solubility supporting the use of the 12/08 Draft Guidance state that up to 83.8ml[61] is required to dissolve a 250mg capsule of Vancocin, a volume that may not be present in the upper GI tract of CDI patients.

Gastrointestinal pH

Along the same lines, OGD has not recognized that the gastrointestinal pH ranges of patients with CDI are likely to be different from healthy subjects. OGD failed to highlight that Willmann et al., the authors of the pH ranges OGD references in footnote 3 of the 12/08 Draft Guidance, based their estimates of GI pH ranges on observations in young, healthy individuals and made no claim that these same values are appropriate characterizations of the pH ranges observed in the stomach or along the GI tract of CDI or SAE patients.[62] Nor for that matter did OGD present any data to support such a claim. Given that patients with CDI or SAE do not have "healthy" GI tracts and that most are not "young", this pH range may be entirely inappropriate for modeling in vivo conditions associated with the use of oral vancomycin.

Interestingly, an article by Dressman et al., which OGD had originally cited in its first publicly available version of the 12/08 Draft Guidance but which OGD subsequently deleted, observed that "fasted state gastric pH values of pH 6 and higher are found in . . . those receiving gastric acid blocker therapy and those over the age of 65 years."[63] Thus, OGD was aware of this finding but chose to omit the source from its footnotes in its unannounced revised draft rather than acknowledge and discuss it. In the end, because

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[60] See Dial S et al. Use of Gastric Acid-Suppressive Agents and the Risk of Community-Acquired *Clostridium difficile*-Associated Disease. *JAMA*. 294:2989-2995 (2005).

[61] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

[62] Willmann et al. clearly stated that the mean gastric pH range of 1.5-2.5 was the "pH determined in healthy volunteers". Willmann S et al. A Physiological Model for the Estimation of the Fraction Dose Absorbed in Humans. *J Med Chem.* 47: 4022-4031, 4023 (2004). What's more, the source Willmann et al. cite in their paper to support the mean gastric pH range of 1.5-2.5 is even titled "Upper Gastrointestinal (GI) pH in Young, Healthy Men and Women." Id. at 4023 & 4030 n.22.

[63] Dressman JB et al. Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms. *Pharm Res.*15: 11-22, 14 (1998); OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 n.5 (Dec. 15, 2008) (citing to Dressman JB et al. Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms. *Pharm Res.*15: 11-22 (1998) for the proposition that "The average transit time in the small intestine is 199 minutes with the standard deviation of 78 minutes."); OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 n. 5 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf (citing to Davis S et al. Transit of Pharmaceutical Dosage Forms Through the Small Intestine. *Gut.* 27:886-892, 891 (1986) for the proposition that "The average transit time in the small intestine is 3 to 4 hours."). OGD's unannounced revision of the 12/08 Draft Guidance is discussed further below.

OGD has no data to suggest that the pH ranges of healthy individuals are the same for patients with CDI and SAE, the pH ranges of the GI tract OGD cites cannot truly inform or substantiate OGD's 12/08 Draft Guidance claim "that vancomycin is highly soluble at pH conditions encountered in the GI tract".[64]

Moreover, it is well documented that aging is associated with reduced acidity in the stomach, either as a result of reduced acid secreting parietal cell volume or due to the increased incidence of atrophic gastritis (which occurs in 25% of those older than 50 years).[65] Additionally, as alluded to above, many of these patients are receiving proton pump inhibitors or H2 receptor antagonists that profoundly reduce the acidity of the stomach. 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 stomach pH may be 7.0 or greater due to either underlying pathology or therapeutic intervention, or both causes. This contrasts with the usual pH range of a healthy individual which can be as low as 1.5.

These observations question the OGD assertion that vancomycin is highly soluble when the pathophysiologic conditions found in patients are taken into account. Even OGD's own data on vancomycin solubility made public with the 12/08 Draft Guidance indicate that up to 83.8ml is required to dissolve a 250mg capsule of Vancocin at pH 4[66], a pH level that is commonly observed in the stomach of older patients susceptible to CDI and for reasons elaborated above is a volume that may not be present in the stomach or upper GI tract of patients with CDI.

Gastrointestinal Transit Time

There are no data in the literature on GI transit time in CDI patients, consequently important parameters such as gastric emptying, small intestinal transit or colonic transit times are unknown. Patients may suffer profound diarrhea and rapid GI transit at one extreme and no GI transit (ileus) on the other extreme. Taken in combination with the low fluid volume and high pH levels elaborated above these clinical observations further undermine the assertions from OGD that healthy subject data can be extrapolated to patients and that "vancomycin is expected to be in solution long (e.g., hours) before it reaches the site of action in the lower GI tract."[67]

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[64] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

[65] Geokas M, Haverback BJ. The Aging Gastrointestinal Tract. *Am J Surg*. 117(6):881-92 (1969); Hammerlein A et al. Pharmacokinetic Changes in the Elderly. Clinical Implications. *Clin Pharmacokinet*. 35(1):49-64 (1998).

[66] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

[67] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%20

Even according to the publications OGD cited in the 12/08 Draft Guidance, an average transit time in the small intestine of 3 to 4 hours does not appear to be a particularly representative—let alone conservative—estimate of this parameter, even in the healthy population. In its guidance, OGD failed to even acknowledge that these same cited publications also identified more rapid transit times. In fact, Davis et al., the authors of the article OGD cites for the proposition that "[t]he average transit time in the small intestine is 3 to 4 hours", noted that in the case of a drug that "is absorbed exclusively from the small intestine there is a good chance that the time the delivery system spends in that region could be as short as one to two hours."[68] Interestingly, the article that appeared in footnote 5 of the original version of the 12/08 Draft Guidance and later was deleted by OGD without notice or acknowledgment, also mentioned that a small intestinal transit period could be as short as one hour.[69]

As with the other articles OGD references in its 12/08 Draft Guidance, the intent of the Davis et al. publication was to suggest a model of what occurs in the normal healthy gastrointestinal tract. However, Davis et al. discussed a variety of deviations from a 3-4 hour transit time and emphasized that variations are likely depending on the age and health of the individual.[70] OGD failed to point out that Davis et al. explicitly recognized that:

> It should be remembered that [sic] majority of the data discussed above have been obtained in a large group of healthy male young subjects who were able to take moderate exercise during the studies. It is known that certain disease conditions, such as inflammatory lesions, or disorders of gut motility can affect transit, as can the presence of administered drugs . . . .[71]

Notably, the 3-4 hour transit time OGD asserts in its current 12/08 Draft Guidance is based on a citation to an article published in 1986 but this transit time is inconsistent with a public statement made by FDA in November of 2000. In a slide presentation before the FDA's Advisory Committee for Pharmaceutical Science by FDA's then Chair of the BCS Working Group Biopharmaceutics Coordinating Committee, Ajaz Hussain, FDA stated that the "[r]esidence time is between two to four hours" in the small intestine.[72] Thus,

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2008.pdf. In footnote 5 of the 12/08 Draft Guidance, OGD notes: "The average transit time in the small intestine is 3 to 4 hours." Id. 2, n.5.

[68] Davis S et al. Transit of Pharmaceutical Dosage Forms Through the Small Intestine. *Gut.* 27:886-892, 891 (1986).

[69] Dressman JB et al. Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms. *Pharm Res.*15: 11-22, 18 (1998) (noting that "the transit time [in the small intestine] is on the order of one to three hours.")

[70] Davis S et al. Transit of Pharmaceutical Dosage Forms Through the Small Intestine. *Gut.* 27:886-892, 891 (1986) (noting "The shortest small intestinal transit time found in the present work is of the order of 1-3 h, while the longest is about six hours. One individual had a value of nine hours [sic] the reason for this slow transit is not known.").

[71] Id. at 891.

[72] Transcript of FDA Advisory Committee for Pharmaceutical Science at 21(Nov. 16, 2000), *available at* http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3657t2.pdf; Hussain A, "An Update on the BCS

leaving aside the effects on motility caused by CDI, the transit time asserted in the new 12/08 Draft Guidance is inconsistent with a previous public statement by the Agency and is based on a cherry picked range from an article that predates the subsequent Agency statement by 14 years.

3. Initial Findings in Patients Substantiate the Inapplicability of OGD's Healthy GI Data

Initial data from work sponsored by ViroPharma at Temple University[73] substantiate that patients with CDI do not exhibit the healthy GI physiology asserted by OGD. For example, OGD cites a gastric pH range of 1.5 to 2.5, but the Temple investigators report gastric pHs as high as 6.4 in patients for whom Vancocin is indicated. Similarly, the Temple investigators thus far have not observed small bowel pHs in patients lower than 7 (and as high as 7.7), but OGD cites the duodenal pH range as 5.0 to 6.0, jejunal pH as 6.0 to 7.0, and ileal pH as 7.5. This study is the first to attempt to describe the GI parameters of patients with CDI and enrollment is ongoing. The results of this sentinel study will provide valuable data for in vitro BE methodology development for locally acting agents used to treat CDI. However, based on these early data points, it is clear that OGD's assertion that patients with CDI exhibit normal healthy GI physiology needs further evaluation.

Given the risk to patients and public health associated with the approval or marketing of a bioinequivalent generic product and the uncertainties associated with extrapolation from a healthy gut model, there is a need for detailed explanation, justification and validation of the proposed method and a need for an overt consideration of the risk-benefit to patients associated with the use of an in vitro only approach to establishing BE for this agent. The Dressman et al. publication which OGD originally cited, but later deleted, aptly describes how OGD's approach significantly increases the risk of bioinequivalence:

> [I]f [in vitro dissolution] tests are not performed under appropriate conditions, ***the prediction of which drugs and which dosage forms will exhibit the desired release profiles in vivo may be completely erroneous***.[74]

Guidance: Waiver of In Vivo Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" at 11 (Nov. 16, 2000), *available at* http://www.fda.gov/ohrms/dockets/ac/00/slides/3657s2.htm.

[73] The purpose of this study is to examine the intestinal environment of patients with CDI and compare the findings to a population of healthy subjects. Results from this study will assist the medical management of patients with CDI because there is little information on factors which may influence the bioavailability of Vancocin. FDA and OGD should be interested in using this information to establish bioequivalence methods for Vancocin generally, and in evaluating the appropriateness of using in vitro dissolution tests for this purpose specifically. ViroPharma previously submitted the protocol for this study to FDA. ViroPharma Incorporated letter to Dr. Edward Cox, Supervisory Medical Officer at FDA, and Helen Winkle, Director of the Office of Pharmaceutical Science (Mar. 16, 2007) (subsequently posted to Docket No. FDA-2006-P-0007 by FDA). ViroPharma also offered to work together with FDA to seek a better understanding of the *in vivo* environment of Vancocin patients, but has not heard back from the Agency on this issue.

[74] Dressman JB et al. Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms. Pharm Res.15: 11-22, 1 (1998) (emphasis added).

In sum, OGD's "model" of the GI tract of patients with CDI and SAE was developed without any data derived from the diseased GI tracts of these very patient populations. The comparative dissolution BE method proposed in the 12/08 Draft Guidance is thus a hypothesis that has yet to be tested against physiologic reality. The very authorities cited by OGD in support of its method indicate that in vitro testing must be shown to mimic in vivo conditions, which early work sponsored by ViroPharma indicates vary substantially from the healthy human GI tract.

Similar to the BCS in the early 1990s, more work must be done before OGD's hypothesis might enable BE methods suitable for approval of generic versions of Vancocin. Because OGD has not met its burden to correlate the comparative dissolution test described in the 12/08 Draft Guidance with in vivo data, this method is not yet appropriate for determining whether generic formulations are bioequivalent to Vancocin.

B. OGD Misapplies the BCS to Vancocin

As explained above, OGD attempted to apply a model to Vancocin which explicitly was not developed for locally acting drugs. To do so OGD also had to ignore the fact that Vancocin did not meet one of the three key parameters upon which the BCS Guidance was developed – high permeability. Then, rather than publicly propose its new approach, OGD hid from collegial scrutiny. It fell to a Canadian stock analyst to tell the world what OGD was up to.[75]

Yet even after this embarrassing revelation and the ensuing criticism, OGD steadfastly refused to explain itself. We now know that OGD at some point actually did test the categorical statement it had made to the Canadian stock analyst (and others), i.e., that Vancocin "is rapidly dissolving". However, in another breach of the scientific method, OGD tested this claim only after having made it.

Moreover, in what must have been a disturbing revelation, OGD's own data showed that OGD had gotten it wrong with respect to this basic physical chemical property of Vancocin.[76] Vancocin is not rapidly dissolving. As ViroPharma has said all along, and OGD now apparently concedes, this fact fatally undermined OGD's March 2006 BE method for Vancocin, which was predicated on and required Vancocin and generic copies to be rapidly dissolving.

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[75] For a more detailed explanation of these events, see, e.g., *May 31, 2006 Filing to PSA, supra* note 6, 4-6.

[76] Of note, when OGD belatedly did evaluate whether Vancocin rapidly dissolves, it conducted 19 different dissolution studies. FDA, *Report to Office of Generic Drugs: Vancomycin Dissolution Study* at 3 (Feb. 5, 2008), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510att2.pdf. It will be interesting to review the chronology of these studies, as perhaps OGD did not like the initial results, so ordered more, etc. ViroPharma of course expects the chronology and any correspondence regarding these studies will be disclosed when FDA answers ViroPharma's December 16, 2008 FOIA request for the administrative record of OGD's development of the 12/08 Draft Guidance.

But rather than revoke its March 2006 rapid dissolution BE test for Vancocin, OGD left the test in place and kept the contradictory data secret. Indeed, when a generic firm (Akorn) gave a presentation to an FDA Advisory Committee suggesting that Vancocin is rapidly dissolving, OGD chose not to advise their scientific colleagues on the Committee that OGD's own data demonstrated the generic firm's suggestion was false.[77] This action by OGD was wholly inconsistent with statements made by the Office as to how important scientifically sound decisions are to ensuring the quality of generic drugs.

With rapid dissolution disproven by OGD's own data, only one of the three key parameters on which the BCS-based waiver is based (high solubility) still (arguably) applied to Vancocin. Consequently, OGD's claim to the BCS imprimatur for its Vancocin BE method, tenuous to begin with, devolved into a model based solely on the solubility of the drug, which itself was subject to question. In response to these findings, and having discovered that the extrapolation of a BCS-1 based waiver to Vancocin was never appropriate, OGD simply gutted the scientific rationale and model on which it based its recommendation for in vitro testing in the first place, acknowledged the high degree of variability around its assumptions, and in December 2008 put forth a new scientifically baseless BE recommendation to take its place. OGD posited that as long as a generic exhibited dissolution "comparable" to Vancocin and was Q1Q2 the same as Vancocin[78], it would be deemed bioequivalent to Vancocin.

In support of this approach, OGD could not point to a well-developed model like such as the BCS, indeed OGD could point to no model at all. As discussed above, OGD could only make data-free assertions, and cite GI data derived from healthy subjects whose relevance to the diseased GI tract of Vancocin patients OGD likewise asserted, but could not substantiate.

OGD's contorted efforts to support a recommendation for in vitro BE testing for Vancocin in the face of eroding scientific justification and contradictory data stand in stark contrast to the deliberate, scientific approach FDA has taken to consideration of extending BCS-based waivers to other BCS drug classes, particularly the BCS III drugs. The concept of replacing in vivo BE studies for BCS III drugs with BCS-based in vitro dissolution has been a topic of active research and open discussion for more than a decade.[79] However, despite this substantial body of work and the fact that BCS III drugs

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[77] See Alam A, Akorn presentation at July 22-23, 2009 FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, at 6-8, 10 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4370s2-04-OPH-Alam_files/frame.htm; Transcript of FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/cder08.html#PharmScience.

[78] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 1 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf (stating that "If the test product formulations are qualitatively (Q_1) (i.e., contain all of the same inactive ingredients) and (Q_2) the same as the reference listed drug [RLD] with respect to inactive ingredients, bioequivalence (BE) of all capsule strengths my be established based on comparative dissolution.").

[79] See, e.g., Transcript of FDA Advisory Committee for Pharmaceutical Science at 68, 193-207 & 240 (May 7, 1997), *available at* http://www.fda.gov/ohrms/dockets/ac/97/transcpt/3296t1.pdf; Transcript of

are part of the BCS model, the conclusion to date has been that there is insufficient data to support the extension of waivers to these agents.[80] By contrast, OGD apparently sees no issue with extrapolation of the same biowaiver to Vancocin, a non-BCS drug, based data derived from on a few literature citations describing the GI tract of healthy subjects and an abbreviated, 60-day comment period (later expanded to 90 days only after ViroPharma noted that the comment period offered by OGD for the 12/08 Draft Guidance was substantially shorter than comment periods afforded other individual product BE guidances).

C. OGD Misrepresents the Position of FDA's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

OGD claims to rely on the advice of FDA's Advisory Committee for Pharmaceutical Science & Clinical Pharmacology (ACPS) in support of its BE methods for generic copies of Vancocin. In fact, OGD asserts the 2004 ACPS meeting that discussed BE for locally acting GI drugs came to conclusions which the record shows it did not. Moreover, when the ACPS again considered BE issues for locally acting GI drugs in 2008, OGD repeated its mischaracterization of the 2004 meeting, withheld its new data showing Vancocin is not rapidly dissolving, and allowed a generic company to mislead the Committee to believe that there is no clinically significant absorption of vancomycin in Vancocin-treated patients, when in fact Vancocin's labeling contains cautions that absorption can occur. Rather than open scientific discussion with all of the facts on the table, OGD is abusing the FDA Advisory Committee process, and manipulating it to OGD's pre-determined ends.

1. OGD Continues to Misrepresent the Views of the Experts at the 2004 ACPS Meeting

OGD asserts in the 12/08 Draft Guidance that "[t]he [Advisory] Committee [for Pharmaceutical Science and Clinical Pharmacology] concluded that dissolution testing along with PK studies should be acceptable to establish BE for [locally acting GI drugs]."[81] OGD then claims that the 12/08 Draft Guidance is consistent with this "conclusion".

In fact, OGD is mischaracterizing a wide-ranging discussion of general principles for possible BE approaches to locally acting GI drugs as, instead, a concrete Committee

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FDA Advisory Committee for Pharmaceutical Science at 230, 241 & 251 (May 7, 2002), *available at* http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3860T1.pdf.

[80] FDA response to Petition and Petition for Stay of Action assigned Docket No. FDA-2007-P-0418, 6 & n.20 (May 7, 2008) (explaining that the BCS does not apply to locally acting drugs, these must be considered on a case-by-case basis; "[T]he BCS Guidance does not address the bioequivalence criteria for dugs that do not act systemically . . . .").

[81] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 3 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

consensus on a specific BE method for these agents. This is clear from a simple review of the 2004 ACPS meeting transcript of the topic. No Committee "conclusions" are apparent from the transcript. The Committee took no votes. At no point did the Committee endorse a consensus position on anything.

Rather, a handful of Committee members made various statements, asked questions of FDA and each other, engaged in discussion, and identified open questions and areas for further research. At the end, FDA's Ajaz Hussain summarized the discussion. Dr. Hussain mentioned no "conclusions" about particular BE methods. In fact, he did not say the Committee had agreed on anything about locally acting GI drugs.[82]

The 2004 ACPS meeting barely addressed the potential applicability of BCS-based in vitro dissolution for purposes of BE for locally acting GI drugs, and when the concept was raised it was always discussed in the context of rapidly dissolving drugs.[83] Of course, rapid dissolution was specifically identified by OGD in its March 2006 letters as necessary for a finding of bioequivalence to Vancocin using the BCS in vitro dissolution method. Now that OGD's own data confirm Vancocin is not rapidly dissolving, OGD no longer has any basis to claim that the 2004 ACPS discussion somehow laid the groundwork for OGD's 12/08 comparative dissolution method for Vancocin.

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[82] Several weeks after the 2004 ACPS meeting, FDA issued Summary Minutes of the meeting which contained the statement "In conclusion, the Committee agreed it was difficult to reach a consensus, but that in order to prove bioequivalence in vitro dissolution along with pharmacokinetics should be acceptable." Hilda F. Scharen, FDA, Summary Minutes of the October 19-20, 2004 Advisory Committee for Pharmaceutical Science Meeting, 6 (Nov. 16, 2004), *available at* http://www.fda.gov/ohrms/dockets/ac/04/minutes/2004-4078M1.pdf. OGD appears to have paraphrased this statement in the 12/08 Draft Guidance. However, this statement does not alter the underlying transcript of the 2004 ACPS meeting anymore than the 12/08 Draft Guidance can. Both statements are simply unsubstantiated by what the transcript itself says. See Transcript of FDA Advisory Committee for Pharmaceutical Science (Oct. 20, 2004), *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf.

[83] In the background materials for the meeting, FDA hypothesized that "rapidly dissolving GI acting drugs whose delivery to the intestine is limited by gastric emptying. . . . could be covered under a BCS type waiver" and that "application of the scientific basis of the BCS would suggest that a high solubility drug in a rapidly dissolving formulation . . . may be eligible for a biowaiver." FDA, Background Information for Advisory Committee for Pharmaceutical Science October 20, 2004: Bioequivalence Testing for Locally Acting Gastrointestinal Drugs, at 3 n.1, 5 (Oct. 2004), *available at* http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4078B1_07_Bioequivalence-Testing.pdf. At the meeting itself Dr. Amidon mentioned the possibility once (Transcript of FDA Advisory Committee for Pharmaceutical Science at 285-286 (Oct. 20, 2004), *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf) as did FDA's Dr. Robert Lionberger (Transcript of FDA Advisory Committee for Pharmaceutical Science at 318-319 (Oct. 20, 2004), *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf) but no discussion ensued. Near the end of the meeting, FDA's Dr. Hussain said it would be a "significant challenge" to apply BCS I in vitro dissolution to locally acting GI drugs, to which Dr. Morris agreed, after which there was a discussion of whether PK could be measured for BCS III drugs. Transcript of FDA Advisory Committee for Pharmaceutical Science at 332-335 (Oct. 20, 2004), *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf. At no point was it suggested the requirement for rapid dissolution could be ignored.

What was said at the 2004 ACPS meeting supports ViroPharma's contention that more work must be done before the BE method in the 12/08 Draft Guidance can be finalized. For example, Dr. Gordon Amidon, a key figure in the development of the BCS, was asked by FDA to open with a discussion of relevant "Scientific Principles". Dr. Amidon opined that "we need to establish that connection between the in vitro dissolution methodology and the in vivo dissolution process, and I think that is where there is a big gap in our knowledge today, not just for GI drugs, for all drugs."[84, 85]

Dr. Amidon's work has been central to OGD's effort to move toward in vitro dissolution as the means for establishing bioequivalence. ***Importantly, Dr. Amidon's statement post-dates the publications cited in the 12/08 Draft Guidance***. Thus, OGD's invited expert was saying that despite the literature OGD now cites in the 12/08 Draft Guidance there remained a "big gap" before in vitro dissolution could be connected to in vivo dissolution. As the 12/08 Draft Guidance does not reference any later publications that might connect in vitro dissolution with the dissolution of Vancocin in diseased patients, OGD has yet to fill the gap identified by Dr. Amidon – another reason not to finalize the 12/08 method.

Consider also the statement of Committee Chair Arthur Kibbe: "I love in vitro tests if I have control of all the variables, and when I start losing control of the variables, then, I start to get worried about the test."[86] OGD at least asserts that its 12/08 method addresses the variables of pH and transit times, although (as ViroPharma explains elsewhere in this document) OGD gets it wrong by using healthy GI data. However, OGD makes no effort to justify the pH ranges, dissolution media, or fluid volumes in its 12/08 method as biorelevant, despite clear evidence that luminal conditions and contents are substantially different in CDI patients.[87]

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[84] Transcript of FDA Advisory Committee for Pharmaceutical Science at 282 (Oct. 20, 2004) , *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf. Variations on this point are sprinkled throughout Dr. Amidon's remarks. "We talk more about the physiology of [sic] gastrointestinal tract and product disintegration, dissolution, and spreading along the gastrointestinal tract. That is where the investigation is. That is where we need to do more investigation." Id. at 283. "[F]or the in vitro dissolution test, we should cover the range of in vivo variables". Id. at 284-285. "So, I think we should require a dissolution test for bioequivalence in the bioequivalence criteria for acceptance criteria for GI drugs, that we need to consider the pH and time that the drug will spend in the stomach and in the gastrointestinal tract. I can propose those if you want to discuss them." Id. at 287. "So, what you want to do is ensure the two products will dissolve under any of the pH conditions that we would see." Id. at 291-292. Amidon continued "But I believe that a bioequivalence methodology needs to look at reflecting in vivo processes, and we should start with that" and Dr. Morris agreed, stating: "I agree with your premise." Id. at 296-297.

[85] OGD, in its background materials for the 2004 ACPS meeting, at least concurred with Dr. Amidon on the core underlying issue: "[t]he main concern is, of course, how well in vitro dissolution reflects in vivo dissolution." FDA, Background Information for Advisory Committee for Pharmaceutical Science October 20, 2004: Bioequivalence Testing for Locally Acting Gastrointestinal Drugs, 4 (Oct. 2004), *available at* http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4078B1_07_Bioequivalence-Testing.pdf.

[86] Transcript of FDA Advisory Committee for Pharmaceutical Science at 297 (Oct. 20, 2004) , *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf.

[87] Gerding D, "*Clostridium difficile* Infection (CDI): Increasingly Severe and Rapidly Fatal Disease Requires High Certainty of Treatment Efficacy" (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4370s2-05-OPH-Gerding_files/frame.htm.

Dr. Amidon and other Committee members also critiqued established dissolution methodology, and suggested changes. For example, the relevance of fluid volumes typically used in dissolution testing was challenged by Dr. Amidon and Dr. Paul Fackler:

> DR. FACKLER: If I can just make a couple of points. First, I agree about the dissolution and how inappropriate the dissolution we do today is to certainly the way orally absorbed drugs are taken. I can't remember the last time I saw somebody drink 900 milliliters of water with their tablets.
> DR. AMIDON: Or even 250 ml.
> DR. FACKLER: Or even the 240 or 250 that we use in the clinics.[88]

Similarly, Dr. Kenneth Morris raised the issue of whether dissolution apparati are appropriate: "I think there is a fair amount of concern, hydrodynamic at the very least, with the current apparati."[89] These concerns are of particular relevance to Vancocin, as ViroPharma has also explained, because Vancocin patients are typically averse to drinking much liquid and their GI pathophysiology has not been shown to be replicated by available apparati.[90] Moreover, the experience of Mylan Pharmaceuticals Inc. ("Mylan") indicating that there may not be consistent results as between USP apparati I and II when used in vancomycin capsule dissolution studies leaves more important questions unanswered.[91]

OGD's almost reflexive avoidance of the biorelevant media and in vitro-in vivo correlation issues raised by their own experts is disturbing. Has FDA permitted OGD simply to adopt the "expediency" mindset suggested by OGD's Dr. Robert Lionberger at the May 2007 FDA/AAPS Workshop on BE, BCS and Beyond, when he expressed the view that validation of bioequivalence tests that present unusual challenges may not be required due to costs, resource requirements and the unwillingness of generic manufacturers to conduct such studies?[92]

OGD's mischaracterization of the 2004 ACPS meeting is another example of how OGD distorts the views of this FDA Advisory Committee. The 12/08 Draft Guidance first claims (erroneously, as ViroPharma explains above) that "[t]he Committee concluded that dissolution testing along with PK studies should be acceptable to establish BE for [locally acting GI drugs]."[93] Two paragraphs later, OGD invents its own exception to this

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[88] Transcript of FDA Advisory Committee for Pharmaceutical Science at 293 (Oct. 20, 2004), *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf.
[89] Id. at 296.
[90] See discussion above; *June 30, 2006 Filing to PSA, supra* note 14, 38.
[91] Mylan Pharmaceuticals Inc. Comment Filing to Petition for Stay of Approval, June 13, 2008, at 3, Docket No. FDA-2006-P-0007.
[92] Lionberger R, "Critical Path Initiatives: Opportunities for Generic Drug Development", at 9 (May 23, 2007).
[93] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 3 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf. As ViroPharma explains above, in reality the Committee did not endorse this or any other particular "conclusions" at its October 2004 meeting.

supposed rule: PK studies can be dispensed with because vancomycin levels are generally not detectable in plasma.[94] However, one need only review the transcript to confirm that OGD has no basis to claim that the Committee adopted either the rule or this exception.[95] OGD apparently sees no harm in first inventing conclusions the ACPS never adopted, and then brazenly modifying them. One can be forgiven for concluding that the ACPS is not so much a source of advice for OGD, but rather a sort of scientific "cover" for whatever actions OGD wishes to take, however unscientific.

Finally, several Committee members expressed support for the idea, which OGD and ViroPharma both endorse, that BE for locally acting GI drugs requires a case-by-case analysis.[96] However, the 12/08 Draft Guidance uses general data for the specific case of Vancocin. Nor did the 2004 ACPS meeting ever include a discussion of the case of Vancocin.[97] None of the specific differences and uncertainties regarding the GI pathophysiology of patients with CDI or SAE – or the patient risk associated with bioinequivalence – were presented at that Committee meeting. By contrast, the 2004 ACPS discussed at some length drug-specific data regarding the BE of mesalamine products which, unlike Vancocin, are regularly systemically available, permitting pharmacokinetic verification of in vitro BE testing, and are not used to treat acute, life-threatening conditions.

In its attempt to preserve in vitro dissolution testing for generic copies of Vancocin, OGD has taken to repeating material misrepresentations of the proceedings of an FDA Advisory Committee. It is therefore another reason why OGD should be disqualified from further decision-making authority regarding BE method development for Vancocin.

2. OGD Misled and Withheld Data from the ACPS at the July 2008 ACPS Meeting

At the July 2008 ACPS meeting, OGD's Director of Science Dr. Lawrence Yu also repeated the material misrepresentation of the 2004 ACPS meeting in the guise of reminding the Committee of its previous deliberations. Thus the Committee was told it had come to a "conclusion" four years earlier which in fact is not substantiated anywhere in the transcript of the 2004 meeting. This misrepresentation permitted Dr. Yu to characterize the use of in vitro dissolution as a BE method for highly soluble locally acting GI drugs as settled science that required no further discussion.

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[94] Id. at 3.

[95] In addition, as discussed elsewhere in this document, the experts at the 2008 ACPS agreed that in cases where low solubility locally acting GI drugs could be measured in the blood, that should be done just to ensure safety of a generic formulation. There is no reason to think the same general principle should not apply for high solubility locally acting GI drugs as well.

[96] E.g., Transcript of FDA Advisory Committee for Pharmaceutical Science at 277, 289 (Oct. 20, 2004), *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf.

[97] In fact, the only mention of Vancocin occurred when Dr. Yu stated at the 2004 meeting that the BE approach for Vancocin generics was a clinical endpoint study. Transcript of FDA Advisory Committee for Pharmaceutical Science at 274-275 (Oct. 20, 2004), *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T2.pdf.

Moreover, at the time of the July 2008 ACPS meeting Dr. Yu also knew of but did not mention two key issues important to OGD's in vitro BE efforts on Vancocin. First, Dr. Yu did not tell the Committee that OGD had generated data showing its originally proposed March 2006 method was wrong, because it showed Vancocin and certain generic versions are not rapidly dissolving. Second, Dr. Yu did not disclose that OGD was in the process of changing its in vitro BE method for Vancocin generics so that it did not rely on rapid dissolution or the BCS-I waiver and thereby was moving into uncharted waters never contemplated in the 2004 ACPS discussions.

Instead of sharing this with the Committee, Dr. Yu was worse than silent and allowed the Committee to hear a misrepresentation of fact by a generic firm (Akorn) both with respect to absorption from the gut and dissolution rates of Vancocin[98]. ACPS members presumably took Dr. Yu's silence as a tacit acceptance of the validity of Akorn's presentation. At the very least, they would not expect that OGD at that time knew Akorn's presentation was contradicted by OGD's own data and that the thinking being presented by Akorn was, by that point, not OGD's view on the issue.

3. OGD Failed to Disclose to the ACPS, then Itself Ignored a Labeled Vancocin Safety Issue

At the July 2008 ACPS meeting Dr. Yu was also aware of but did not mention ViroPharma's arguments regarding absorption in patients. In its discussion of low solubility locally acting GI drugs and use of in vitro testing the 2008 ACPS agreed that in those cases where the drug could be measured in the blood, that should be done just to ensure safety of a generic formulation. This general principle endorsed by the Committee was ignored by OGD in the 12/08 Draft Guidance, but OGD nonetheless claims that the method in the 12/08 Draft Guidance follows from general principles endorsed by the ACPS.

Thus, OGD cites Vancocin's labeling which states based on a healthy volunteer study that the drug is poorly absorbed and almost nonabsorbed from the healthy gut, and states therefore that "traditional BE studies with pharmacokinetic (PK) measurements are of limited utility".[99] The Vancocin labeling, however, goes on to state that "[c]linically significant serum concentrations have been reported in some patients who have taken multiple oral doses of vancomycin for active *C. difficile*-induced pseudomembranous colitis . . . . Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of vancomycin."[100] Indeed, Vancocin's labeling states categorically that in patients with renal insufficiency and/or colitis, monitoring of serum concentrations may be appropriate, and in patients with underlying renal dysfunction or

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[98] See Transcript of FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology at 91-101 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/cder08.html#PharmScience.

[99] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 3 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

[100] Vancocin capsules, product labeling, precautions section, ViroPharma Incorporated, Jan. 2005. See also *June 30, 2006 Filing to PSA, supra* note 14, 17-20.

those receiving concomitant therapy with an aminoglycoside, "serial monitoring of renal function should be performed".[101] OGD ignores this safety issue entirely.[102]

OGD relies on vancomycin's poor systemic absorption in healthy volunteers as the basis for not measuring in vivo levels of drug. OGD should explain why it believes it can do this without acknowledging or discussing the fact that Vancocin's labeling also cautions that in some patients, systemic absorption occurs to a degree that toxicity may result. In effect, by mischaracterizing the Vancocin labeling language OGD avoids addressing the issue of potential systemic exposure of toxic drug levels in some patients. Instead, OGD uses the mischaracterized labeling as a justification for not requiring blood sampling. This also frees OGD from having to square its position on blood sampling with the recommendation of the July 2008 ACPS that suggested that if any drug enters systemic circulation, blood sampling should be done. OGD must explain why it can ignore the 2008 ACPS recommendation regarding blood sampling yet rely on a 2004 ACPS discussion that, as explained above, did not inform the scientific rationale for OGD's new comparative dissolution BE method for Vancocin.

D. OGD's 12/08 Draft Guidance is Not a Clarification, But a New Method for Which OGD Has Misrepresented the Uncertainty of the Underlying Science

It appears that in 2006 when OGD switched to the use of *in vitro* dissolution testing for Vancocin, the scientific rationale was a simplistic view that assumed that the drug was highly soluble and rapidly dissolving, so it would exhibit "solution-like" behavior at the site of action. This was a hypothesis that was never tested. OGD instead relied on the existing database for rapidly dissolving systemic drugs as evidence that the hypothesis was valid and the method sound. When it became clear that Vancocin was not rapidly dissolving, however, OGD lost the ability to cite the behavior of rapidly dissolving systemic drugs as evidence that the proposed method was correct. Thus, it now has a burden to generate data supporting the new hypothesis underlying the 12/08 methodology.

Instead OGD takes a different path to avoid meeting this burden. After realizing that the model from which it had extrapolated the 2006 Vancocin method was not applicable (since Vancocin is not rapidly dissolving), OGD seems to have embarked on an exercise to justify the assumptions key to the original model (e.g., that the drug would be 'solution-like' when it reached the site of action, defined by OGD as the colon). To do this, OGD selectively picked values for relevant parameters of GI physiology from the literature to build an argument that demonstrates the drug would be in solution before

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[101] Vancocin capsules, product labeling, precautions section, ViroPharma Incorporated, Jan. 2005.
[102] ViroPharma has discussed this issue in previous filings. E.g., ViroPharma Inc., "Vancocin® Bioequivalence (BE): Appropriate Method Development" at 17, 24, 27 (Jan. 7, 2008), *available at* http://www.viropharma.com/About%20Us/~/media/Files/ViropharmaFDAmeeting10708final.ashx. See, e.g., *June 30, 2006 Filing to PSA, supra* note 14, 17-20, 47-48; *May 17, 2007 Filing to PSA, supra* note 14, 8, 10.

reaching the colon. Thus, as discussed above, the 12/08 Draft Guidance only shares handpicked values for these relevant parameters that support OGD's reverse-engineered approach to the issue. Most concerning is that OGD has made a point to ignore the uncertainty associated with these values (and their range of variability) in the literature cited, and the limitations on those data expressed by the study authors in support of their method.

In the 12/08 Draft Guidance, OGD asserts that based on the literature values cited, even though there is no understanding of how different the GI tract of patients receiving the drug might be, there is no reason to assume that the drug would not be dissolved prior to reaching the colon. This assertion – not data – is OGD's basis for establishing the validity of the proposed method. As such, the basis for the new method has changed from relying on a database of rapidly dissolving systemic drugs (always a suspect position) to use of guesswork. The 12/08 Draft Guidance is a "close enough" approach supposition that the drug will be in solution before reaching the target is based on assumptions drawn from inapplicable data.

This is not an evidence-based bioequivalence method but a poorly done risk-assessment based wholly on assumptions drawn from a selective and incomplete review of the literature whose applicability to Vancocin OGD has not established. To date, there is no mechanism that allows for the implementation of a selectively culled literature-based and unvalidated method for establishing bioequivalence of generic drugs. It is inconsistent with how OGD publicly describes the use of science in developing BE methods. OGD has selected Vancocin, an antibiotic that treats an acute, life-threatening infection, as the test case to move bioequivalence standards from evidence-based methods to literature-based risk assessments.

E. OGD's Development of BE Methods for Vancocin Has Been Riddled with Bad Judgment

We have already seen how OGD got it wrong about whether Vancocin rapidly dissolves, a basic physical chemical property of the drug product. This has not been the only glitch in OGD's attempts at vancomycin capsule BE method development. Myriad other errors conclusively demonstrate that OGD has been at least grossly negligent in developing bioequivalence methods for Vancocin.

1. By Its Own Admission, OGD's 2006 BE Method for Generic Copies of Vancocin May Have Put Patients' Safety at Risk

In March 2006, OGD advocated rapid dissolution in laboratory flasks as sufficient for generic drugs to demonstrate bioequivalence to Vancocin. ViroPharma protested, arguing (in part) that OGD had offered no basis to depart from its longstanding approach to require clinical endpoint bioequivalence studies for locally acting drugs like Vancocin as the only method to ensure generics were as safe and effective.

Nearly three years later, OGD now agrees with ViroPharma and has returned to its original policy requiring clinical studies, at least for generic products that do not have the same inactive ingredients in the same quantities as Vancocin. Per OGD, this is because "[i]nactive ingredients in oral formulations may affect the transport of drug through the GI tract and/or the effectiveness of drug at the site of action. To ensure that differences in inactive ingredients will not affect the safety and effectiveness of generic vancomycin HCL oral capsules, [OGD] recommend[s] a BE study with clinical endpoints" for generic drugs that do not have the same inactive ingredients as Vancocin.[103]

It is noteworthy that prior to the Canadian stock analyst's disclosure, OGD had no such concerns about approving generic versions of Vancocin with different inactive ingredients in the absence of clinical endpoint studies. But for the protests of many concerned parties including ViroPharma, patients at acute risk of life or serious injury could today be receiving generic "copies" of Vancocin based on a method OGD now concedes might have affected "the safety and effectiveness of generic vancomycin HCl oral capsules".[104]

2. OGD's New BE Method Does Not Account for *S. Aureus*, Which Can Infect the Entire GI Tract

As discussed above, there can be little confidence in OGD's assumptions about GI transit times and other aspects of the in vivo environment of patients with CDI. Even worse, OGD failed entirely to consider the in vivo conditions in patients afflicted with enterocolitis caused by *Staphylococcus aureus*, the other GI infection for which Vancocin is indicated.

Unlike CDI, SAE involves both the upper and lower GI tract. OGD, however, states that "[v]ancomycin acts locally in the lower gastrointestinal tract".[105] This forms the basis for OGD's assertion that there will be sufficient upper GI transit time for a vancomycin capsule to solubilize "long (e.g., hours) before it reaches the site of action in the lower GI tract".[106] While OGD can claim (unpersuasively, as ViroPharma explained above) that this might be relevant to CDI, OGD has no such claim with regard to SAE which can involve the proximal small intestine.

Had OGD been thinking properly about BE method development for Vancocin or had it been required to consult with infectious disease experts, it would not have based its 12/08 Vancocin BE method so heavily on an assumption which clearly does not apply to enterocolitis caused by *S. aureus*. OGD's oversight of SAE in its thinking points out yet another example of the deficient BE method development effort for Vancocin. As with

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[103] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 3 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.
[104] Id. at 3.
[105] Id. at 2.
[106] Id. at 2.

CDI, proper BE method development for Vancocin must include consideration of the in vivo characteristics of patients suffering from *S. aureus*-associated enterocolitis.

Additionally, OGD's apparent lack of appreciation of SAE underscores the need for FDA to insist on the participation of experts from outside OGD and the Agency to address generally issues related to the risks of antimicrobial resistance when considering bioequivalence criteria for antibiotics that treat severe and life-threatening diseases. As shown by OGD's glaring oversight regarding SAE, OGD simply is not equipped to perform this task. As previously noted by ViroPharma,[107] recommendations to prevent the spread of vancomycin resistance and control vancomycin-intermediate and vancomycin-resistant *S. aureus* (VISA/VRSA) were published by the CDC in 1995 and 1997,[108] respectively. These organisms have recently been identified by the Infectious Diseases Society of America (IDSA) as "problem pathogens."[109] 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 *S. 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.

3. OGD Cannot Decide Whether the BCS Applies to Locally Acting GI Drugs

In OGD's March 2006 letters to the Canadian stock analyst and others, OGD cited the BCS Guidance and said generic Vancocin applicants could seek waivers if they met the conditions specified therein. Similarly, in May 2007 OGD stated that "[b]ased on the BCS, FDA has granted biowaivers for immediate release high solubility drugs that act locally in the GI tract".[110]

However, when discussing the locally acting GI drug acarbose in May 2008, OGD denied that the BCS applied to locally acting drugs at all: "the BCS Guidance does not address the bioequivalence criteria for drugs that do not act systemically (i.e., do not act following absorption into the bloodstream)".[111]

It is disturbing that OGD placed the BCS at the core of its scientific thinking around developing the BE approach to Vancocin, stated publicly it had already used the BCS to

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[107] *June 30, 2006 Filing to PSA, supra* note 14, 14-15.

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

[109] 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.* 42:657-668 (2006).

[110] OGD, *Critical Path Opportunities for Generic Drugs* at 4.3.4 (May 1, 2007), *available at* http://www.fda.gov/oc/initiatives/criticalpath/reports/generic.html.

[111] FDA response to Petition and Petition for Stay of Action assigned Docket No. FDA-2007-P-0418, 6 (May 7, 2008).

permit biowaivers for locally acting GI drugs, and then belatedly recognized that the BCS does not address BE for locally acting drugs like Vancocin. One wonders what became of the BCS-based biowaivers OGD says it granted to locally acting GI drugs. Have they been revoked? Were some (all?) of them for generic versions of Vancocin? Or, having stated in May 2008 that the BCS does not address BE criteria for locally acting drugs, has OGD suddenly changed its mind again? OGD's inconsistency regarding the BCS and locally acting GI drugs underscores once again how OGD does not possess the scientific rigor to develop in vitro BE methods for Vancocin.

4. OGD Disavows Its Own Prior Statements Regarding Vancocin BE Methods

OGD's dissolution study report also offered a hasty post hoc revision of what OGD's March 2006 letters posited as the relevant, established time limit for defining rapid dissolution for Vancocin. OGD now claims there never was such an established time limit: "for site selective dosage forms [apparently a new OGD term for "locally acting"] such as vancomycin hydrochloride, the time limit for 85% dissolution has not been established so far."[112]

In fact, OGD's March 2006 letters did establish such a time limit (85% dissolved in 30 minutes, per the BCS), so presumably OGD will explain the basis for its change of position on this. This apparently data-free change in thinking regarding a critical parameter providing scientific support for the waiver of in vivo BE and the desire by OGD to avoid consulting with experts within FDA (in particular the BCS-BE committee) or outside the Agency suggests that OGD has deliberately avoided any discussion of the scientific issues in any forum where there might be a dissenting viewpoint expressed.

For difficult and complex scientific issues, OGD does not possess the depth and breadth of knowledge to define BE methods without the participation of others from outside of the Office. It is unfortunate that a vigorous discussion of the scientific issues and uncertainties may have been stifled by OGD's misguided belief that consulting with scientific experts outside of OGD only serves to slow the approval of generic drugs and does not add to scientific understanding or appropriate decision-making.

5. OGD's Unannounced Changes to the 12/08 Draft Guidance Highlight Both that It Cannot Agree with Itself on Relevant GI Parameters and Its Desire for Secrecy

OGD also cannot keep its stories straight with respect to the GI parameters of patients who will receive Vancocin or the literature it cites for those parameters. For example, OGD can't make up its mind regarding the pH range it considers physiologically relevant to Vancocin. From one paragraph to the next, the 12/08 Draft Guidance caps the

[112] This statement is made in the Introduction to the Dissolution Study Report attached to the 12/08 Draft Guidance; FDA, *Report to Office of Generic Drugs: Vancomycin Dissolution Study* at 3 (Feb. 5, 2008), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510att2.pdf.

"physiologically relevant" pH range for Vancocin first at 7.5 (paragraph 3) and then at 6.8 (paragraph 4).[113]

OGD's last-minute, unannounced revision of the 12/08 Draft Guidance also evidences both OGD's equivocation regarding basic physiologic parameters that are critical to the 12/08 method, and its penchant for behind-closed-door behavior.[114] Compared to the original, the new version of the 12/08 Draft Guidance currently on FDA's website changes significantly what OGD asserts are the physiologic parameters of the GI tracts of patients who take Vancocin. Thus, the new version claims different pH ranges than the old version; OGD states the new pHs are fasted pHs, whereas the old version did not specify whether its ranges were based on fed or fasted conditions.[115] The new version also states that the physiological fluid volume of the small intestine varies from 500 mL (fasting) to 1000 mL or more (fed).[116] By contrast, the original version said this same parameter could reach much lower – as low as 50 mL – with an upper limit of 1100 mL and an average of 500 mL under fasted conditions.[117] Finally, OGD substantially modified what it asserted is the small intestine transit time, from 199 minutes with a standard deviation of 78 minutes (old version) to 3-4 hours (new version).[118] OGD also changed the literature it cited for these numbers, although, as above, all were based on observations of the healthy GI tract.[119, 120]

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[113] To the extent OGD did conduct dissolution testing at pHs above 6.8, those data should be disclosed.

[114] For weeks after issuance of the 12/08 Draft Guidance, ViroPharma was preparing comments based on what turned out to be a withdrawn version of the Guidance (copy attached at Tab 2), when ViroPharma discovered that a different version had been posted on FDA's website. ViroPharma does not know when this new version was posted, as there does not appear to have been a Federal Register notice acknowledging the revisions. FDA first publicly posted a version of the Draft Vancomycin Guidance on December 15, 2008 in conjunction with the pre-publication notice announcing its availability. Based on a conversation with the FDA Dockets Management Office, it seems the newer version of the draft Guidance may have replaced the original shortly thereafter. However, in the absence of OGD's acknowledgment of the revisions to the original version, the actual timing of the replacement remains unclear. Out of concern that others might continue laboring under the same misimpression as had ViroPharma, ViroPharma has requested that FDA issue a notice announcing that the guidance was changed from the original version, and explaining the basis for the changes. See ViroPharma Inc., Request for New Notice and Explanation Filing to 12/08 Draft Guidance, Feb. 27. 2009, Docket No. FDA-2008-D-0626.

[115] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 n.3 (Dec. 15, 2008); OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 n.3 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

[116] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 n.4 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

[117] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 n.4 (Dec. 15, 2008).

[118] Id. at 2 n.5; OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 2 n.5 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

[119] OGD deleted one literature citation (there were only 2 to begin with) and added two new ones. Id. at 2 nn. 4 & 5. Thus, for example, OGD curiously replaced its more current reference to Dressman JB et al. Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms. *Pharm Res.*15: 11-22 (1998) with a reference 12 years older— Davis S et al. Transit of Pharmaceutical Dosage Forms Through the Small Intestine. *Gut.* 27:886-892, 891 (1986).

It is unsettling that OGD would make unannounced, last-minute changes regarding data fundamental to the bioequivalence recommendation proposed in the 12/08 Draft Guidance. OGD's apparently hasty and disorganized approach calls into question whether the 12/08 Draft Guidance is in fact the result of a well-thought out and fully researched effort or instead a hurried attempt to cherry pick data better-suited to OGD's foreordained conclusion that in vitro dissolution is appropriate for vancomycin capsules—a troubling notion for an Agency ostensibly committed to valid science.

6. OGD's Undisciplined Approach to Vancocin BE Method Development is Further Illustrated by OGD's February 2008 Dissolution Study Report

The February 2008 Dissolution Study Report evidences a number of inconsistencies and errors, including the use of an expired reference material (which risks artificially accelerating dissolution rates), the use of overfilled test products (same problem), and the use of an assay that is not the recognized USP method. This topic is discussed in more detail in Appendix A.

It is hard to have confidence in OGD's science when OGD simply assumes, wrongly, a key physical chemical property of Vancocin, bases its new method on yet another wrong assumption regarding Vancocin's site(s) of action, cannot decide whether or how the BCS applies to drugs like Vancocin, cannot agree even with itself on critical GI parameters of patients with CDI or SAE, and avoided giving patients generics of uncertain safety and effectiveness only by virtue of the fortuitous intervention of a stock analyst from Canada. For a publication that aspires to represent OGD's "current thinking on this topic"[121], the 12/08 Draft Guidance reveals OGD's thinking to be confused, inaccurate, and, consequently, risky. OGD's performance to date should disqualify OGD from leading further BE method development for generic copies of Vancocin.

F. OGD Bad Faith

Besides their failure to inspire confidence, OGD's actions also raise the specter that OGD, despite its status as an office in an agency dedicated to serving the public health, may in this instance be operating in bad faith. This seems clear with regard to OGD's interactions with ViroPharma and the general public, but may also be the case with the representations OGD has made to other parts of FDA.

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[120] For a more detailed discussion of how these literature citations were based on observations of the healthy GI tract, see Section II A 2 above.

[121] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 1 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

For BE methods for generic copies of Vancocin, it seems undisputed that OGD began in bad faith: OGD made no public announcement and hence received no public input when making the significant change in Vancocin BE methods from human studies to in vitro dissolution. Subsequently, OGD chose not to even alert the public of this significant change, but only informed select private parties, some of whom were thus in the possession of material, non-public, market moving information. Moreover, at this point OGD should have, but did not, make public its new in vitro dissolution BE recommendations for generic copies of Vancocin.

Instead, OGD refused to disclose the basis for its new BE recommendations to ViroPharma, the manufacturer of the reference listed drug. (Amazingly, three years later, this refusal continues.) OGD's refusal to disclose forced ViroPharma to ask the Canadian stock analyst and others for copies of their letters in order even to know what new BE method OGD was recommending. Moreover, the Director of OGD's cavalier attitude and a lack of understanding or appreciation of what the drug is used for was shocking to ViroPharma, given the severity of disease with which Vancocin patients are afflicted.

OGD's secrecy also forced ViroPharma to petition FDA in March 2006. OGD has yet to answer ViroPharma's petition. One of ViroPharma's key contentions in the petition was the absence of data to support OGD's new BE method for Vancocin. OGD's Lawrence Yu seemed to answer this with his May 2006 statement that OGD had "science" and "evidence" to support replacing clinical endpoint studies with in vitro dissolution for Vancocin.

But Dr. Yu cited no data. And we now know that at the time Dr. Yu made his statement OGD either had bad data or no data to support its 2006 method. Dr. Yu knew or should have known this, and either way should not have been making public statements claiming that "science" and "evidence" supported OGD's 2006 method. It is hard to imagine a good faith basis for Dr. Yu's statements.

OGD also apparently reassigned its reviewer who initially endorsed the March 2006 method.[122] ViroPharma understands this reassignment occurred because OGD management understood that the March 2006 method was flawed. If so, once again, OGD should have publicly disavowed that method. But it did not.

Similarly, OGD failed to publicly disavow its March 2006 method once it had generated data showing the rapid dissolution assumption key to that method was false. The data should also have led to the granting of ViroPharma's pending citizen petition, but that did not occur. This not only prejudiced ViroPharma, but also FDA counsel, who OGD forced to continue defending an action which OGD had itself already given up on.

By the time FDA met with ViroPharma in January 2008, Lawrence Yu, who was present at the meeting, must have known of OGD's data showing Vancocin is not rapidly dissolving (the final study report is dated less than a month later). Yet when ViroPharma

[122] See Letter from Fahad Habib, counsel to ViroPharma Incorporated, to Michelle Lo, Assistant United States Attorney, 3 (Feb. 26, 2009)(copy attached at Tab 3).

critiqued OGD's March 2006 method and specifically the rapid dissolution assumption on which it was based, Dr. Yu, despite knowing the March 2006 method was flawed, felt no reservations in reassuring the meeting participants that OGD's actions are based on "sound science". One wonders whether Dr. Yu had shared these data with any of the other FDA personnel present at the January 2008 meeting. After all, Helen Winkle (the Director of FDA's Office of Pharmaceutical Science, with direct oversight responsibility for OGD) stated in the meeting that FDA is committed to transparency, but Dr. Yu was being anything but transparent. Did Ms. Winkle know OGD was withholding damaging data when she professed FDA's commitment to transparency?

Despite FDA's professed "commitment to transparency and public process"[123], at the July 2008 ACPS meeting Dr. Yu again failed to disclose OGD's findings that Vancocin is not rapidly dissolving, even when a generic firm (Akorn) gave a presentation suggesting it is. This incident is discussed in greater detail elsewhere in this document, but substantiates once again that OGD has been operating not in good faith, but quite the opposite.

Subsequently, on November 17, 2008, FDA again met with ViroPharma, ostensibly to discuss the scientific issues regarding the March 2006 method. This meeting occurred less than a month before the issuance of the 12/08 Draft Guidance, which included the February 5, 2008 Dissolution Study Report showing Vancocin is not rapidly dissolving. It thus seems unrealistic to claim that none of the FDA personnel present (among them, the Director of OGD) knew of OGD's data showing Vancocin is not rapidly dissolving. Yet no FDA personnel brought it up. How can FDA in good faith call this "transparency"?

While withholding its dissolution data from ViroPharma and the general public, there is strong reason to believe that OGD was sharing its 12/08 comparative dissolution method with at least one generic applicant months before OGD made that method public in December 2008. Generic firm Akorn's comments at the July 2008 ACPS meeting eerily presaged both the comparable dissolution ("And the dissolution profiles in those compartments should be superimposable…the rate and extent of dissolution…should be also similar")[124] and Q1/Q2 ("…if there are a bunch of excipients, they should all match the ethical product…. We go with the Q1, Q2 laws, which is plus/minus 5 percent")[125] components of the as-then unannounced 12/08 Draft Guidance. How could Akorn have known OGD would focus in on precisely both of these standards when it eventually issued the 12/08 Draft Guidance some five months later? The most likely explanation, of course, is that Akorn was tipped off by OGD, just as OGD has tipped off others (e.g., the Canadian stock analyst) about Vancocin BE methods in the past.

How can it be good faith for OGD to selectively disclose its new BE approach to generic applicant(s) months before OGD's public announcement of that approach to the general public? Moreover, how can there be a bona fide public process – where the outcome is

[123] Minutes of Meeting, FDA/ViroPharma Regarding Vancomycin Hydrochloride, Jan. 7, 2008, at 3.
[124] Transcript of FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology at 100 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4370t2-part1.pdf.
[125] Id. at 95.

uncertain and supposedly modifiable by comments received – if OGD and the generic applicants it has tipped are already invested in OGD's new method? How can OGD avoid being biased in this scenario?

The selective disclosure continued. To ViroPharma's great surprise, in the week before the July 23, 2008 ACPS meeting ViroPharma was contacted by yet another stock market analyst, this time from the (since discredited) Stanford Group, who claimed to have spoken with a member of the ACPS about Vancocin. The stock analyst referred to the ACPS member as "our consultant", implying that the ACPS member was being paid by the stock analyst. The ACPS member told the stock analyst that he and other ACPS members disagreed with ViroPharma that clinical endpoint studies are needed to demonstrate bioequivalence to Vancocin, and also indicated disagreement with OGD's in vitro approach for Vancocin bioequivalence. Based largely on what the ACPS member said, the analyst downgraded ViroPharma.

The 12/08 Draft Guidance continues OGD's bad faith approach to Vancocin BE method development. As discussed above, in the 12/08 Draft Guidance OGD continues to twist the 2004 ACPS meeting to its own ends, cherry picks passages from academic papers as superficial support for its scientific theories while ignoring their inapplicability to Vancocin patients, and ignores the advice of its own experts to ensure the in vivo relevance of in vitro conditions used to assess BE. Moreover, without seeing the need to notify anyone, OGD eliminated potentially problematic references and re-released the Draft Guidance. In addition, OGD now acknowledges the existence of but still refuses to disclose the data on which its 2006 method was based, despite ViroPharma's asking for them three years ago and OGD having no problem disclosing in the guidance its more recent vancomycin solubility and dissolution study reports.[126]

On a different note, it strains credulity for OGD to assert that the 12/08 Draft Guidance simply "further clarifies" the March 2006 method, when it in fact: (a) redefines a basic physical chemical property of Vancocin – dissolution rate – which was key to the March 2006 method and which is dropped in the 12/08 Draft Guidance and (b) moves from a reliance on the BCS-1 based biowaiver to reliance on a Q1/Q2 justification for waiving in vivo studies.

The change in sampling times from the March 2006 letters to the 12/08 Draft Guidance (e.g., extending from 40 to 45 minutes), also seems to show that OGD is less interested in making a good faith effort to follow where the science leads than in catering to whatever is easiest for generic applicants. OGD should explain the reason for the sampling time changes, why it believes they were scientifically appropriate, and clarify whether this change was simply to accommodate ANDA applicants, i.e., so they would not have to

[126] "[A]fter obtaining data showing that vancomycin HCl is highly soluble at pH conditions encountered in the GI tract and expected to be in solution long before it reaches the site of action in the lower GI tract, FDA revised its recommendation in early 2006 to include in vitro dissolution studies to demonstrate BE of generic vancomycin HCl oral capsules." OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 3 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

conduct additional dissolution tests. Given all the other evidence of seemingly arbitrary OGD action, this cloud should be dispelled, or if there is underlying intent to mislead, owned up to.

In sum, FDA should have granted ViroPharma's petition when the data showed OGD's March 2006 method – the subject of ViroPharma's petition – would have to be abandoned. Instead, OGD forced ViroPharma and FDA to continue disputing an (unknown to them) abandoned method while it concocted a new, even less scientific approach, which is now the latest method du jour OGD is obligating the rest of FDA to defend. FDA must investigate OGD's conduct in this matter and hold it accountable.

G. Patient Risk of Bioinequivalence Must Be Considered Before In Vitro Dissolution BE Methods Can Be Used to Approve Vancocin Generics

FDA and the World Health Organization have both accepted the need to consider the patient risk of bioinequivalence when considering the waiver of in vivo BE studies.[127] OGD, however, has told ViroPharma that OGD's science is sufficiently rigorous such that the risk to patients of bioinequivalence need not be considered.[128]

In fact, as described above, OGD's science regarding Vancocin BE has been characterized by a general lack of rigor as well as outright mistakes. OGD stated Vancocin dissolves rapidly, but it does not. OGD claims healthy GI physiology applies to Vancocin patients, but the infectious disease and pharmaceutical science experts disagree. OGD proclaims plasma measurements unnecessary based on a healthy volunteer study in Vancocin's labeling, but ignores that same labeling's precaution that toxic levels of vancomycin have been observed in patients.[129] OGD also claims that plasma measurements are unnecessary despite the fact that the July 2008 ACPS experts acknowledged that little is known about the effects of excipients on the rate and extent of absorption, and accordingly the ACPS recommends plasma measurements for locally acting GI drugs to the extent any systemic exposure may occur.

Moreover, the risk of bioinequivalent generic drugs is not merely hypothetical. OGD in the past has approved generic drugs that were not bioequivalent. Bioinequivalent topical corticosteroids (another type of locally acting drug) were on the market for years before

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[127] See ViroPharma Inc, "Vancocin Bioequivalence (BE): Appropriate Method Development" at 16-19 (Jan. 7, 2008), *available at* http://www.viropharma.com/About%20Us/~/media/Files/ViropharmaFDAmeeting10708final.ashx; *May 17, 2007 Filing to PSA*, *supra* note 14, at 9 & nn. 51-52.

[128] OGD's Director of Science, Dr. Lawrence Yu, said this at a meeting with ViroPharma on January 7, 2008. Letter from Thomas Doyle, ViroPharma Inc., to Helen Winkle, Director, Office of Pharmaceutical Science, FDA, 3 (Jan. 30, 2008) (subsequently posted to Docket No. FDA-2006-P-0007 by FDA), available as document FDA-2006-P-0007-0020at Docket No, FDA-2006-P-0007.

[129] Systemic toxicity consequent to oral administration of vancomycin, while uncommon, is nonetheless well-documented and associated with a number of adverse events (e.g., nephrotoxicity, ototoxicity), as ViroPharma documented extensively in an earlier filing. *June 30, 2006 Filing to PSA*, *supra* note 14, at 17-20.

FDA removed them. Indeed, OGD's waiver of the in vivo BE requirement led to the approval of bioinequivalent copies of the locally acting GI drug propanthaline bromide based on in vitro testing.[130] But not until the innovator conducted an in vivo BE study showing the generic versions were not bioequivalent were they removed from the market.[131]

Dissolution as the basis for bioequivalence for generic copies of Vancocin is also suspect based on early work comparing Vancocin solution with Vancocin capsules. An attempt to demonstrate bioequivalence between these formulations failed.[132] Similarly, studies on teicoplanin, an antibiotic in the same class as Vancocin, found significantly different clinical outcomes between equivalent doses of solution and solid oral formulations suggesting that the 'solution-like' hypothesis may not be an appropriate basis for a BE method for Vancocin.[133]

Finally, given the morbidity and mortality associated with CDI and SAE, post-marketing surveillance is unlikely to detect bioinequivalent Vancocin generics. Even if a marketed bioinequivalent generic could be detected after approval, it will not avail patients who die or lose their colons in the interim.

Vancocin treats acute, potentially life-threatening infections. Consequently, it is more important than with most other drugs that Vancocin BE methods ensure that generic versions are truly bioequivalent. OGD should follow the rest of the FDA and the WHO and explicitly consider the patient risk of bioinequivalent generic copies of Vancocin associated with the BE method proposed in the 12/08 Draft Guidance.

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[130] CDER Office of Compliance Annual Report Fiscal Year 1996 Annual Report, 114-116, *available at* http://www.fda.gov/cder/compliance/fy96fin.pdf. This issue was discussed in more detail in ViroPharma's 6/06 filing. *June 30, 2006 Filing to PSA*, *supra* note 14, at 23.

[131] Id.

[132] Lucas RA et al. Disposition of Vancomycin in Healthy Volunteers from Oral Solution and Semi-Solid Matrix Capsules. *J Clin Pharm Ther*. 12: 27-3l (1987). This was discussed in more detail in ViroPharma's 6/06 filing. *June 30, 2006 Filing to PSA*, *supra* note 14, at 30.

[133] Wenisch C et al. Comparison of Vancomycin, Teicoplanin, Metronidazole, and Fusidic Acid for the Treatment of *Clostridium difficile*-associated diarrhea. *Clin Infect Dis*. 22:813-818 (1996); 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*. 36:1292-1296 (1992); 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*. 26:309-316 (1994); *June 30, 2006 Filing to PSA*, *supra* note 14, at 30-31. This was also mentioned by a commenter to the 12/08 Draft Guidance docket, Dr. Marya Zilberberg. Letter from Marya Zilberberg, Adjunct Assistant Professor with the University of Massachusetts School of Public Health and Health Sciences, President and CEO Evi*Med* Research Group, Comment Filing to 12/08 Draft Guidance, Jan. 30, 2009, Docket No. FDA-2008-D-0626, 2.

H. For Vancocin OGD Has Failed to Conduct the Minimum Quantum of Case-by Case, Drug-Specific, Data-Driven Process It Has Accorded Drugs with Substantially Less Patient Risk of Bioinequivalence

OGD has made clear that BE methods for agents that act locally in the GI tract should be developed on a case-by-case basis.[134] ViroPharma concurs. However, in OGD's previous case-by-case development of BE methods for locally acting GI drugs OGD has advanced drug-specific data in support of its proposed methods and sought the advice of outside experts.[135] OGD should do the same for Vancocin. OGD should rescind the 12/08 Draft Guidance and re-propose BE methods for Vancocin after it has developed data adequate to characterize the in vivo GI environment of patients with CDI and SAE and correlated its new method(s) with those data. As described above, ViroPharma has taken the lead in this regard and again offers to collaborate with FDA and provide the data generated from the study being conducted at Temple University as well as collaborate and/or support other efforts directed at the development of a validated and robust method to determine BE for Vancocin.

The contrast between the process OGD has afforded BE development for other locally acting GI agents and Vancocin becomes more stark when one considers that the other drugs, unlike Vancocin, do not treat acute, life-threatening diseases. Rather, they are used for non- life-threatening, chronic conditions such as hypercholesterolemia, diabetes, and mild/moderate inflammatory GI conditions.[136] Bioinequivalence of generic versions of these drugs is less of a risk to patients than the risk of bioinequivalent generic versions of Vancocin, who could die or have their colons removed. Vancocin should therefore receive at least the same quantum of case-specific, data-driven public process OGD has afforded these other agents.

Indeed, OGD required clinical endpoint BE studies for another locally acting GI drug, sucralfate, which also does not treat an acute, life-threatening disease, but rather the chronic pain of gastric/duodenal ulcers.[137] ViroPharma reiterates that OGD should

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[134] Abbreviated New Drug Application Regulations; Final Rule, 57 Fed. Reg. 17950, 17972 (Apr. 28, 1992) ("The preferred method for establishment of bioequivalence, including the need to confirm that drugs not intended to be absorbed are not unintentionally absorbed, is determined on a case-by-case basis, depending on the drug under study."). Examples of this are evident in OGD's approach to bioequivalence methods for other drugs, e.g., cholestyramine, mesalamine, and more recently, acarbose.

[135] ViroPharma has previously discussed this issue at length in various submissions. See, e.g., *May 17, 2007 Filing to PSA*, *supra* note 14, at 4-5; Letter from Thomas Doyle, ViroPharma Inc., to Helen Winkle, Director, Office of Pharmaceutical Science, FDA, 1-2 (Jan. 30, 2008)(subsequently posted to Docket No. FDA-2006-P-0007 by FDA), available as document FDA-2006-P-0007-0020at Docket No, FDA-2006-P-0007.

[136] Questran (cholestyramine for oral suspension USP) is indicated for patients with hypercholesterolemia and partial biliary obstruction. Questran oral suspension product labeling, indications and usage section, Par Pharmaceutical Companies, Inc, May 2006. Precose (acarbose tablets) is indicated for patients with type 2 diabetes mellitus. Precose tablets product labeling, indications and usage section, Bayer HealthCare Pharmaceuticals Inc., Aug. 2008. Colazal (the mesalamine prodrug balsalazide disodium) is indicated for the treatment of mildly to moderately active ulcerative colitis. Colazal capsule product labeling, indications and usage section, Salix Pharmaceuticals, Inc., May 2008.

[137] *June 30, 2006 Filing to PSA*, *supra* note 14, at 44-45; *May 17, 2007 Filing to PSA*, *supra* note 14, at 3-5.

follow the decision made for sucralfate and require clinical BE studies for generic versions of Vancocin as the best course for minimizing patient risk of bioinequivalent generic copies of Vancocin.

In addition, given the agreed need for case-by-case consideration, FDA still needs to consult the advice of outside experts regarding Vancocin BE methods. To date, there is no public indication that this has occurred, and certainly no public meetings have been held. The 2004 ACPS meeting did not discuss the specific case of Vancocin. Thus, OGD's citation to the 2004 ACPS meeting as supporting its 12/08 Draft Guidance is another reason to rescind that Guidance, because without having discussed the specific case of Vancocin, the 2004 meeting does not fulfill the case-by-case standard OGD has stated is necessary for appropriate development of BE methods for locally acting GI drugs. Likewise, the 2008 ACPS panel, despite public presentations mentioning the drug, did not discuss Vancocin.[138, 139] Neither, to ViroPharma's knowledge, has FDA sought publicly the advice of experts at other times, whether from ACPS members or others.

Finally, OGD's superficial development of the 12/08 Draft Guidance for Vancocin makes that method invalid as a matter of law because Vancocin has been treated differently from similarly situated locally acting GI drugs. Agency actions can violate the Administrative Procedure Act if they treat similarly situated parties differently.[140] Thus, in addition to making the 12/08 Draft Guidance scientifically flawed, the lack of case-by-case, drug-specific data-driven development for the 12/08 Draft Guidance makes it arbitrary and capricious, because it is the first time that OGD has developed a BE method for a locally acting GI drug without this quantum of process.

I. OGD's Q1Q2 Standard for Generic Copies of Vancocin is Flawed and Incomplete

1. It is Undisputed that Inactive Ingredients May Affect Product Performance

The 12/08 Draft Guidance recognizes that "[i]nactive ingredients in oral formulations may affect the transport of drug through the GI tract and/or the effectiveness of drug at

[138] Indeed, simply to preserve FDA's scientific integrity, the ACPS members present at the 2008 meeting should be informed of OGD's misleading presentation to them, as well as OGD's failure to disclose to the Committee the problems it knew existed with the data which Akorn presented to the Committee.

[139] Indeed, FDA made quite explicit that the meeting would not discuss specific drugs. See, e.g., Transcript of FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology at 117-118 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4370t2-part1.pdf (recording that Lawrence Yu, OGD's Director for Science stated: "I should emphasize, this morning's discussion on locally acting drugs will be focused on -- in general of bioequivalence -- general bioequivalence of locally acting GI drugs; will not focus on any specific drug or drug product. Again, this morning's discussion will focus on bioequivalence of locally acting GI drugs in general; do [sic] not focus on any specific drug or drug product.").

[140] *May 31, 2006 Filing to PSA*, *supra* note 6, at 13.

the site of action".[141] OGD's Dr. Lawrence Yu expressed the challenging breadth of the issue at the July 2008 ACPS meeting:

> [W]e [are] not aware that there's strong evidence that those excipients have no impact, whatsoever, because…one of the challenges is that there's [sic] so many excipients out there, how do we …conclusively the make [sic] a statement that those excipients will -- will not impact the performance. So this is, indeed, is [sic] a challenge.[142]

OGD therefore proposes in the 12/08 Draft Guidance that in vitro dissolution BE will be allowed for generic copies of Vancocin only if they "are qualitatively (Q1) (i.e., contain *all* of the same inactive ingredients) and qualitatively (Q2) the same as the reference listed drug (RLD) with respect to inactive ingredients".[143]

2. OGD Fails to Establish the Applicability of Q1Q2 to Vancocin

As noted previously by ViroPharma, FDA regulations prior to enactment of Hatch/Waxman provided that BE could be presumed self-evident for locally acting GI drugs, as it was presumed for oral and topical solutions.[144] However, the Hatch/Waxman in vivo BE requirement prompted FDA to remove the self-evident waiver for locally acting GI drugs and instead require case-by-case demonstration of the suitability of waiving in vivo testing.[145]

The Q1/Q2 sameness standard seems to derive from 21 C.F.R. § 320.22(b), which specifies that:

> [I]n vivo bioavailability or bioequivalence [for certain solution products] may be considered self-evident based on other data in the application if the

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[141] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 3 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

[142] Transcript of FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology at 83-84 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4370t2-part1.pdf. See also, e.g. the remarks of ACPS chair Kenneth R. Morris, Ph.D.: "they want to be sure that the formulation changes that are made, in fact, don't affect safety negatively. So in that sense, changes in excipients that might – whether or not these excipients are actually activating transporters or changing membrane permeability, whatever it is, it should be manifest in the PK. And that's the safety issue." Transcript of FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology at 212 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4370t2-part3.pdf.

[143] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 1 (currently posted on FDA's website) (emphasis added), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

[144] July *25, 2008 Filing to PSA*, *supra* note 14, at 4.

[145] Abbreviated New Drug Application Regulations, Final Rule; 57 Fed. Reg. 17950, 17972 (Apr. 28, 1992) ("The preferred method for establishment of bioequivalence, including the need to confirm that drugs not intended to be absorbed are not unintentionally absorbed, is determined on a case-by-case basis, depending on the drug under study."); id.

> product . . . is an *oral solution* . . . and . . . [c]ontains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application; and [c]ontains no inactive ingredient *or other change in formulation* from the drug product that is the subject of the approved full new drug application or abbreviated new drug application . . . that may significantly affect systemic or local availability for products intended to act locally. (emphasis added).

Thus, oral solutions may seek waiver of the requirement of in vivo BE if they can show they are Q1Q2 to a reference oral solution.

In the 12/08 Draft Guidance, OGD seeks to extend the "self-evident" BE approach from oral solutions to vancomycin capsules. Without saying so explicitly, OGD effectively amends the regulatory language to read that the Q1Q2 self-evident biowaiver is available to an oral solution "or any other product that is highly soluble and dissolves into solution before it reaches the site of action." Stating the obvious, Vancocin is not an oral "solution" that is given ***to*** patients, it is an oral capsule that may become a solution ***in*** patients. Even if OGD had unilateral authority to change FDA's regulation (which it does not), this regulatory sleight of hand magnifies the need to ensure that test criteria (solubility, dissolution, etc.) are fully understood and evaluated in the environment in which the capsule is expected to become a solution: ***in patients***.

As ViroPharma explains elsewhere[146], the 12/08 Draft Guidance is fatally undermined because it makes no citation of legal authority. That said, there is only one waiver in FDA's BE regulations permitting an in vitro dissolution BE test for generic applicants seeking to copy Vancocin. It allows FDA to use an in vitro dissolution test instead of an in vivo method to determine BE for generic copies of Vancocin only if the method has, based on "scientific evidence", been "shown to meet an in vitro test that has been correlated with in vivo data".[147] As noted above, OGD effectively seeks to re-write the regulations permitting biowaivers for Q1Q2 oral solutions to include oral capsules that may release drug into solution. We assume OGD resorts to this maneuver because it cannot meet its burden to validate its *in vitro* approach. However, unless and until a notice-and-comment proceeding to modify the regulations to accommodate OGD's new approach has successfully concluded,[148] OGD cannot of its own volition apply the Q1Q2 biowaiver which the regulations only permit for solutions to the approval of generic copies of Vancocin.

[146] See Section II K for further discussion of this.
[147] 21 CFR 320.22(d)(3).
[148] It is of course black letter law that agency regulations can only be changed through notice-and-comment rulemaking. See e.g., *May 31, 2006 Filing to PSA*, *supra* note 6, at 22.

3. OGD Does Not Consider Q3 or Other Potential Changes in Formulation that Might Affect Bioavailability of Vancocin Generics

While OGD de facto rewrites FDA's regulations so as to consider Vancocin capsules as an oral solution product, OGD has conspicuously chosen to focus only on the composition of inactive ingredients, and neglected that the regulation also addresses any "other change in formulation" that could also affect local bioavailability. OGD fails to provide any explanation why, notwithstanding its decision to treat Vancocin capsules like an oral solution, only differences in inactive ingredients and not "any other change in formulation", as the regulation requires, are relevant to establishing BE.

For instance, it has been demonstrated that particle size distribution and other factors may affect BE even where the constituent ingredients are both Q1 and Q2. OGD has therefore begun to discuss a concept of Q3 sameness, referring to structural identity among two products.[149] The concept of Q3 sameness has developed mainly in the context of topical drugs for which standard pharmacokinetic studies are not available. It has not been applied to oral drugs because the significance of any structural differences in oral drug products may be detected and assessed through rate and extent of drug absorption as reflected in PK studies, a BE approach OGD concedes is unavailing in the case of Vancocin. Dr. Yu has stated:

> Where the Q3 concept is especially important is for products that are locally acting and do not have demonstrated in vivo bioequivalence methods such as topical products.[150]

Of course, locally acting GI drug products, like locally acting topical drug products, share the same lack of an in vivo BE method beyond clinical endpoint studies. Consequently, in the absence of assurance that no structural factors besides Q1/Q2 sameness pose any risk of affecting drug performance, such structural parameters must be considered before waiver of the in vivo testing requirement can be permitted for generic versions of Vancocin.

Even in the absence of applying the yet-to-be-fully developed Q3 concept to locally acting GI drugs, 21 C.F.R. § 320.22(b)(3), as noted above, indicates that Q1/Q2 sameness alone is not sufficient to justify an in vivo waiver. An ANDA applicant must also demonstrate that its proposed product does not contain any "other change in formulation" that could affect local bioavailability. ViroPharma has consistently argued that neither the BCS waiver nor any other specified criteria in 21 C.F.R. § 320.22 apply to Vancocin capsules and thus ANDA applicants must conduct clinical endpoint BE studies unless and

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[149] See, e.g., Letter from FDA responding to David Fox, regarding petition originally assigned Docket No. 2003P-0140 and later Docket No. FDA-2003-P-0179 (Nov. 7, 2004), at 9 *available at* http://www.regulationsfda.gov/fdmspublic/component/main?main=DocketDetail&d=FDA-2003-P-0179ohrms/dockets/dailys/03/Nov03/111403/03p-0140-pdn0001-vol1.pdf.

[150] Yu, L. "Research for Generics – Bioequivalence of Topical Products" prepared for ACPS Oct. 21-22, 2003 meeting, at 3 (Sept. 22, 2003), *available at* http://www.fda.gov/ohrms/dockets/ac/03/briefing/3996B1_18_Yu-Bioequiv%20of%20Topical%20Products.pdf.

until an in vitro method can be validated. However, if OGD chooses to treat Vancocin like a solution, OGD should, per the regulation, ensure that a generic product does not contain any other formulation difference that could affect local bioavailability even where Q1/Q2 sameness is assured.

4. FDA Must Ensure OGD Either Enforces Exact Q1/Q2 Sameness or Develops Data to Support Safe Tolerance Limits

The 12/08 Draft Guidance is also problematic because it fails to specify standards for Q1/Q2 sameness.[151] OGD simply requires generic formulations to have "*all*" of the same inactive ingredients as Vancocin.[152] As noted above, OGD concedes the science is uncertain regarding whether different excipients, qualitatively or quantitatively, would impact product performance, and OGD has not advanced any *in vivo* data from patients with CDI or SAE. Without such data it is not possible for OGD to propose any tolerance limits around qualitative and quantitative differences that may be found in the inactive ingredients for generic formulations of Vancocin. In other words, and assuming that OGD's proposed method is ultimately validated, in the face of admittedly uncertain science and the complete absence of data-driven tolerance limits to assess Q1Q2 variations, the generic product must contain *exactly* the same inactive ingredients, in *exactly* the same amounts used to manufacture the RLD. This is the only way to mitigate (to some degree) the risk of suboptimal product performance in the face of the potentially life-threatening disease treated by oral vancomycin.

5. Development of Q1Q2 Tolerance Limits Must be Product and Disease Specific

As described above, OGD's current emphasis on Q1Q2 sameness requires the development of standards to evaluate Q1Q2 variations. To be meaningful, these standards also must be *product-specific* and *disease-specific*, as FDA's expert advisors have explained. For example, in discussing the conduct of PK studies in healthy volunteers, rather than in patients, Dr. Marilyn E. Morris, Ph.D. stated:

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[151] It appears that one of the ANDA applicants assumes that the applicable standard is plus/minus 5 percent similarity in ingredients. Transcript of FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology at 95 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4370t2-part1.pdf (recording Dr. Abu Alam of Akorn, Inc. stating: "…if there are a bunch of excipients, they should all match the ethical product…. We go with the Q1, Q2 laws, which is plus/minus 5 percent...").

[152] "If the test product formulations are qualitatively (Q1) (i.e., contain all of the same inactive ingredients and quantitatively (Q2) the same as the reference listed drug (RLD) with respect to inactive ingredients, bioequivalence (BE) of all capsule strengths may be established based on comparative dissolution." OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 1 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf. In contrast to this Q1/Q2 standard outlined by OGD for vancomycin, OGD has detailed that for acarbose "[a] generic acarbose will be considered Q1/Q2 if (1) the amount of any excipient is no more than ± 5 % different from the corresponding excipient in Precose [, the RLD], and (2) the total weight of the test product tablet is no more than ± 5 % different from the total weight of the Precose tablet." FDA response to Petition and Petition for Stay of Action assigned Docket No. FDA-2007-P-0418, 7 n.7 (May 7, 2008).

> [M]y concern is that it's been shown that certain transporters – for example, in the colon – can be induced with disease. For example, with ulcerative colitis, it's been shown that the peptide transporter pep-T1 (?) [sic] and also monocarboxylate acid transporter MCT-1 can be induced. Therefore, there would be differences in tissue uptake and potentially in absorption.[153]

Dr. Kenneth Morris, the current ACPS chair, has also raised the question of whether inactive ingredients activate transporters or change membrane permeability.[154] These comments underscore the need to closely consider the interplay between the inactive ingredients used in a product and the conditions caused by the disease the product is intended to treat.

Given that little is known about the interaction of excipients with transport or impact on BE in the normal healthy gut, it is difficult to see how in the absence of product-specific data from a validated diseased gut model one could justify any deviation from the RLD formulation. This lack of knowledge as to how the diseased tissue will respond to excipients obligates OGD to begin from the conservative position of clinical demonstration of no effect. This is the main reason biowaivers have yet to gain acceptance in the topical area – no one is willing to guess on how diseased skin will respond to drug or excipient.

6. The "Same" Excipients from Different Manufacturers May Not Be the Same

The Q1/Q2 sameness approach to addressing the unknowns acknowledged by FDA's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology regarding the impact of excipients on product performance is grounded on the proposition that inactive ingredients are always the same, regardless of source or manufacturing process. On what data does OGD base this assumption?

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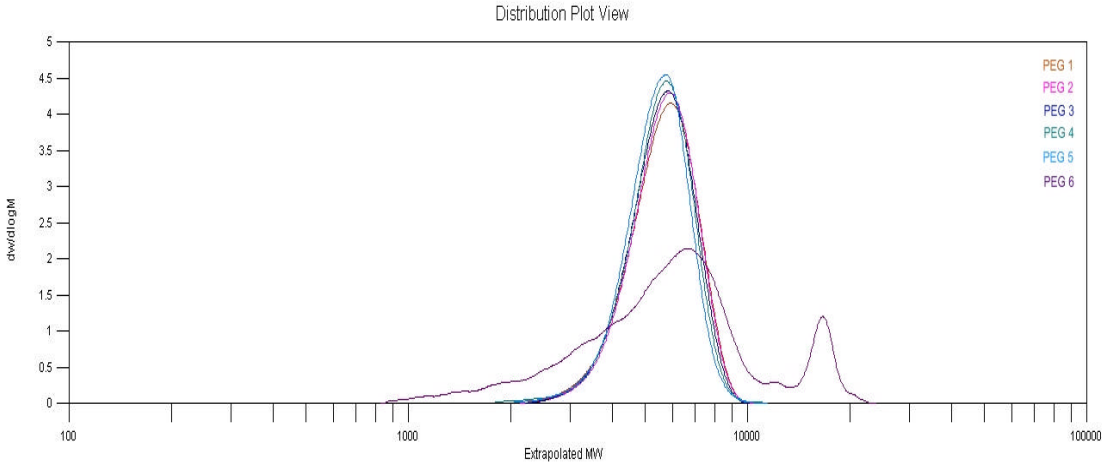
[153] Transcript of FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology at 162 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4370t2-part2.pdf. Later in the discussion, Dr. Marilyn Morris also stated: "Some of the transporters . . . are OPI (?) [sic] regulated in certain GI diseases, such as inflammatory diseases. And some of these haven't been well characterized, like the monocovicylic acid transporters. So I think it's an area that needs to be looked at, because we don't have the data for those types of transporters, and they may be very relevant for some of the drugs that are used to treat GI diseases and important for the gastrointestinal uptake. So that was just the point I wanted to make." To which, Lawrence Yu, OGD's Director of Science replied: "Well, it makes sense. Thank you." Id. at 178-179.

[154] "[T]hey want to be sure that the formulation changes that are made, in fact, don't affect safety negatively. So in a sense, changes in excipients that might – whether or not these excipients are actually activating transporters or changing membrane permeability, whatever it is, it should be manifest in the PK. And that's the safety issue." Transcript of FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology at 212 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4370t2-part3.pdf.

For example, in the case of Vancocin, one inactive ingredient used is polyethylene glycol (PEG). ViroPharma obtained samples of the molecular weight PEG used by ViroPharma from five additional PEG manufacturers, and conducted molecular weight and oligomer distribution analyses on these samples relative to the PEG used in the manufacture of Vancocin. Graphical presentation of the data of the molecular weight profile of all PEGs tested is shown below:



These data demonstrate that samples of PEG of a similar nominal molecule weight are not, in fact, the same. It is unknown what effect these differences might have on the *in-vivo* performance of an oral vancomycin product. This uncertainty is exacerbated in a diseased GI tract such as in CDI where local tissue uptake and interaction at the site of bacterial infection in the colonic mucosa may be compromised and/or (as noted by Dr. Kenneth Morris) absorption may be enhanced resulting in unwanted systemic exposure to drug.

In light of the demonstrated risk that the "same" inactive ingredients produced by different manufacturers are not in fact the same, FDA must require that generic applicants submit comparative analyses showing their inactive ingredients are actually the same as those used in Vancocin.

7. Vancocin Trade Secret Inactive Ingredient Highlights Need for Development of Product Specific Tolerance Limits

There is another inactive ingredient used in formulating Vancocin, which has been kept by ViroPharma as a trade secret. ViroPharma has information that suggests a link between the absence of this particular inactive ingredient to a loss of antibiotic potency. More information is required (1) to conclusively determine the contribution of this inactive ingredient to the potency of Vancocin, and (2) to assess whether alternative inactive ingredients may offer similar benefit, in order to (3) be able to assess whether the absence of this particular inactive ingredient, or the use of an alternative, would "affect the safety or efficacy of the proposed generic drug product."

8. Pure, Unadulterated Drugs Critical for Vancocin Patient Population

Generic drug ingredients are largely sourced from other countries and there recently have been significant problems regarding the quality and purity of these sources. OGD says there can be confidence that generic vancomycin capsules approved based on in vitro dissolution testing will not perform differently than Vancocin because they will have the exact same excipients. However, given OGD's concern that variation in impurities can negatively impact safety and effectiveness of this drug, how will such variation be avoided in the real world where FDA's inspections policy has been shown to be severely lacking? As an acute-use drug that is given to very sick patients, there should be a mechanism in place to assure, each time and every time, that the Q1Q2 formulation parameter is being met.[155]

9. No Self-Exemptions from Q1Q2 Without Safeguards

Directly related to the absence of data-driven tolerance limits for Q1Q2 sameness, it is of significant concern that having stated that Q1Q2 sameness is necessary to ensure safe and effective generic copies of Vancocin, the 12/08 Draft Guidance later says generics can circumvent Q1Q2 sameness. To wit, the 12/08 Draft Guidance provides that generics need not be Q1Q2 if "the ANDA sponsor provides evidence that the differences in excipients will not affect the safety or efficacy of the proposed generic drug product."[156] Even assuming Q1Q2 could one day apply to generic copies of Vancocin, OGD should not permit exceptions to the Q1Q2 requirement without first developing appropriate standards for granting such exceptions, and an appropriate process to ensure those standards are enforced.

In developing its proposal of how to police exceptions to the Q1Q2 requirement, there are a number of factors OGD should consider. First, if no one other than the ANDA applicant and OGD will be privy to the "evidence" (in whatever form that takes) purporting to justify deviation from Q1Q2 sameness, OGD will perpetuate more closed-door bioequivalence method development. As we have seen with OGD's Vancocin BE method work generally, this is a formula for bad decisions. Thus, OGD should propose how to ensure the administration of exceptions to the Q1Q2 requirement will not result in bioinequivalent generic drugs.

The submissions of various generic manufacturers to the 12/08 Draft Guidance illustrate the risks of permitting exceptions to Q1Q2. On one hand, Akorn Inc. endorses the Q1Q2

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[155] In this conjunction, ViroPharma notes that USP specifications are not designed to detect adulteration. Thus, the emphasis placed on USP specifications by some generic manufacturers, including some who have commented on the 12/08 Draft Guidance, is misplaced to the extent it exemplifies a belief that the USP alone is a sufficient standard to ensure product quality.

[156] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 3 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

approach without a self-affirming opt-out exception, but instead believes that if a generic is not Q1Q2 it must demonstrate BE through clinical endpoint studies:

> [Akorn] fully agree[s] with the scientific rationale of the Q1 and Q2 concept for a safe and effective generic formulation of Vancomycin HCl Capsules. We also agree that if the Q1 and Q2 criteria of the generic formulation differ from the RLD, then BE studies with clinical end points will be necessary because different inactive ingredients may alter the transport, permeation, absorption and effectiveness for the local action of vancomycin in CDAD.[157]

On the other hand, several other generic manufacturers ask for various exceptions to the Q1Q2 requirement. Encap, as described above, asks that the Q2 criterion simply be removed or be reduced to "quantitatively similar".

APP, also as mentioned above, seeks permission to use Simulated Gastric Fluid and Simulated Intestinal Fluid instead of the BCS-based dissolution media proposed by OGD.[158] Apparently the gelatin with which APP's vancomycin is encapsulated does not, when dissolved in OGD's specified media, allow APP to show equivalence to Vancocin.

Similarly, back when it was still adhering to its March 2006 rapid dissolution BE method, OGD apparently granted Mylan an exception to the apparatus specified in the March 2006 letters. Thus, Mylan was allowed to conduct its dissolution studies using USP Apparatus II rather than USP Apparatus I,[159] the apparatus specified in OGD's March 2006 letters. Again, presumably Mylan needed this exception because it could not show equivalence to Vancocin using OGD's specified apparatus.

Finally, Wockhardt asks OGD generally to permit "minor" qualitative and quantitative changes as long as they are "not intended" to affect drug transport or the effectiveness of the drug.[160] Wockhardt also contends that the cost of clinical studies for generic manufacturers to demonstrate bioequivalence to Vancocin should be a factor in determining appropriate BE methods for this drug.[161]

The diversity of these comments from different generic companies illustrates the need for further discussion and elucidation of OGD's proposed Q1Q2 standard. One company (Akorn) apparently likes the standard as it is, with no exceptions.[162] The others all

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[157] Akorn, Inc. Comment Filing to 12/08 Draft Guidance, Jan. 22, 2009, Docket No. FDA-2008-D-0626, 3.
[158] APP Pharmaceutical Products, LLC Comment Filing to 12/08 Draft Guidance, Feb. 11, 2009, Docket No. FDA-2008-D-0626, 2.
[159] Mylan Pharmaceuticals Inc. Comment Filing to Petition for Stay of Approval, June 13, 2008, Docket No. FDA-2006-P-0007.
[160] Wockhardt Limited Comment Filing to 12/08 Draft Guidance, Feb. 6, 2009, Docket No. FDA-2008-D-0626, 1.
[161] Id. at 2.
[162] Interestingly, as described above, Akorn appears to have been tipped off months ago about OGD's Q1Q2 approach – before that approach became public. That may explain why Akorn endorses OGD's approach while other generic commenters (who may not have been tipped by OGD) have reservations.

propose different exceptions. This diversity of opinion merits attention from FDA Advisory Committees as well as the general public. Is Q1Q2 appropriate for a biologic-like product such as Vancocin? Which if any exceptions to Q1Q2 sameness should be allowed? What impact would any exception to absolute Q1Q2 identity have in the context of the diseased GI environment? What other scientific standards must these exceptions meet? On what data will these standards be developed? What is their legal basis? What level of public process is necessary to prevent generic applicants from simply "self-affirming" that they meet the exception? If various different exceptions are permitted, will the resulting generics not be bioequivalent to each other?

Because OGD proposes no standards for policing its proposed exception to Q1/Q2 for generic vancomycin capsule applicants, the 12/08 Draft Guidance cannot be finalized. OGD must propose what it believes is the level of evidence needed to permit Q1Q2 deviations and how this evidence will be evaluated. FDA Advisory Committees and the general public must have the opportunity to review and comment on OGD's proposal. Relevant offices from FDA's Office of New Drugs should be consulted.[163] Through this process answers can be found to the important questions posed above.

10. Q1Q2: Conclusion

At present, using Q1Q2 sameness as a component of the determination of bioequivalence for a locally acting GI drug that treats a potentially life-threatening disease remains an interesting but untested, unvalidated hypothesis. However, if OGD is permitted to ignore these properties and grant in vivo BE waivers based on analogizing Vancocin capsules to an oral solution, then in addition to correlating the proposed method with in vivo data as required by FDA's regulations, OGD must propose a standard for ANDA approvals that provides clear direction about how Q1/Q2 sameness is to be demonstrated. At a minimum, this would include:

- Determining whether exceptions to the Q1Q2 requirement can be allowed, and if so, developing appropriate public procedures for review and approval of such exceptions;

- Proposing a process for the open, product-specific, data-driven development of Q1Q2 tolerance limits to address the unique properties of Vancocin, and the uncertainties as to whether different inactive ingredients would impact product performance; and

- Developing the tolerance limits themselves, which should include at a minimum the development of methods to evaluate:

[163] In this conjunction, ViroPharma notes that the Director of OGD recently conceded in Naples Florida that OGD has yet to recruit the internal competence necessary to assess the impact of Q1Q2 changes on safety and effectiveness. Buehler G, "Strategic Initiatives—An Historic Evolution", presentation at the February 23-25, 2009 GPhA Annual Meeting, at 8 (Feb. 25, 2009) (copy attached at Tab 4), Hence, the need for the consult with experts who can make this assessment.

- the effect on product performance of missing, or different, inactive ingredients in the generic copy versus Vancocin;
- the effect on product performance of differences noted between similar inactive ingredients manufactured by different suppliers; and
- how differences in inactive ingredients interrelate with the conditions caused by the disease the product is intended to treat, including the effects of excipients on transporter enzymes in diseased bowels as seen with C. difficile infections.

J. OGD Must Rule Out Risk of BE Fraud with Generic Versions of Vancocin.

OGD recently finalized its regulation requiring submission of failed BE studies, but it only applies to applications submitted on or after July 15, 2009.[164] As such, some applications for generic versions of Vancocin may not be required to submit their failed study data. As ViroPharma explained in 2006,[165] if this requirement is not applied to Vancocin generics OGD will be unable to certify them as bioequivalent to Vancocin.

This concern is particularly germane to Vancocin. As discussed in more detail below, at least two applicants filed ANDA's under the March 2006 "rapid dissolution" approach to bioequivalence. FDA, however, recently confirmed that Vancocin and certain other generic products are not rapidly dissolving. Thus if these ANDA's now contain data that suddenly show that their products are not rapidly dissolving; i.e., possess dissolution profiles that are "comparable" to Vancocin, then these ANDAs are immediately suspect.

ViroPharma notes that the 12/08 Draft Guidance almost invites dissolution "gerrymandering" by not preventing the applicant from cherry picking the 12 generic capsules and the 12 Vancocin capsules with the most favorable dissolution results. This problem is compounded by the relatively low cost of continuing to run dissolution studies until the desired results are obtained. Given the ease with which BE fraud could occur with OGD's in vitro dissolution BE methods, OGD must ensure that all data generated by generic applicants on their to-be-marketed formulations have been submitted to OGD. Otherwise, OGD will be unable to conclude with any reasonable degree of certainty that the generics are in fact bioequivalent to Vancocin.

K. The 12/08 Draft Guidance Must Be Re-Proposed Because It Has No Legal Basis

The 12/08 Draft Guidance offers no legal basis for use of the comparative dissolution BE method it proposes for generic copies of Vancocin. For this additional reason, the 12/08 Draft Guidance cannot be finalized.

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[164] Requirements for Submission of Bioequivalence Data; Final Rule, 74 Fed. Reg. 2849, 2858 (Jan. 16, 2009).

[165] *May 31, 2006 Filing to PSA*, *supra* note 6, at 23-24.

As OGD knows, FDA's BE regulations require an in vivo showing of bioequivalence.[166] However, the 12/08 Draft Guidance proposes an in vitro BE method for Vancocin generics. Consequently, pursuant to FDA's regulations, to be legally valid the 12/08 comparative dissolution method must qualify for a waiver of the in vivo BE requirement. OGD, however, did not proffer any legal basis for the 12/08 Draft Guidance. Thus, before it can be finalized OGD must re-propose the 12/08 Draft Guidance with a legal basis for public review.

Public review of OGD's asserted legal basis for the 12/08 Draft Guidance is critical because OGD has a history of asserting improper legal bases for its bioequivalence methods. For example, ViroPharma has explained elsewhere how the BCS Guidance, the only authority cited in OGD's March 2006 letters, has no valid legal basis.[167] ViroPharma has also explained why OGD cannot rely on the "good cause" waiver in FDA's BE regulations as the legal basis for any in vitro dissolution test for Vancocin generics.[168]

As mentioned above, there is only one waiver in FDA's BE regulations appropriate for an in vitro dissolution test for Vancocin. It allows FDA to use an in vitro dissolution test instead of an in vivo method to determine BE for generic copies of Vancocin only if the method has, based on "scientific evidence", been "shown to meet an in vitro test that has been correlated with in vivo data".[169] Without a demonstration that the 12/08 Draft Guidance somehow complies with this requirement, the guidance has no legal basis and cannot therefore serve to permit generic Vancocin applicants to circumvent the in vivo requirement. Because, as explained above, OGD's 12/08 comparative dissolution method does not meet this burden, it must be rescinded. Moreover, this problem must be remedied if and when OGD re-proposes the 12/08 method with a legal basis.

L. With Clinical Studies, Generic Applicants Can Seek to Demonstrate BE to Vancocin

OGD and a number of generic companies have voiced concerns related to utilizing clinical endpoint studies to determine bioequivalence, stating that they are insensitive, require large numbers of patients, are expensive to conduct and not feasible or even

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[166] ViroPharma discussed the BE regulatory requirements relevant to Vancocin at length in its 7/25/08 filing. *July 25, 3008 Filing to PSA*, *supra* note 14 *passim*. See also *May 31, 2006 Filing to PSA*, *supra* note 6, passim.

[167] *May 31, 2006 Filing to PSA*, *supra* note 6, 16-19.

[168] *May 31, 2006 Filing to PSA*, *supra* note 6, 17-18; *July 25, 3008 Filing to PSA*, *supra* note 14, 10-11. Among other reasons why it does not apply, the "good cause" waiver is only for drugs which will otherwise become unavailable without the waiver, a concern that does not apply to Vancocin, and requires a showing of compatibility with the public health, which would at a minimum require OGD to explain why its science will ensure that inequivalent generics will not exacerbate the current epidemic of CDI and why subpotent generics will not be approved under OGD's test and contribute to microbial resistance to Vancocin.

[169] 21 C.F.R. 320.22(d)(3). See also *July 25, 3008 Filing to PSA*, *supra* note 14 *passim*.

unethical.[170] On the contrary, well-controlled clinical studies are the most relevant and rigorous way to assess relative safety and effectiveness between products and do not need to be large or prohibitively expensive. There are multiple recent and ongoing clinical studies in CDI demonstrating that such studies are feasible. The results of clinical trials for investigational drugs and generic follow-on products (including non-absorbed, locally acting agents) [171] have repeatedly been able to distinguish between active and inactive products and demonstrate that one cannot rely on theoretical, in vitro or even animal data alone to predict clinical outcome in patients with CDI.

Clinical trials remain the gold-standard upon which appropriate patient care is based. In light of the significant morbidity and mortality associated with CDI, the concerns of expert clinicians who care for and treat these patients, and the unavailability of a validated non-clinical BE method, the concerns stated by OGD and generic companies are not accurate and not in the best interest of safe and effective patient care. The prudent path forward at this time that most effectively balances the risk to patients with the desire to provide the most cost-effective care is the continued use of clinical endpoint studies to determine BE for generics versions of Vancocin.

As noted above, clinical studies in CDI are commonplace and are not difficult to conduct. These studies in patients with CDI have typically utilized a primary endpoint of the proportion of subjects in whom diarrhea resolves by the end of the course of therapy, which has resulted in studies involving 200-250 subjects per arm. However, both the FDA Anti-infective review division and SHEA/IDSA recognize that a potential primary clinical endpoint for studies of CDI is time to resolution of diarrhea. Utilizing the same clinical measure (resolution of diarrhea) and analyzing it from the "time to event" perspective (which is currently recommended as the preferred primary endpoint to be used in clinical studies by the SHEA/IDSA draft guidelines for the management of CDI) would:

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[170] At the May 7, 2002 ACPS meeting. Dr. Dale Conner, OGD's Director of the Division of Bioequivalence, spoke of the justifications for the BCS and the fact that "we have a need to decrease or reduce our reliance on in vivo studies as much as possible." Transcript of FDA Advisory Committee for Pharmaceutical Science at 59 (May 7, 2002), *available at* http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3860T1.pdf. Among the reasons Dr. Conner described for this included the time-consuming nature of these studies. Id. at 59-60 (Dr. Conner stating "the more in vivo studies you do, the more the time of drug development is extended and the more time on our part to review those studies as well."). More recently, as stated above, Dr. Robert Lionberger of OGD has expressed that validation of bioequivalence tests that present unusual challenges may not be required due to costs, resource requirements and the unwillingness of generic manufacturers to conduct such studies. Lionberger R, "Critical Path Initiatives: Opportunities for Generic Drug Development", at 9 (May 23, 2007). Further, OGD issued a report in May of 2007 stating "The current method of comparative clinical trials [for assessing bioequivalence for locally acting and targeted delivery products] can be prohibitively expensive and is the least efficient way to detect differences in product performance (as well as being relatively insensitive). . . ." OGD, *Critical Path Opportunities for Generic Drugs* at 4.3 (May 1, 2007), *available at* http://www.fda.gov/oc/initiatives/criticalpath/reports/generic.html. The report also explained that demonstrating bioequivalence for certain drug products "present a challenge for the design of bioequivalence (BE) studies [because, f]or example, [some] drug[s] would require a study in 100 subjects to demonstrate equivalence . . . ." Id. at 4.2.4.

[171] Recent clinical trials in CDI include tolevamer**,** OPT-80, nitazoxanide, ramoplanin and teicoplanin; examples outside of CDI include sucralfate and propantheline.

- decrease the number of subjects required to demonstrate clinical bioequivalence by greater than fifty percent (to less than 100 patients per arm);

- provide the FDA a robust and reproducible endpoint to safely review and approve generic versions of Vancocin; and

- provide concerned clinicians and patients reassurance when they prescribe/receive vancomycin capsules to treat CDI or SAE that regardless of whether the innovator or a generic version is dispensed by the pharmacist that the product should be safe and effective.

This approach provides generic manufacturers a feasible and manageable study that could lead to the approval of their version of oral vancomycin should bioequivalence be demonstrated. Had such a recommendation been made by OGD in March of 2006, generic versions of Vancocin might now be approved and marketed.

M. The 12/08 Draft Guidance Continues OGD's Disregard for American Laws of Open Government and Selective Disclosure of Material Information

Like OGD's March 2006 letters, the 12/08 Draft Guidance is invalid because it is not a notice-and-comment rulemaking under the Administrative Procedure Act. As ViroPharma has previously explained, because a BE study with clinical endpoints in patients was OGD's previous interpretation of its BE regulations[172], that interpretation can only be changed via notice-and-comment rulemaking.[173] The 12/08 Draft Guidance does not comply with this requirement, and is therefore invalid under the APA.

The 12/08 Draft Guidance also appears to have been selectively disclosed by OGD at least as early as July 2008, months before its December 2008 public issuance. The transcript of the July 2008 ACPS meeting makes clear that Dr. Abu Alam of Akorn was alluding to comparable dissolution and Q1Q2 sameness for Akorn's generic vancomycin capsule product.[174] However, at that time OGD had not made public its shift from the

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[172] The 12/08 Draft Guidance confirms this, when it indicates that in 1996 OGD told a prospective generic vancomycin capsule applicant that it would need to conduct clinical endpoint BE studies in patients. OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 3 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

[173] *May 31, 2006 Filing to PSA*, *supra* note 6, 22.

[174] Transcript of FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology at 91-101 (July 23, 2008), *available at* http://www.fda.gov/ohrms/dockets/ac/cder08.html#PharmScience. Dr. Alam presented hypothetical criteria for when in vivo bioequivalence is unnecessary, including reference to Q1, Q2 plus/minus 5 percent, and then explicitly claimed "vancomycin . . . meets those criterion." In addition, Dr. Alam reconfirmed this in Akorn's January 22, 2009 comments on the 12/08 Draft Guidance. Akorn, Inc. Comment Filing to 12/08 Draft Guidance, Jan. 22, 2009, Docket No. FDA-2008-D-0626, 2.

March 2006 method to its new Q1Q2 method. Thus, it seems likely that OGD tipped Akorn about its 12/08 method in the same way it tipped the Canadian stock analyst and others about its March 2006 method.[175] This, for all of the reasons previously explained by ViroPharma, violates the law and FDA's regulations.[176]

N. The 12/08 Guidance Must Comply with the Obama Administration Directives

ViroPharma has consistently explained how OGD's promulgation of new BE recommendations for vancomycin hydrochloride capsules violated basic principles of due process, transparency, accountability, and fair disclosure. The inauguration of President Barack Obama further highlights the defects in OGD's practices because President Obama has taken immediate action to emphasize the importance of government transparency and accountability.

In a January 21, 2009, memorandum to the heads of all agencies and departments, [177] President Obama stated that his administration "is committed to creating an unprecedented level of openness in Government"[178] and emphasized how "[t]ransparency promotes accountability and provides information for citizens about what their Government is doing."[179] President Obama has also indicated that he will not hide information from the public. He explained, "[m]y Administration will take appropriate action, consistent with law and policy, to disclose information rapidly in forms that the public can readily find and use."[180] President Obama understands that public disclosure does not undermine agency action. To the contrary, "[p]ublic engagement enhances the Government's effectiveness and improves the quality of its decisions."[181]

In a second January 21 memorandum,[182] President Obama outlined his administration's approach to Freedom of Information Act requests. President Obama began by stating that "[a] democracy requires accountability, and accountability requires transparency."[183] And he plainly stated that FOIA "is the most prominent expression of a profound

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[175] In addition, a member of the July 2008 ACPS was apparently paid by another stock analyst for inside information about ACPS and FDA views regarding Vancocin BE methods. ViroPharma has previously raised this issue with FDA.
[176] *May 31, 2006 Filing to PSA*, *supra* note 6, *passim*.
[177] President Barack Obama, Memorandum for the Heads of Executive Departments and Agencies Regarding Transparency and Open Government (Jan. 21, 2009), *available at* http://www.whitehouse.gov/the_press_office/TransparencyandOpenGovernment.
[178] *Id.*
[179] *Id.*
[180] *Id.*
[181] *Id.*
[182] President Barack Obama, Memorandum for the Heads of Executive Departments and Agencies Regarding Freedom of Information Act (Jan. 21, 2009), *available at* http://www.whitehouse.gov/the_press_office/FreedomofInformationAct/.
[183] *Id.*

national commitment to ensuring an open Government."[184] The clear guiding principle under the Obama administration is "a presumption in favor of disclosure"[185] and the President directs this presumption to apply to all FOIA-related decisions.

In a more recent March 9, 2009 memorandum,[186] President Obama has emphasized that "[s]cience and the scientific process must inform and guide decisions of [his] Administration."[187] President Obama stated that "[w] hen scientific . . . information is considered in policy decisions, the information should be subject to well-established scientific processes, including peer review where appropriate, and each agency should appropriately and accurately reflect that information in complying with and applying relevant statutory standards".[188] He instructed that "each agency should make available to the public the scientific or technological findings or conclusions considered or relied on in policy decisions".[189]

OGD should be held accountable to the standards of the new Obama administration. As noted above, ViroPharma has reluctantly been forced to sue FDA because, after nearly three years, the Agency continues to withhold information from the public that ViroPharma has requested under FOIA. Furthermore, as also described above, it appears that OGD may have allowed a perceived mandate to expedited generic market entry to take precedence over appropriate scientific development of BE methods. Although FDA has espoused a commitment to transparency and science, OGD has, in the case of Vancocin, clearly failed to live up to FDA's public pronouncements and those of our new President. OGD should, therefore, adhere to the President's demand for a presumption of disclosure of information and enable ViroPharma and the scientific community, once and for all, to evaluate the entirety of the data, process, and science according to which OGD believe its current *in vitro* BE methods are permissible and valid.

Most saliently, OGD should suspend work on the 12/08 Draft Guidance until it has fully disclosed the administrative record of both that document and of OGD's March 2006 method for Vancocin. This not only will fulfill ViroPharma's outstanding FOIA requests for these records, but also comport with President Obama's pledge that his Administration will "disclose information rapidly in forms that the public can readily find and use."[190]

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[184] *Id.*
[185] *Id.*
[186] Memorandum for the Heads of Executive Departments and Agencies, March 9, 2009, *available at* http://www.whitehouse.gov/the_press_office/Memorandum-for-the-Heads-of-Executive-Departments-and-Agencies-3-9-09/.
[187] Id.
[188] Id.
[189] Id.
[190] President Barack Obama, Memorandum for the Heads of Executive Departments and Agencies Regarding Transparency and Open Government (Jan. 21, 2009), *available at* http://www.whitehouse.gov/the_press_office/TransparencyandOpenGovernment.

O. CONCLUSION

The 12/08 Draft Guidance should be rescinded. OGD's actions in this matter have not been scientifically rigorous or in accord with the law. Making categorical statements without ensuring their truth, not sharing pertinent data with Advisory Committee colleagues when circumstances clearly warrant it, and abandoning critical parameters of a well-developed in vitro model when they don't fit the facts of a particular drug are conduct unbecoming science-based regulators of generic drugs. Absent a reform of how it approaches science-based decision-making, OGD should no longer be allowed to lead the bioequivalence method development effort for Vancocin. The 12/08 Draft Guidance should be revoked, and all OGD statements regarding Vancocin reviewed using the highest standards of scientific rigor and evidence. In the words of Senator Arlen Specter:

> Having already committed itself, OGD is unlikely to adjudicate impartially whether it secretly engaged in flawed science. Instead, an impartial review is needed. Once OGD has proposed its new test and comments have been received, the infectious disease specialists at the CDC and FDA's Office of Antimicrobial Drug Products, as well as FDA's Anti-Infective Drugs Advisory Committee and Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, should review OGD's proposal and the comments received. This review should be coordinated by the experts in FDA's Office of Medical Policy, who ultimately would decided [sic] whether to accept, reject, or modify OGD's proposal.[191]

No patients should be exposed to generic drugs approved based on the inadequate science and process OGD has engaged in to date with respect to Vancocin.

III. Even Under OGD's New Method, Existing Vancomycin Capsule Generic Applications Not Approvable

ViroPharma explained above why OGD's new BE method for Vancocin generics is flawed and an insufficient basis on which to approve generic copies of Vancocin. However, it is also the case that even if OGD's new BE method were someday to become valid, additional reasons also prevent approval of generic versions of Vancocin based on that method.

A. Vancocin Trade Secret Inactive Ingredient Prevents Generic Approvals

Even if OGD's new 12/08 comparative dissolution method for Vancocin generics were valid, no generic copies of Vancocin could use it to be approved. This is due to a non-public, trade secret-protected inactive ingredient in Vancocin mentioned above.

[191] Letter from Senator Arlen Specter to FDA Commissioner Andrew von Eschenbach, 2 (Apr. 3, 2007) (copy attached at Tab 5).

The 12/08 comparative dissolution method requires generic products to have the same inactive ingredients as Vancocin (Q1Q2) "unless the ANDA sponsor provides evidence that the differences in excipients will not affect the safety or efficacy of the proposed generic drug product".[192] To have the same inactive ingredients, or to demonstrate that differences in inactive ingredients will not affect safety or efficacy of a generic formulation, a generic firm must first know which inactive ingredients are present in Vancocin (Q1), and in what quantities (Q2). Due to the existence of a Vancocin inactive ingredient that is a nonpublic trade secret, and the fact that OGD only announced its proposed Q1Q2 approach in December 2008, it is highly unlikely that any generic applicant is presently in a position to be Q1Q2 to Vancocin.

In accordance with FDA regulations, when the information regarding Vancocin's trade secret inactive ingredient was submitted to FDA, it was designated as confidential information exempt from disclosure under the Freedom of Information Act.[193] If FDA had received a request for this information, it would have had to notify ViroPharma, who would have had the opportunity object to disclosure of the information if FDA were considering such disclosure.[194]

ViroPharma has received no such notice from FDA. This confirms that the unlikely possibility of a generic applicant making a Freedom of Information Act (FOIA) request for the identity and quantity of a Vancocin inactive ingredient it did not know exists has not occurred.

If a generic applicant were to make a FOIA request for the Q1Q2 details regarding the Vancocin trade secret inactive ingredient, it would take a substantial period of time, as ViroPharma well knows. ViroPharma's March 2006 FOIA request for the administrative record of OGD's March 2006 BE test for Vancocin has yet to be answered. This lengthy delay caused ViroPharma recently to bring suit against FDA in an effort to get FDA's response to the request. The government's response to ViroPharma suit was to ask the judge to make ViroPharma mind the FOIA queue. It obviously would be arbitrary and capricious for FDA to permit a generic company to jump the FOIA queue regarding the Vancocin trade secret inactive ingredient at the same time the government is refusing ViroPharma's three-year old FOIA request for the administrative record of OGD's decision to permit in vitro dissolution BE testing for this agent.

Moreover, until December of 2008, no generic applicant would have had reason to verify Vancocin's inactive ingredients, because OGD's previous approach did not require Q1Q2 sameness. Thus, while on a going forward basis generics may seek to identify and quantitate Vancocin's trade secret inactive ingredient, at present it is extremely unlikely

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[192] OGD, FDA, *Draft Guidance on Vancomycin Hydrochloride*, at 3 (currently posted on FDA's website), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510dft2%20Yu%20Dec.%2015%202008.pdf.

[193] 21 CFR 20.61(d).

[194] 21 CFR 20.61(e).

they have done so. As a result, they are not currently in a position to receive final approvals under OGD's proposed Q1Q2 standard.

B. Data Released in 12/08 Draft Guidance Make Existing ANDAs Not Approvable

To the extent existing applications for generic copies of Vancocin were considered approvable based on OGD's March 2006 rapid dissolution test, they are not approvable now because they contain untrue statements of material fact.

To be approvable under OGD's March 2006 BE method, ANDAs had to demonstrate that both their formulations and Vancocin were rapidly dissolving. However, data submitted by ViroPharma indicate Vancocin is not rapidly dissolving, and OGD's Dissolution Study report says the same thing. Thus, there is a data dispute between the ANDA applicants and OGD.

Because OGD now states that Vancocin is not rapidly dissolving, ANDAs which were approvable under OGD's March 2006 method now contain untrue statements about this material fact regarding both Vancocin and their own formulations. OGD cannot approve ANDAs if they contain an untrue statement of material fact. FFDCA 505(j)(4)(K). Thus, existing vancomycin capsule ANDAs are not approvable.

Nor is it likely these applications will become approvable, because the data are the data and the applicants have represented the data as showing rapid dissolution. Thus, if the same applicants eventually wish to obtain approvals of generic copies of Vancocin, they will need to reformulate and develop formulations that are not rapidly dissolving, and submit those new formulations in new applications for approval.

Perhaps the rapid dissolution shown by all pre-existing generic applicants was the result of their having formulation differences vis-à-vis Vancocin. If so, that is an additional reason why they are not approvable now.

C. FDA Should Audit Existing Vancomycin Capsule ANDA Applicants' Data

It is of more than passing interest that a number of generic applicants were able to show both their vancomycin capsules and Vancocin to be rapidly dissolving.[195] How so many

[195] ViroPharma understands that certain manufacturers filed ANDAs for generic copies of Vancocin in which they purported to demonstrate BE to Vancocin based on FDA's March 2006 rapid dissolution method. At least two such manufacturers have said this publicly. One, as discussed above, is Akorn. Another is Mylan Pharmaceuticals Inc ("Mylan"). Mylan filed a comment to ViroPharma's Vancocin petition in which Mylan stated that it had submitted a vancomycin capsule ANDA containing data showing "Mylan's vancomycin HCl capsules and Vancocin Capsules are rapidly dissolving according to FDA BCS waiver guidelines" contained in FDA's BCS Guidance. Mylan Pharmaceuticals Inc. Comment Filing to Petition for Stay of Approval, June 13, 2008, Docket No. FDA-2006-P-0007, 3. Although OGD's March

applicants could disagree with OGD (who conducted 19 separate dissolution studies) and the RLD manufacturer on this basic physical chemical characteristic of Vancocin is worthy of further investigation by FDA. It seems that generic applicants either uniformly generated bad data, or their applications were made in bad faith. Their applications should be denied, and FDA should investigate how they were able to generate data in direct conflict with OGD's own data.

In addition, FDA should review the data on which OGD made its statement in the March 2006 letters that Vancocin "is rapidly dissolving". Given that OGD has now abandoned this statement, but has never revealed publicly the basis for it, this seems worthy of review. Did these data come from a generic firm? Has FDA gone back and scrubbed them in an effort to understand what went wrong?

To the extent the dissolution profile graphs presented by Akorn at the July 2008 ACPS meeting reflect the data Akorn generated in dissolution studies of its generic oral vancomycin candidate and Vancocin, FDA should also investigate how Akorn got exactly the same dissolution results at the three different pH levels as specified by the BCS-based waiver method. These data seem, quite literally, impossible. Moreover, it does not accord with OGD's and ViroPharma's data sets, which show that as pH rises dissolution slows. That said, the fact that Akorn's Dr. Alam resubmitted this technical information to this docket in January 2009 after having presented them to the July 2008 ACPS meeting would seem to indicate that Dr. Alam does not believe his findings are in error.

Finally, FDA should also investigate whether any generic company received nonpublic information about the 12/08 Draft Guidance before it was publicly released.[196]

IV. OGD's Vancocin Actions Contribute to Rising Tide of Skepticism about Generic Drugs

FDA's leadership has spoken of the Rising Tide of Skepticism among the general public about generic drugs. OGD's data-free, behind-closed-doors approach to Vancocin, where it appears OGD discovered its own mistakes only in response to outside criticism, and where OGD continues to withhold the data for its new bioequivalence approach, would seem to contribute to this skepticism.

ViroPharma, Vancocin's manufacturer, has taken the lead in demanding answers from OGD about Vancocin. However, numerous other individuals and organizations have also asked OGD to explain itself.

2006 letters specified that generics must use USP Apparatus I, Mylan apparently was unable to demonstrate rapid dissolution using that method, and so used Apparatus II. In addition to demonstrating that Mylan's ANDA did not, in fact, meet the method of OGD's March 2006 letters, this more importantly indicates that USP Apparati I and II may not in fact produce the same results when used to dissolve vancomycin capsules.

[196] ViroPharma has already asked FDA to investigate whether a stock analyst received inside information from an ACPS member.

For example, the Infectious Diseases Society of America (IDSA) wrote OGD requesting the opportunity to "review the data upon which the Agency made its decision" to abandon clinical endpoint bioequivalence for Vancocin "before it is used to approve potentially non-equivalent formulations".[197] IDSA expressed concern "that allowing a precedent that excludes a public process could lay the groundwork for future such decision-making on other locally acting anti-infective agents", and stated that "our faith waivers when the Agency makes its decisions behind closed doors rather than through an open data-driven process".[198]

United States Senators have also expressed concern. Senator Specter of Pennsylvania stated his office has been "in contact with FDA on this issue of bioequivalence for a life-saving antibiotic because leading infectious disease experts in my state have expressed concern that FDA did not take appropriate steps to establish this new standard for demonstrating bioequivalence."[199] Senator Hatch of Utah stressed the "need to ensure that FDA is applying high scientific standards and allowing for public input when these standards are developed by the Office of Generic Drugs".[200] Senator Brown of Ohio stated his desire that the Senate "exercise appropriate oversight over FDA and hold the agency, and in this case, the Office of Generic Drugs, accountable for its decisions".[201]

These concerns and those of many others were expressed before OGD's 12/08 decision to change bioequivalence methods for Vancocin. They appear to have been vindicated by OGD's decision to abandon the very bioequivalence method about which the Senators, IDSA, ViroPharma and others had expressed concern. While it is heartening to ViroPharma that it helped prevent the approval of potentially inequivalent generic copies of a life-saving antibiotic like Vancocin, the effort that entailed, as well as the potential that OGD may be engaging in secret science for other drugs (and again for Vancocin itself), suggest the need for systemic change in OGD's approach to these issues.

In fact, Vancocin is not the only locally acting drug for which OGD has abandoned established bioequivalence methods without public explanation, despite OGD's acknowledgement that this is a complex and challenging area of science. For example, OGD approved generic copies of the locally acting anesthetic product EMLA based on an unvalidated BE test OGD adopted in secret over the objections of its own staff and in contradiction to stated OGD policy.[202] OGD now appears to be using the erroneous foundation of its generic EMLA approvals again, as the basis for changing bioequivalence methods behind closed doors for a far more complex locally acting drug, Lidoderm.[203]

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[197] Letter from the Infectious Diseases Society of America to Janet Woodcock, Acting Director, CDER (Nov. 14, 2007) (copy attached at Tab 6).
[198] Id.
[199] "Bioequivalence Standards" Cong. Rec. S5649, S5650 (May 7, 2007) (Statement of Senator Specter).
[200] Id. at S5649 (Statement of Senator Hatch).
[201] Id. at S5649 (Statement of Senator Brown).
[202] ViroPharma has discussed this at greater length in its December 30, 2007 filing. *Dec. 30, 2007 Filing to PSA*, *supra* note 14, 3-4.
[203] Id. at 3-4.

OGD's misadventures with locally acting bioequivalence are joined by other problems, such as the ongoing bioequivalence concerns with epilepsy medications and Wellbutrin XL, the 140 drugs that OGD left on the market despite having "serious questions" about their bioequivalence data, and the scientific integrity of OGD's research and publications.[204] OGD should instead be operating in accord with the Obama Administration's commitment to scientific integrity:

> The public must be able to trust the science and scientific process informing public policy decisions. . . . To the extent permitted by law, there should be transparency in the preparation, identification, and use of scientific and technological information in policymaking.[205]

A better approach for all concerned would be for OGD to release the complete basis – including all data—on which it proposes new bioequivalence methods for locally acting drugs. Especially in light of the skepticism OGD's previous actions have engendered, the public should have an opportunity to review and comment on OGD's entire scientific rationale before OGD uses potentially mistaken approaches to approve generic drugs, as it nearly did once and may try to do again in the case of Vancocin.

V. ViroPharma Willing To Work with FDA on Vancocin Bioequivalence

In its May 1, 2007 "Critical Path Opportunities for Generic Drugs" document, FDA's Office of Generic Drugs identified BE methods for locally acting GI products among a list of Critical Path opportunities "where collaborative activities could advance public health by more efficient development of high quality generic products".[206] Vancocin, of course, is a locally acting GI product.

Moreover, in his February 2009 "Report on Status of Regulatory Science at FDA: Progress, Plans and Challenges", Dr. Frank M. Torti, FDA's Chief Scientist and Acting Commissioner, stated:

> It is neither technically feasible nor economically advisable for FDA to develop research programs and expertise in all areas - FDA must partner with external experts to a greater extent than it currently does. This will be cost effective compared to developing research agendas in all areas and will increase the transparency of regulatory decisions.[207]

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[204] *Dec. 30, 2007 Filing to PSA passim*.

[205] Memorandum for the Heads of Executive Departments and Agencies, March 9, 2009, *available at* http://www.whitehouse.gov/the_press_office/Memorandum-for-the-Heads-of-Executive-Departments-and-Agencies-3-9-09/.

[206] OGD, Critical Path Opportunities for Generic Drugs, May 1, 2007, at 4, *available at* http://www.fda.gov/oc/initiatives/criticalpath/reports/generic.html.

[207] Torti F, FDA's Chief Scientist and Acting Commissioner, "Report on Status of Regulatory Science at FDA: Progress, Plans and Challenges" (Feb. 2009), *available at* http://www.fda.gov/ohrms/dockets/ac/09/briefing/chiefscientistrpt.html.

Dr. Torti further noted that FDA needs to effectively partner with academia, industry and others in areas where their expertise can support and amplify the scientific base that underpins FDA regulatory decisions.

ViroPharma renews its call for a collaborative approach to this scientifically challenging issue. ViroPharma pledges to provide unrestricted financial support for the development of a bioequivalence method that will ensure the approval of safe and effective generic copies of Vancocin. If FDA declines to engage in this collaborative effort, then, at a minimum, FDA should at least consider the results of the ongoing work at Temple University to help further characterize the diseased GI tract of patients with CDI before finalizing any BE guidance that relies in whole or in part on in vitro dissolution.

VI. Next Steps

Based on the above, ViroPharma proposes the following next steps:

First, the 12/08 Draft Guidance should be rescinded, and FDA should announce publicly that the only BE method under which generic copies of Vancocin currently may be approved is a clinical endpoint study.

Second, FDA should answer ViroPharma's FOIA requests for the administrative record of OGD's decisions regarding BE methods for generic copies of Vancocin.

Third, given OGD's documented failure of candor, development of BE methods for generic copies of Vancocin should be discontinued until another FDA office other than OGD has been given lead responsibility for Vancocin BE method development. A new FDA office will start with the presumption of trustworthy conduct and scientific rigor that OGD has now lost.

Fourth, FDA should propose and finalize any new BE method for generic copies of Vancocin pursuant to the procedures for notice-and-comment rulemaking.

Fifth, FDA should consult with outside experts regarding its proposed new BE method(s) for Vancocin, including the Anti-Infective Drugs Advisory Committee, the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology and the Centers for Disease Control and Prevention.

VII. Conclusion

The 12/08 Draft Guidance suffers from multiple flaws, and should be rescinded. For this reason, and because ViroPharma's trade secret inactive ingredient would likely prevent them from meeting the requirements of the 12/08 Draft Guidance method even if that method were validly promulgated, no generic copies of Vancocin are at present approvable based on that method. Given OGD's data showing Vancocin is not rapidly dissolving, existing applications for generic versions of Vancocin are also unapprovable to the extent that they claimed to meet OGD's now-abandoned "rapid dissolution" in vitro test. OGD's mistakes and lack of candor regarding bioequivalence method development for Vancocin disqualify it from leading any further such efforts, add to the Rising Tide of Skepticism About Generics Drugs, and should be reviewed so that FDA may avoid repeating those or similar mistakes in the future. Finally, ViroPharma reiterates its desire to work collaboratively with FDA to develop a rigorous bioequivalence method that will ensure the approval of safe and effective generic versions of Vancocin.

Appendix A

OGD's Dissolution Study Was Poorly Conducted and Unreliable

OGD's unreliable approach to Vancocin bioequivalence efforts is further demonstrated by OGD's Vancocin dissolution study. The report for this study was dated February 5, 2008, but OGD did not release it until December 16, 2008, in conjunction with the 12/08 Draft Guidance.

The purpose of the Dissolution Study was "to determine the dissolution characteristics of oral vancomycin drug products."[208] The introduction to the Dissolution Study notes that "Vancomycin is a locally acting gastrointestinal (GI) drug product . . . . Vancomycin has very low gastrointestinal absorption with low systemic exposure. Therefore an *in vivo* bioequivalence study **is not usually feasible**. Dissolution is an *in vitro* method that can be performed relatively easily . . . . Dissolution under various GI pH conditions **may** provide *in vitro* evidence of its availability for pharmacological action."[209]

As a preliminary matter, but one that underscores OGD's dogged pursuit of the path of least resistance to establish bioequivalence for Vancocin, we note that an *in vivo* bioequivalence study is *entirely* feasible, and that in vivo human testing had been the historical standard for Vancocin bioequivalence until March 2006. We also note that the Dissolution Study report studiously avoids suggesting that dissolution testing for drugs that are locally acting, not systemically absorbed and not rapidly dissolving has been proven to predict bioequivalence. Rather, the Dissolution Report carefully states only that dissolution testing "may" provide evidence of in vitro availability. Nonetheless, OGD continues to promote the use of this unvalidated method to predict bioequivalence.

In addition, there are a number of inconsistencies and errors in the Dissolution Study.

Use of Expired Material

From the outset, the Dissolution Study report fails basic standards of scientific rigor and good laboratory practices. OGD stated that it obtained vancomycin hydrochloride, lot 015K08251, from Sigma-Aldrich to use as a reference standard for calibration of the assay used in its dissolution test (the "Reference Material").[210] ViroPharma obtained the Certificate of Analysis issued by Sigma Aldrich for this Reference Material, which stated it expired on October 30, 2006. The use of expired material as a reference standard raises substantial risk that the potency of the material has degraded. The use of a sub-potent reference standard can serve to artificially inflate dissolution results (i.e., overstate the dissolution rates).

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[208] FDA, *Report to Office of Generic Drugs: Vancomycin Dissolution Study*, 3 (Feb. 5, 2008), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510att2.pdf.
[209] Id. at 3 (emphasis added).
[210] Id. at 6.

ViroPharma considered the possibility that OGD, at some point, re-qualified the Reference Material. The Dissolution Report, however, does not indicate that any re-qualification occurred. ViroPharma also considered the possibility that OGD performed its dissolution analysis before the Reference Material expired. Taken in its best light, this would suggest that OGD's "only" transgression in this regard was keeping secret the results of its dissolution test for over two years. However, we also noted the release and expiration dates for the Vancocin drug products obtained by OGD were as follows:

Lot Used	Release Date	Expiry Date	How Acquired
431233	February 2007	November 2008	Purchased by FDA
429915	September 2006	July 2008	Purchased by FDA
431737	March 2007	January 2009	Supplied by OGD
A200240	June 2006	March 2008	Supplied by OGD

Because half of the lots identified in the Dissolution Study report were not available until after the expiration of the Reference Material, it appears that OGD conducted its tests using an expired Reference Material.

Use of Overfilled Test Products

The Dissolution Study report notes multiple examples of test products demonstrating dissolution release in the range of 109 to 116%.[211] These data suggest that test products used in OGD's analysis had meaningfully high overages in the amount of drug product contained in the formulation. Excess amounts of drug product also will contribute to artificially inflating dissolution results. The use of product overages in this study conflicts with FDA's own Guidance for Industry, Q8 Pharmaceutical Development (May 2006).[212]

Use of Non-Compendial Method

The Dissolution Study report states that "the vancomycin dissolution samples were…then assayed by a validated high pressure liquid chromatographic (hplc) method to determine drug product dissolution characteristics according to the BCS guidance and USP <711>."[213] The Dissolution Study report later states that "[t]he analytical method for vancomycin was developed in house by DPQR."[214] The turbidimetric biological potency analysis, and not HPLC, is the USP method for assessing dissolution characteristics of oral vancomycin. The use of the HPLC method represents a significant change. The use of a non-compendial method is an acceptable practice for the testing of compendial articles if the method is determined to be superior or equivalent to the compendial

[211] Id. at 14.
[212] FDA, CDER, CBER, ICH Guidance for Industry—Q8 Pharmaceutical Development, (May 2006), 8 *available at* http://www.fda.gov/cber/gdlns/ichq8pharm.pdf. Section 2.2.2 of this Guidance provides that: "In general, use of an overage of a drug substance to compensate for degradation during manufacture or a product's shelf life, or to extend shelf life, is discouraged."
[213] FDA, *Report to Office of Generic Drugs: Vancomycin Dissolution Study*, 3 (Feb. 5, 2008), *available at* http://www.fda.gov/Cder/Guidance/bioequivalence/recommendations/8510att2.pdf.
[214] Id. at 9.

method. If the chemical analysis, HPLC, procedure is demonstrably superior to the currently accepted validated turbidimetric biological potency analysis, industry and the public would benefit from any relevant information pertaining to the superiority or equivalence of the HPLC method. ViroPharma is unaware of any such information.