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May 31, 2006

VIA HAND DELIVERY
Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA Docket Number 2006P-0124

Dear FDA,

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

In its petition, ViroPharma indicated that it would subsequently file grounds establishing the bases for its disagreement with OGD's new bioequivalence test. This document is the first of those filings. It sets forth a number of bases demonstrating that OGD's new standard cannot, as a matter of law, be used in the review or approval of vancomycin hydrochloride capsule ANDAs. ViroPharma anticipates filing additional documents, at least one of which will detail how OGD's new standard is unsupported as a matter of science.

In developing these submissions, ViroPharma has been hampered by OGD's refusal to disclose any details regarding its decision to adopt the new *in vitro* test. Consequently, ViroPharma reserves the right to modify and augment its submissions after it has received access to the administrative record of OGD's decision, and a reasonable time to review it.

[1] ViroPharma's petition also sought the same relief regarding applications filed under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act that reference Vancocin. References to "ANDAs" in this document should therefore be read also to refer to applications under section 505(b)(2).

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BACKGROUND

Vancocin® Capsules, a Locally-Acting Gastrointestinal Drug for Treatment of Life-Threatening Disease

Vancocin was first approved in 1986 to treat two serious and life-threatening infections of the gastrointestinal (GI) tract caused by, respectively, the bacteria *Clostridium difficile* and *Staphylococcus aureus*. Most of the use of Vancocin is in patients with *Clostridium difficile*-associated disease (CDAD), for which it is the antibiotic of last resort and remains the only antibiotic approved by FDA for the treatment of this potentially life-threatening condition.

Clostridium difficile is a spore-forming, gram-positive bacillus that produces exotoxins that are pathogenic to humans. CDAD ranges in severity from mild diarrhea to fulminant colitis and death. In recent years, an epidemic, toxigenic strain of *C. difficile* has appeared. It appears to be more virulent than other strains, producing approximately 20 times the level of toxins compared to non-epidemic strains that cause disease. (McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med.* 2005;353:2433-2441.) The hypervirulence of the epidemic strain of *C. difficile* can trigger fulminant disease more quickly (in as little as 2-3 days) than most other strains of the bacterium. On May 12, 2006, FDA, the Centers for Disease Control, and the National Institute for Allergy and Infectious Disease held a public conference to define the research agenda to combat this emerging threat.

Vancomycin hydrochloride was discovered by Eli Lilly and Company ("Lilly"), and first marketed as an intravenous product for systemic infections. However, systemically administered vancomycin does not enter the GI tract, and is therefore ineffective against GI tract infections caused by *C. difficile* or *S. aureus*. Hence, Lilly sought approval of Vancocin capsules, which is an oral dosage form and thus effective against such infections because it releases vancomycin directly into the GI tract. In addition, the vancomycin released by Vancocin capsules stays in the GI tract, because it is poorly absorbed into the bloodstream.

Bloodstream measurements are the standard bioequivalence (BE) test for ANDA copies of pioneer drugs. This is based on the fact that (unlike Vancocin) most drugs are absorbed systemically, and the blood transports the active ingredient to the drug's site of action. Consequently, standard BE tests compare the blood levels of a proposed ANDA drug to the blood levels of the pioneer drug it seeks to copy. If the rate and extent of absorption are the same, resulting in similar blood levels over time, the ANDA product is deemed bioequivalent to the pioneer. If a proposed ANDA product is demonstrated BE to the pioneer and complies with certain other requirements, it can be approved for marketing by FDA's Office of Generic Drugs (OGD).

The Requirement of Clinical Studies

For drugs that act locally, like Vancocin capsules, measurement of levels of the drug in blood are insufficient and inappropriate to establish bioequivalence. FDA has therefore sought to develop alternate methods for generic applicants to demonstrate bioequivalence for such drugs.

There are a number of types of locally acting drugs. For some of them, FDA has issued Guidance documents. Thus, for certain drugs, FDA has issued Guidances indicating that *in vitro* studies can be sufficient. See, e.g., *Draft Guidance, Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* [solution formulations], April 2003; *Interim Guidance, Cholestyramine Powder In Vitro Bioequivalence*, July 1993.

For other drugs, human pharmacodynamic data is required. See, e.g., *Guidance, Topical Dermatologic Corticosteroids: In Vivo Bioequivalence*, June 1995. Finally, FDA has also issued Draft Guidances indicating that human clinical trials should be used to demonstrate bioequivalence to certain locally acting pioneer drugs. See, e.g., *Draft Guidance, Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* [suspension formulations], April 2003. Additionally, for many drugs not covered by a product-specific Guidance document, FDA has required clinical studies to establish BE of the generic version. See, e.g., sucralfate (ANDAs 70-848, 74-415); ammonium lactate (ANDAs 75-570, 75-575); tretinoin (ANDA 75-213). In each case, FDA's recommendation has been that *in vivo* clinical data is necessary to demonstrate bioequivalence to a pioneer drug.

FDA has not issued any specific Guidance regarding BE testing for Vancocin capsules. The Agency has, however, indicated that ANDA applicants seeking to copy Vancocin would need to conduct clinical studies. FDA's general Guidance on BE studies for orally administered drug products indicates that for orally administered drugs that produce their effects by local action in the GI tract:

> "documentation of BE for ANDAs . . . can be achieved using BE studies with clinical efficacy and safety endpoints and/or suitably designed and validated *in vitro* studies, if the latter studies are either reflective of important clinical effects or are more sensitive to changes in product performance compared to a clinical study."

Guidance, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, March 2003, at 20. Thus, either a study with clinical efficacy and safety endpoints, and/or an *in vitro* study that has been validated to correlate with important *in vivo* effects (which correlation could only flow from clinical data) is FDA's general requirement for locally acting GI drugs like Vancocin.

In addition, OGD personnel have stated publicly that clinical endpoint BE studies are generally needed for locally acting drugs like Vancocin. This point was made, e.g., in a

slide presentation at the March 12, 2003, meeting of FDA's Advisory Committee for Pharmaceutical Science by OGD's Associate Director of Medical Affairs, Dena R. Hixon, M.D.

OGD officials have also publicly confirmed that clinical studies are required to demonstrate BE in the specific case of ANDA applicants seeking approval to market copies of Vancocin. At the October 20, 2004, meeting of the Advisory Committee for Pharmaceutical Science, Lawrence X. Yu, Ph.D., OGD's Director for Science, stated that for vancomycin specifically the bioequivalence approach OGD has used is a clinical study. (Meeting transcript at 274-75.) While there was much discussion at this latter meeting, it did not result in any particular recommendations from the Advisory Committee regarding what, other than clinical studies, would be appropriate BE studies for locally acting GI drugs.[2]

OGD's public statements were reinforced by communications that ViroPharma and its consultants had with Agency representatives prior to March 16, 2006, the most recent of which occurred in November 2005. In these discussions, OGD consistently indicated that clinical trials were required for an ANDA drug to demonstrate BE to Vancocin. OGD's representations regarding the requirement of clinical studies to demonstrate BE to Vancocin were a key factor in ViroPharma's decision to acquire Vancocin from Lilly in late 2004.

OGD also had, until its recent decision, consistently communicated to ANDA applicants that clinical trials were OGD's standard for ANDA products to demonstrate BE to Vancocin.

Finally, as recently as February 18, 2006, at the Generic Pharmaceutical Association Annual Meeting, slides presented by OGD's Director, Gary Buehler, indicated that "Bioequivalence of Locally Acting GI Drug" was an ongoing topic of research inside OGD. Thus, as of February 18, 2006, OGD publicly indicated that there was ongoing work regarding BE of locally acting GI drug, but announced no new standard for ANDA applicants to demonstrate bioequivalence to Vancocin or other locally acting GI drugs, or any proposed public process or discussion of such a standard.

OGD Communications Indicating That Clinical Studies Will No Longer Be Required

Less than two weeks later, on March 1, 2006, Mr. Buehler's deputy, Dale P. Conner, Pharm.D., the Director of OGD's Division of Bioequivalence, signed a letter to a Canadian stock analyst at Infinium Capital Corp., indicating that OGD would no longer require *in vivo* studies for ANDA applicants to demonstrate BE to Vancocin. (Copy of letter attached at Tab 1.) According to OGD's letter, in correspondence dated February

[2] FDA's minutes of this meeting do not reflect the Advisory Committee's actual comments, as a comparison with the meeting transcript makes clear. The April 13, 2005 Citizen Petition of Salix Pharmaceuticals (2005P-0146) conducted such an analysis, which documented how FDA's conclusion in the meeting minutes regarding BE requirements for oral locally-acting GI drugs is not supported by what the Advisory Committee members actually said. Salix Citizen Petition (2005P-0146), at 17-20.

3, 2006, Infinium had requested BE recommendations from OGD regarding Vancocin. OGD's March 1 response commented that only dissolution testing would be required:

> "Vancomycin is a highly soluble drug and the reference listed drug (RLD) product [i.e., Vancocin] is rapidly dissolving. Waivers of *in-vivo* bioequivalence testing can be requested in abbreviated new drug applications (ANDAs), provided that the test product is rapidly dissolving at the 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)*."

March 1, 2006, letter from Dale P. Conner, Office of Generic Drugs, to Bernadine Leung, Ph.D., Infinium Capital, at 1.

Six days later, on March 7, 2006, Mr. Buehler signed two additional letters which were virtually identical to OGD's March 1, 2006 letter to Infinium. One of the March 7 letters went to Lazard Capital Markets LLC, the other to a law firm in Boston. Curiously, according to the OGD letters, the Boston law firm had requested information about BE standards for Vancocin on November 4, 2005, and Lazard had made its request on November 22, 2005. (Copies attached at Tab 2.) Why these requests, made earlier in time, were responded to nearly a week after Infinium received a response to its much later request (February 3, 2006) was not explained.

One potential applicant for approval of an ANDA copy of Vancocin, Akorn Inc., also apparently was notified of OGD's decision not to require *in vivo* studies. ViroPharma was informed that in an investor meeting with Akorn on April 24, 2006, Akorn confirmed that OGD had informed Akorn of its lowered BE standards for Vancocin sometime in February 2006. OGD has not explained how this notification can be reconciled with Mr. Buehler's public slideshow on February 18, 2006 indicating that "Bioequivalence of Locally Acting GI Drug" was merely an ongoing topic of research inside OGD, as opposed to something on which OGD had already come to a decision.

<u>Infinium Announces OGD's New Bioequivalence Standard for Vancocin</u>

On March 16, 2006, some two weeks after its letter from OGD describing the lowered BE standard for ANDA copies of Vancocin, Infinium issued a report on ViroPharma entitled "Generics . . . sooner than you think". Infinium's report stated that "Our recent communications with the FDA regarding the approval process for a potential generic competitor to Vancocin lead us to believe a generic could enter the market 1-2 years sooner than current expectations." What "recent communications with FDA" might mean, beyond OGD's March 1, 2006 letter to Infinium, is unclear to ViroPharma.

Infinium's report was the first public disclosure of OGD's new standard. ViroPharma itself had not previously heard that OGD had lowered its BE standard for Vancocin. Nor it would seem, except those to whom OGD had privately communicated, had anyone else.

Infinium's announcement triggered urgent communications from ViroPharma to FDA seeking to learn what in fact had happened. These communications were met in the first instance by silence, then contradictory statements. While ViroPharma eventually received verbal confirmation from OGD that a change in standards had been made, FDA nevertheless refused to supply ViroPharma with copies of FDA's correspondence with Infinium or anyone else on this topic (a refusal that continues to this date). ViroPharma first received copies of the letters sent to Infinium and certain other persons from third parties following the issuance of Infinium's stock market analyst report.

FDA has not publicly disclosed or discussed the OGD letters. The press agency Reuters did conduct an email interview with FDA, in which FDA sent a March 17 email to Reuters stating that "[OGD] has recently revised the bioequivalence recommendations for oral vancomycin from a clinical trial with bioequivalence endpoints to an *in vitro* method involving dissolution testing". Reuters inserted this email in a story that same day (copy attached at Tab 3). Subsequently, on May 2, 2006, Lawrence X. Yu, the OGD official who previously had told FDA's Pharmaceutical Science Advisory Committee that clinical trials were OGD's BE standard for Vancocin, stated that OGD had sufficient scientific evidence to allow for in vitro testing of vancomycin to demonstrate BE. Dr. Yu made this one-sentence statement at the start of his presentation (which did not otherwise discuss Vancocin) in a scientific meeting on The Challenges of Dissolution Testing for the 21st Century held at the Hyatt Regency Crystal City in Arlington, Virginia. Dr. Yu did not seek to explain why or on what basis OGD had abandoned its clinical trials standard and instead adopted *in vitro* dissolution testing as the standard for ANDA applicants seeking to demonstrate BE to Vancocin.

ViroPharma has sought the administrative record of OGD's decision through a Freedom of Information Act request, additional written correspondence, and telephonic inquiries, to no avail. Consequently, ViroPharma hereby reiterates once again its request for the administrative record of OGD's decision to discontinue its requirement of clinical studies or appropriately validated *in vitro* tests for generic applicants to demonstrate BE to Vancocin, including OGD Reference Numbers 05-1400, 05-1435, and 06-0200.

Lacking any understanding of OGD's decision beyond copies of some of OGD's letters obtained from third-party sources, ViroPharma is in no position to specifically address what OGD has done. ViroPharma therefore reserves its rights to respond to OGD's decision once ViroPharma has had a reasonable opportunity to review the full administrative record. However, as described further below, based only on what is publicly known, OGD's decision violates the law and should therefore be rescinded.

OGD'S ACTION VIOLATES THE LAW

OGD's decision to lower the standards for generic copies of Vancocin is plagued by numerous failures to observe the requirements of the law and FDA's own regulations. OGD's multiple violations all lead to one basic outcome: the legal invalidity of OGD's new bioequivalence standard for ANDA copies of Vancocin.

I. The Limited Public Disclosure of OGD's Action Violates the Law

A. OGD's Ongoing Violations of the Freedom of Information Act

The Freedom of Information Act (FOIA) guarantees the American public and American companies access to the records of administrative agencies, subject to certain limited exceptions. 5 U.S.C. § 552. OGD has violated and continues to violate the FOIA in several respects.

First and foremost, until ViroPharma has had a reasonable opportunity to review the administrative record of OGD's decision, no ANDA copies of Vancocin can be approved under OGD's new standard for bioequivalence. OGD's new standard:

"may be relied on, used, or cited as precedent [by FDA against ViroPharma] only if—

> (i) it has been indexed and either made available or published as provided by this paragraph; or
>
> (ii) the party has actual and timely notice of the terms thereof."

5 U.S.C. § 552(a)(2). This provision remedies "the plight of those forced to litigate with agencies on the basis of secret laws or incomplete information". Bannercraft Clothing Co. v. Renegotiation Bd., 466 F.2d 345, 352 (D.C. Cir. 1972), *rev'd on other grounds*, 415 U.S. 1 (1974). FDA has explicitly applied this principle to bioequivalence requirements proposed by the Agency:

> "The Commissioner believes it is inconsistent with due process to issue a proposed bioequivalence requirement on the basis of 'secret data and information' that interested persons can neither see nor comment upon."

Bioequivalence Requirements, Final Rule, 42 Fed. Reg. 1624, 1634 (Jan 7, 1977).[3]

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[3] This quotation comes from the preamble to FDA's bioavailability regulations promulgated in 1977. At that time FDA issued BE "requirements". Today OGD issues BE "recommendations". The Agency may be tempted to respond that its 1977 preamble statement does not apply to OGD's current BE "recommendations" but only applied in the past, to proposed BE "requirements". This is a distinction without a difference. The effect in both situations is the communication *vel non* of what BE standards the Agency considers sufficient to demonstrate bioequivalence for a particular drug. In 1977 FDA thought it inconsistent with due process merely to propose a (non-final) BE "requirement" "on the basis of 'secret data and information' that interested persons can neither see nor comment upon". How then could FDA not also find a due process violation when a final BE "recommendation" is made based on similarly 'secret

Although ViroPharma has asked, it has not been allowed to see or comment on any data or information regarding OGD's proposed BE standard for ANDA copies of Vancocin. OGD has neither indexed its decision to lower BE standards for ANDA versions of Vancocin, nor given ViroPharma actual or timely notice of its terms. What little ViroPharma knows comes from the OGD letters ViroPharma has obtained from third party sources. Those letters, however, do not contain the terms of OGD's decision or any data or information which may support it. They merely notify recipients of how to comply with OGD's new approach by describing how to conduct *in vitro* testing, with no explanation or justification for this new *in vitro* approach. OGD's decision that *in vivo* clinical trials are no longer necessary is not included in the letters, nor do the letters contain any reasoning, data, or information on which that decision might have been based.

In sum, until either OGD's decision and its associated administrative record have been indexed and made available or published, or ViroPharma has had actual and timely notice of the terms thereof, 5 U.S.C. § 552(a)(2) precludes OGD from using its new standard against ViroPharma in the approval of ANDA copies of Vancocin.

Second, OGD's failure to respond also violates the legal deadlines for action on FOIA requests. FOIA requires administrative agencies to determine whether to comply with a FOIA request and to notify the requester within 20 days (excluding weekends and legal holidays) of the agency's determination, including any reasons why any records will be denied. 5 U.S.C. § 552(a)(6)(A)(i); 21 C.F.R. § 20.41(b). These time limits may be extended in unusual circumstances by written notice to the requester setting forth the unusual circumstances for such extension and the date on which a determination is expected to be made. 5 U.S.C. § 552(a)(6)(B)(i); 21 C.F.R. § 20.41(b)(3)(i)(A). Such extension cannot be for more than ten working days, unless the agency notifies the requester, explains that the timeframe cannot be met, and offers the requester an opportunity to arrange an alternate timeframe or narrow the scope of the request. 5 U.S.C. § 552(a)(6)(B)(i)-(ii); 21 C.F.R. § 20.41(b)(3)(i)(B).

OGD has not complied with any of these provisions. ViroPharma's FOIA request was delivered more than two months ago, on March 21, 2006. To date, the only response ViroPharma has received is a letter acknowledging receipt of our request. (Copies of request and acknowledgement attached at Tab 4.) OGD has not notified ViroPharma of its determination of whether to comply with our request, which it should have done within twenty working days. ViroPharma has received no written communication asserting any unusual circumstances for an extension of this timeframe. Nor has OGD asked ViroPharma to agree to an alternate timeframe or to narrow the scope of its request.

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data and information' today? Put another way, FDA previously thought it necessary to make public the data and information on which a proposed BE standard was based, thus permitting public notice and comment from the outset of the process of developing a new BE standard. Today, OGD refuses to release any data or information about a BE standard already adopted. Can it be the Agency's position that since 1977 the law of due process has actually changed that much?

OGD's ongoing refusal to comply with the Freedom of Information Act is, of course, grounds for immediate review in federal district court. 5 U.S.C. § 552(a)(4)(B). Moreover, OGD's ongoing refusal to reveal anything about its decision to lower BE standards for Vancocin naturally leads to questions about the quality of that decision. As outlined above, BE standards for other locally acting drugs have not been secretly developed and secretly applied, but rather have been the subject of open public discussion and scientific interaction. To assuage concerns about the scientific and legal validity of OGD's decision, and to comply with the law, OGD should immediately release the administrative record in this case.

B. OGD's Actions Violate the Data Quality Act

Pursuant to the Data Quality Act (Pub. L. No. 106-554, § 515 Appendix C, 114 Stat. 2763A-153 (2000)), certain Federal agencies must "issue guidelines ensuring and maximizing the quality, objectivity, utility, and integrity of information" that they disseminate. Id., § 515(b)(2)(A). To comply with this law, the Department of Health and Human Services (HHS) issued *HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public*, October 1, 2002. These guidelines contain specific provisions regarding information disseminated by FDA, one of the agencies within HHS. Id. at F. They provide that:

> "Information dissemination is an important part of [FDA's] mission to promote and protect the public health. FDA recognizes that public access to high quality information is critical to achieving this mission and public input, in turn, improves the quality of the information we disseminate."

Id. at F.II. The guidelines go on to state that:

> "Transparency is one of the Agency's key goals. It is critical that our audience understand what we do, how we do what we do, and why we do something."

Id. at F.IV.

The guidelines apply to "new substantive information not covered by previous information dissemination" and to oral presentations in public forums. Id. at F.II and F.IV. FDA's email interview with Reuters disseminated new substantive information not previously disseminated – the change in OGD's BE standard for vancomycin.[4] Dr. Yu's public statement at the scientific meeting also disseminated new information – his claim (unsubstantiated) that OGD had sufficient scientific evidence to allow for *in vitro* testing of vancomycin to demonstrate BE.

These disseminations announced OGD's decision and asserted a scientific basis for it, but did not give the "public access to high quality information" to back them up. They were

[4] Unless, of course, FDA takes the position that the new information was actually disseminated in OGD's letters. Those letters, however, also failed to comply with the guidelines, as the discussion in this section demonstrates.

opaque rather than transparent, furnishing no information to help the audience understand what scientific work OGD had done, how OGD had conducted that work, or why OGD felt that the science it had generated justified the *in vitro* dissolution test mentioned in OGD's letters. The HHS Guidelines have therefore failed to ensure or maximize "the quality, objectivity, utility, and integrity of information" disseminated by FDA, in violation of the Data Quality Act. (Pub. L. No. 106-554, § 515(b)(2)(A), Appendix C, 114 Stat. 2763A-153 (2000)).

The FDA information quality guidelines further require that special quality standards be utilized when the information FDA disseminates is considered influential. "Influential information" is defined as "information that results from or is used in support of agency actions that are expected to have an annual effect on the economy of $100 million or more or will adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local or tribal governments or communities." Id. at F.VII.A.

OGD's decision and any information OGD relied upon in support of the modification of the BE requirements for vancomycin capsules meet the criteria for influential information. Given the size of the vancomycin capsule market, OGD's decision will have an annual effect on the economy of more than $100 million. Moreover, OGD's decision materially threatens public health and safety, because it risks approval of vancomycin capsules that are not equivalent to Vancocin (as forthcoming submissions by ViroPharma will make clear) and because cheaply priced, potentially inequivalent copies will exacerbate inappropriate use and microbial resistance concerns associated with this drug.

Higher standards of transparency apply to influential information to ensure that third parties may accurately reproduce the information and reach the same conclusion. Id. at F.VII.B. "Our [FDA's] goal is to provide a clear explanation of the assumptions and data upon which we base our conclusions, the criteria used to determine the suitability of the data for use, the methods used in our analysis, and the conclusions we have drawn." Id. To ensure such transparency, the guidelines require the process for generating influential information to be "participatory", e.g., incorporating public comment and the submission of scientific data and information from stakeholders that can be used in preparing the information. Id. Additionally, the guidelines state that FDA, as appropriate, will solicit the advice and opinions of advisory committees as well as peer review from experts within and outside the agency. Id.

FDA's one sentence email to Reuters and Dr. Yu's one sentence statement at the scientific meeting clearly fail to meet FDA's higher standards for influential information. These two short, conclusory statements are not accurately reproducible by third parties, do not explain OGD's assumptions, data, criteria for data suitability, or analytic methods, and come after OGD's action which involved no participatory public process. Thus, on this second count OGD has again violated the Data Quality Act by failing to ensure or maximize "the quality, objectivity, utility, and integrity of information" it has disseminated.

FDA's conclusory disseminations of OGD's lowered BE standard for ANDA copies of Vancocin violate the Data Quality Act. This also renders them "not in accordance with law", and their cavalier brevity was arbitrary, capricious, and an abuse of discretion. 5 U.S.C. § 706(2)(A). They must therefore be set aside. Id.

C. OGD's Public Pronouncements Violate the Good Guidance Law and Implementing Regulations

The Reuters email and Dr. Yu's public statement at the scientific meeting also violated the Good Guidance Practices law and implementing regulations by communicating new and different regulatory expectations regarding BE standards for ANDA copies of Vancocin without adhering to Good Guidance Practices (GGPs).

The Federal Food, Drug, and Cosmetic Act (FFDCA) requires FDA to observe certain good guidance practices. 21 U.S.C. § 371(h). FDA has implemented this provision with regulations codified at 21 C.F.R. § 10.115. As an office within FDA, OGD must follow these GGP regulations. Mine Reclamation Corp. v. FERC, 30 F.3d 1519, 1524 (D.C. Cir. 1994) (it is a "well-settled rule that an agency's failure to follow its own regulations is fatal to the deviant action."); Brock v. Cathedral Bluffs Shale Oil Co., 796 F.2d 533, 536 (D.C. Cir. 1986) ("It is axiomatic that an agency adhere to its own regulations").

The GGP regulations provide that OGD:

> "may not use documents or other means of communication that are excluded from the definition of guidance document to informally communicate new or different regulatory expectations to a broad public audience for the first time. These GGP's must be followed whenever regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad public audience." 21 C.F.R. § 10.115(e).

OGD's actions here communicated "new or different regulatory expectations" that were "not readily apparent from the statute or regulation". Nothing in FDA's statute or regulations makes readily apparent that OGD's regulatory expectation for BE testing of would-be ANDA copies of Vancocin is the dissolution test outlined in OGD's letters. On the contrary, as explained above, the regulatory expectation OGD had communicated prior to its recent decision was that clinical testing would be required.

Were any needed, FDA's March 17 email response to Reuters supplied confirmation that the settled regulatory expectation had been that clinical trials were the standard for ANDA copies to demonstrate bioequivalence to Vancocin. FDA's email also communicated that OGD had abandoned clinical trials in favor of a new and different regulatory expectation:

"[OGD] has recently revised the bioequivalence recommendations for oral vancomycin from a clinical trial with bioequivalence endpoints to an *in vitro* method involving dissolution testing".[5]

Media interviews such as this obviously reach a "broad public audience". OGD's communication with Infinium did as well. However, FDA's GGP regulations explicitly state that "Guidance documents do not include . . . media interviews, press materials, . . . or other communications directed to individual persons or firms." 21 CFR § 10.115(b)(3). Because FDA "may not use documents or other means of communication that are excluded from the definition of guidance document to informally communicate new or different regulatory expectations to a broad public audience for the first time", the Agency has violated its own regulations. 21 C.F.R. § 10.115(e). Accordingly, OGD's new lowered BE standard for ANDA copies of Vancocin is invalid and must be set aside.

D. OGD's Actions Violate the Administrative Procedure Act

The law and FDA's regulations require ANDA applicants to submit evidence that their proposed products are BE to the innovator compound they claim to copy. 21 U.S.C. § 355(j)(2)(A)(iv); 21 C.F.R. § 314.94(a)(7). As above, the interpretation OGD had given to these regulations in the case of vancomycin hydrochloride capsules was to indicate that ANDA applicants should submit clinical data to demonstrate BE to Vancocin. The Agency has recently publicly confirmed that OGD has changed this interpretation by indicating that a different standard, *in vitro* dissolution testing, can be used by ANDA applicants to demonstrate BE to Vancocin. However, OGD has neither explained the abandonment of its previous clinical trial standard, nor the adoption of its new *in vitro* dissolution standard. Moreover, OGD selectively disclosed its decision to a limited number of persons and provided those persons with an informational advantage.

i. OGD Has Provided No Rationale for its Decision

Agencies that fail to explain their actions violate the Administrative Procedure Act's admonition against arbitrary and capricious conduct. 5 U.S.C. § 706(2)(A). "It is well established that an agency's action must be upheld, if at all, on the basis articulated by the agency itself." Motor Vehicle Mfrs. Ass'n v. State Farm Mutual Automobile Ins. Co., 463 U.S. 29, 50 (1983). Here, OGD merely stated that it had come to certain regulatory conclusions (that *in vitro* studies were sufficient, and OGD had a scientific basis for them) but made no explanation of how it reached those conclusions. "The requirement that agency action not be arbitrary or capricious includes a requirement that the agency adequately explain its result." Public Citizen, Inc. v. FAA, 988 F.2d 186, 197 (D.C. Cir. 1993). See also, e.g., A.L. Pharma, Inc. v. Shalala, 62 F.3d 1484, 1491 (D.C. Cir. 1995) ("an agency must cogently explain why it has exercised its discretion in a given manner") (quoting State Farm, 463 U.S. at 48)). Consequently, OGD's new dissolution test is invalid. See, e.g., Drug Plastics & Glass Co. v. NLRB, 44 F.3d 1017, 1022 (D.C. Cir. 1995) (agency failure to explain departure from precedent resulted in invalidated agency action).

[5] Copy of Reuters story quoting this email attached at Tab 3.

OGD has not explained its departure from clinical trials to *in vitro* dissolution testing. This failure invalidates OGD's action.

ii. OGD Individual Disclosures Provided Selected Persons with an Informational Advantage

Agency actions that treat similarly situated persons differently, or that fail to consider an important factor, are arbitrary and capricious. 5 U.S.C. § 706(2)(A); D&F Afonso Realty Trust v. Garvey, 216 F.3d 1191, 1195 (D.C. Cir. 2000) ("[W]e must strike down agency action if the agency failed to consider relevant factors or made a clear error of judgment"); Indep. Petroleum Ass'n v. Babbitt, 92 F.3d 1248, 1258 (D.C. Cir. 1996); Bracco Diagnostics, Inc. v. Shalala, 963 F. Supp. 20, 27-28 (D.D.C. 1997) ("If an agency treats similarly situated parties differently, its action is arbitrary and capricious in violation of the APA") (quoting Allergan v. Shalala, 6 Food and Drug Rep. 389, 391 (D.D.C. 1994).

Here, OGD treated similarly situated parties differently by selectively disclosing material information to, and thereby conferring a material informational advantage on, a very few potential market participants to the detriment of all others, including ViroPharma. OGD should have recognized this relevant factor when it received inquiries from stock analysts asking about the BE requirements for ANDA copies of Vancocin. OGD's questionable disclosure practice also treated at least one pharmaceutical company (Akorn) differently than ViroPharma and other pharmaceutical companies affected by OGD's decision.

As a direct result of OGD's conduct, ViroPharma was caught unawares regarding an issue of fundamental concern to the company and its shareholders. OGD's conduct prevented ViroPharma from saying literally anything to its shareholders for a critical period of time during which shareholders understandably were desirous of immediate clarification of what had happened. By contrast, the select few to whom OGD had disclosed its new standard were not grasping for informational straws, but, courtesy of OGD, had a substantial informational advantage.[6]

Nothing could be more arbitrary or capricious than action of an administrative agency conferring a material informational advantage on a select group of potential market participants to the detriment of all others and the share-issuing company itself. OGD should have considered this factor before it took its action, and taken steps to prevent the arbitrary and capricious result. Because it did not, OGD's action must be held "unlawful and set aside". 5 U.S.C. § 706(2).

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[6] Stock trading based on inside information about generic drugs is not merely a theoretical concern. The Securities and Exchange Commission prosecuted such cases resulting from the Generic Drug Scandal of the late 1980's. See, e.g., SEC v. Shah, 1993 U.S. Dist. LEXIS 10347 (S.D.N.Y. 1993). The release of Infinium's report (described above) triggered a multi-day sell-off of ViroPharma's stock that cut the company's market capitalization by 40%, or some $500,000,000.

E. OGD's Actions Violate the Food and Drug Administration's Standards of Conduct

OGD's selective disclosure also violates FDA's regulations regarding standards of conduct and conflicts of interest. 21 C.F.R. Part 19. Specifically, Messrs. Buehler and Conner, via the letters they signed, dispensed special favors by selectively bestowing market-moving inside information upon a limited group of recipients. Consequently, they "discriminate[d] unfairly by the dispensing of special favors or privileges . . . whether for remuneration or not", in direct violation of 21 C.F.R. § 19.6(5). The recipients of the letters signed by Messrs. Buehler and Conner were put in a privileged position to profit because other market participants were kept ignorant of the market-moving information.

F. The Proper Legal Approach

OGD has violated the Freedom of Information Act, the Data Quality Act, the Good Guidance Practices law, the Administrative Procedure Act, and FDA's own regulations. As a result, OGD's new, lowered BE standard cannot be used to approve ANDA copies of Vancocin. Instead, ANDA applicants must meet the only remaining legally valid standard – clinical trials. If OGD nonetheless decides to start over, and wishes to avoid a second invalidation of its efforts on the above grounds, it would, at a minimum (and in addition to other steps necessary to cure its violations of the other laws described herein), be required to observe the following GGP procedures.

The GGP law requires OGD to "ensure public participation prior to implementation" of certain new guidance documents. 21 U.S.C. § 371(h)(1)(C). The level of public participation required is higher for changes in FDA interpretations or policy that "are of more than a minor nature", include complex scientific issues, or involve highly controversial issues. Id., 21 C.F.R. § 10.115(c)(1). OGD's action need meet only one of these criteria to trigger the higher level ("Level 1") of public participation. Id. In fact, OGD's action meets all three criteria.

OGD's contemplated switch from complex clinical trials to simple dissolution testing on a laboratory bench is a "change[] in interpretation or policy . . . of more than a minor nature". It also "[i]nclude[s] complex scientific issues" as will be further developed in subsequent filings by ViroPharma. Finally, it is "highly controversial", as recent events have made clear. 21 C.F.R. § 10.115(c)(1). As such, if OGD wished to use its new dissolution test in the approval of ANDA copies of Vancocin, the following procedures would apply.

Before preparing a draft guidance, OGD could seek or accept early input from individuals or groups outside FDA, e.g., by participating in or holding public meetings and workshops. 21 C.F.R. § 10.115(g)(1)(i). OGD has followed this approach in the past when developing BE guidance documents. To date, OGD has had no public meetings or workshops regarding BE standards for Vancocin.

Once it has prepared a draft guidance, OGD would be required to (A) publish a notice in the Federal Register announcing that the draft guidance is available; (B) post the draft guidance on the Internet and make it available in hard copy; (C) invite comment on the draft guidance. 21 C.F.R. § 10.115(g)(1)(ii). This would permit notice to interested members of the public and an opportunity for them to comment and participate in the development of the guidance. To date of course, in the case of Vancocin, OGD has failed to comply with any of these requirements.

OGD can also, after preparing the draft guidance, choose to hold public meetings or workshops, or present the draft guidance to an advisory committee for review. 21 C.F.R. § 10.115(g)(1)(iii). Once again, OGD has done this for other drug products, but not for Vancocin.[7]

After providing opportunity for public comment, OGD must review all comments and prepare a final version of the guidance that incorporates suggested changes, when appropriate, publish a notice in the Federal Register announcing availability of the guidance, and post the guidance on the Internet and make it available in hard copy. 21 C.F.R. § 10.115(g)(1)(iv). If OGD had complied with these procedures in announcing its new dissolution test, that test would be valid under FDA's GGP regulations (although it would still suffer from the other legal infirmities described in this document). However, because the new dissolution test is invalid due to OGD's failure to comply with the GGP requirements, it cannot be used to approve ANDA copies of Vancocin.

In developing any new guidance going forward, OGD might claim that "prior public participation is not feasible or appropriate". 21 C.F.R. § 10.115(g)(2). It is difficult to see how OGD could justify such a claim, when prior public participation has been used successfully for numerous OGD guidance documents, and there is no imminent threat to public health regarding ViroPharma's Vancocin. In any event, this exception still requires Federal Register publication of the Guidance before it is implemented, 21 C.F.R. § 10.115(g)(3)(i)(A). Consequently, the letters OGD has already issued describing its new dissolution test would remain procedurally invalid even under this provision because the new test has been implemented (via letters to potential ANDA applicants stating that it is a sufficient standard for demonstrating BE to Vancocin), but no Guidance has been published.

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[7] For example, OGD has taken a dramatically different course regarding vancomycin BE than it did for fluticasone, a locally acting nasal spray that was the subject of a recent public dispute regarding the proper BE standards applied by OGD. In formulating the BE standard for fluticasone, which as a locally acting drug product was required to include an *in vivo* comparative clinical trial, OGD was able to point to more than eight years of industry and public input, including advisory committee meetings, technical papers, and the issuance of two draft guidance documents. FDA Consolidated Petition Response re Fluticasone BE, Feb. 22, 2006. OGD's procedure for vancomycin capsule BE pales by comparison.

II. OGD's Dissolution Test Violates The Law

The legal invalidity of OGD's new *in vitro* dissolution test for ANDA copies to demonstrate bioequivalence to Vancocin is not limited to OGD's flawed approach to developing and announcing its new test. The new test itself also suffers from multiple legal infirmities.

A. The BCS Guidance is OGD's Only Possible Basis for the New Dissolution Test

As discussed more fully above, OGD has neither explained the abandonment of its previous clinical trial standard, nor the adoption of its new *in vitro* dissolution standard, and this failure to explain is fatal to OGD's action. In fact, OGD's only attempt at justifying the legality of its new dissolution test was to cite a lone FDA Guidance, the "BCS Guidance":

> "Vancomycin is a highly soluble drug and the reference listed drug (RLD) product [i.e., Vancocin] is rapidly dissolving. Waivers of *in-vivo* bioequivalence testing can be requested in abbreviated new drug applications (ANDAs), provided that the test product is rapidly dissolving at the 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)*." [8]

March 1, 2006, letter from Dale P. Conner, Office of Generic Drugs, to Bernadine Leung, Ph.D., Infinium Capital, at 1.

Thus, the BCS Guidance is the only authority claimed by OGD for its new *in vitro* dissolution test for ANDAs to demonstrate BE to Vancocin. It therefore can only "be upheld, if at all, on [this] basis". State Farm, 463 U.S. at 50. Unfortunately for OGD, the BCS Guidance is invalid, as the following section demonstrates.

B. The BCS Guidance is Invalid

i. The BCS Guidance has no Explained Regulatory Basis

The BCS Guidance is intended to permit applicants to request waivers of the Agency's general requirement of *in vivo* BE studies. As the Guidance states, waivers of FDA's general requirement of *in vivo* bioequivalence ("biowaivers") are available under certain conditions at 21 C.F.R. § 320.22. BCS Guidance, at 1. The specific waiver relied on as the basis for the BCS Guidance is the "good cause" waiver found at 21 C.F.R. § 320.22(e):

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[8] The OGD letters erroneously spell the Guidance's title. Officially, it is the "Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System". It is commonly referred to, and the OGD letters refer to it as, the "BCS Guidance".

> "The BCS approach outlined in this guidance can be used to justify biowaivers for *highly soluble* and *highly permeable* drug substances (i.e., Class 1) in IR solid oral dosage forms that exhibit *rapid in vitro dissolution* using the recommended test methods (21 CFR 320.22(e))."

BCS Guidance, at 2 (emphasis in original). In turn, the "good cause" regulation reads, in relevant part:

> "FDA, for good cause, may waive a requirement for the submission of evidence of *in vivo* bioavailability or bioequivalence if waiver is compatible with the protection of the public health." 21 C.F.R. § 320.22(e).

The BCS Guidance offers no explanation as to why the "good cause" regulation is sufficient authority for the Guidance. Failure to explain this interpretation invalidates the Guidance. "[A]n agency must cogently explain why it has exercised its discretion in a given manner". State Farm, 463 U.S. at 48 (citing Atchison, Topeka & Santa Fe R. Co. v. Wichita Bd. Of Trade, 412 U.S. 800, 806 (1973)); A.L. Pharma, 62 F.3d at 1491 (same); Public Citizen, 988 F.2d at 197 ("the requirement that agency action not be arbitrary or capricious includes a requirement that the agency adequately explain its result.").

ii. The "Good Cause" Waiver Does Not Support the BCS Guidance as Applied to Vancomycin Capsule ANDAs

In fact, FDA's basis for promulgating the "good cause" regulation did not include its use to approve ANDA copies of currently marketed innovator drugs like Vancocin. Rather, FDA inserted the "good cause" regulation *sua sponte* in its 1977 final bioequivalence rule. FDA considered the regulation "necessary to allow FDA to permit the continued marketing of medically important drug products while adequate methodology is being developed or bioavailability studies are being conducted." Bioequivalence Requirements, Final Rule, 42 Fed. Reg. 1638, 1642 (Jan. 7, 1977) (emphasis added). Thus, to the extent an innovator drug continues to be marketed, the "good cause" regulation does not furnish a regulatory basis to grant biowaivers for ANDA copies of that innovator drug.

Here, there is no threat to the "continued marketing" of Vancocin. Vancocin will not be pulled from the market "while adequate methodology is being developed or bioavailability studies are being conducted". Moreover, if there were such a risk, then the "good cause" waiver would appropriately be granted to Vancocin so that the only approved version of this "medically important drug product[]" would remain available. By contrast, a "good cause" waiver would not make ANDA copies of Vancocin available to patients tomorrow, or even next year, if the stock market analysts are to be believed. In any event, ANDA approvals are not necessary to ensure continued marketing of vancomycin hydrochloride capsules; that need continues to be met by Vancocin.[9] The

[9] The only exception to FDA's "continued marketing" interpretation is to permit the approval of medically important innovator drugs, particularly orphan drugs. See, e.g., Preservative-Free Morphine Preparation

"good cause" waiver is clearly not applicable here, and its invocation (without explanation) by OGD was an insufficient legal basis for the BCS Guidance.

iii. No Demonstration of Compatibility With the Public Health

The regulation also requires that a "good cause" waiver must be "compatible with the protection of the public health". 21 C.F.R. § 320.22(e). Thus (if one were to ignore the fact that the waiver does not apply here), to invoke this exception in the case of Vancocin, OGD must also have analyzed (as a part of its decision and prior to issuing its letters), among other things, why market entry of numerous cheaply priced ANDA products with no clinical demonstration of safety and efficacy in real patients will not exacerbate appropriate use and microbial resistance concerns for this life-saving, last resort antibiotic agent. We are unaware of any such analyses undertaken by OGD.

iv. Biowaiver Regulations Narrowly Tailored

Moreover, the "good cause" waiver, although OGD's sole basis for the BCS Guidance, is not the only regulation under which biowaivers can be requested. 21 C.F.R. § 320.22. Other regulatory provisions specify narrowly tailored circumstances under which applicants can request biowaivers for yet to be approved applications, id., in contrast to the "good cause" waiver's focus on the "continued marketing of medically important drug products".

The existence of the other biowaiver provisions underscores the fact that the "good cause" waiver is not a trump card to justify whatever BE standards OGD feels are appropriate. Such an interpretation would render the other regulations superfluous. There is no need for regulations that carefully spell out the few circumstances when BE waivers are permissible, if by invoking "good cause" OGD can waive bioequivalence whenever it chooses. See, e.g., United States v. Alisal Water Co., 431 F.3d 643, 653 (9th Cir. 2005) (a regulation should not be interpreted to render another regulation superfluous).

The reality, of course, is that the regulation writers did not create an open-ended "good cause" waiver that subsumes the other waiver regulations. Rather, the "good cause" regulation is complementary to the other regulations. FDA said the same in 1998, when it stated that "good cause" waivers may be granted if the other biowaiver provisions "do not apply" (assuming, of course, a demonstration of both good cause and compatibility with protection of the public health). Bioavailability and Bioequivalence Requirements; Abbreviated Applications; Proposed Revisions, 63 Fed. Reg. 64222, 64224 (Nov. 19, 1998). Such is not the case here. The BCS Guidance proposes to waive *in vivo* tests in favor of *in vitro* dissolution testing, a type of testing which already has its own narrow waiver provision, 21 C.F.R. § 320.22(d)(3), and so has no need to be justified via resort

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for Epidural Use for Treatment of Severe Chronic Pain; Invitation to Submit New Drug Application, 50 Fed. Reg. 16351 (April 25, 1985); Triethylene Tetramine Dihydrochloride for Treatment of Penicillamine-Intolerant Patients with Wilson's Disease; Invitation to Submit New Drug Application, 47 Fed. Reg. 42175 (September 24, 1982).

to a "good cause" waiver.[10] This further invalidates the notion that the "good cause" regulation is an appropriate legal basis for the BCS Guidance.

In sum, there is no basis for invoking the "good cause" waiver in support of the *in vitro* dissolution approach to bioequivalence outlined in OGD's letters.[11]

C. The BCS Guidance is Inapplicable to Vancomycin Capsules, and Misapplied in OGD's Letters

In addition to the defects in the BCS Guidelines just described, and despite its being the only authority cited by OGD for OGD's new BE dissolution test for vancomycin capsule ANDAs, by its own terms the BCS Guidance does not apply to Vancocin. Moreover, OGD's letters actually misapply the BCS Guidance, by exempting ANDA applicants from all but one of the Guidance components.

i. The BCS Guidance Does Not Apply to Vancomycin Capsules

The BCS Guidance clearly does not apply to Vancocin capsules, for at least two reasons. First, the original academic paper on which the BCS Guidance is based (and which accordingly is cited on the Guidance's first page), explicitly stated that the BCS does not apply to antidiarrial GI drugs like Vancocin capsules:

> "Drug dissolution is a prerequisite to drug absorption and clinical response for almost all drugs given orally. Exceptions to this general requirement such as 'GI' drugs, e.g., resins, antidiarrials, adsorbants, some laxatives, etc. are not considered in this report." Amidon GL, et. al, *A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in vitro Drug Product Dissolution and in vivo Bioavailability*, Pharmaceutical Research, Vol. 12, No. 3, 1995, p.413.

Second, Vancocin capsules are not highly permeable, but drugs must be highly permeable to qualify for biowaivers under the BCS Guidance. "The drug substance for which a waiver is being requested should be highly soluble and highly permeable." BCS Guidance at 10 (emphasis added). For ANDAs, "BCS-based biowaivers can be requested

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[10] Perhaps the BCS Guidance knowingly cites the "good cause" waiver in order to avoid the *in vitro* dissolution test waiver's restriction that *in vivo* BE testing cannot be waived unless the *in vitro* test "has been correlated with *in vivo* data". 21 C.F.R. § 320.22(d)(3). If so, the BCS Guidance effectively amends the *in vitro* waiver regulation to delete the *in vivo* correlation requirement. Such an action would be arbitrary and capricious because not accomplished through notice-and-comment rulemaking, and hence invalidate the BCS Guidance. Moreover, having chosen to rely solely on the "good cause" waiver as authority for the BCS Guidance, FDA could not now rely on the *in vitro* waiver provision, or any of the other waiver provisions in 21 C.F.R. § 320.22, as authority for the BCS Guidance, without engaging in notice-and-comment rulemaking.

[11] Of course, any assertion of "good cause" as the basis for the dissolution test in OGD's letters, to be plausible, would have to predate (at a minimum) the issuance of those letters. Otherwise, such an assertion would not only be a misapplication of the "good cause" waiver, but also an unacceptable post hoc justification for actions previously taken on other, invalid, grounds. See America's Cmty. Bankers v. FDIC, 200 F.3d 822, 835 (D.C.Cir. 2000) ("Post hoc rationalizations cannot support an affirmance of an agency decision based on an otherwise invalid rationale.").

for rapidly dissolving IR test products containing highly soluble and highly permeable drug substances, provided that the reference listed drug is also rapidly dissolving and the test product exhibits similar dissolution profiles to the reference listed drug product (see sections II and III)." BCS Guidance at 10 (emphasis added).

Thus, the sole authority OGD cites in support of its new dissolution test is, by its own terms and according to the original academic work on which it was based, not applicable to Vancocin.

ii. OGD's Letters Ignore The Data Required for BCS-based Biowaivers

The BCS Guidance enumerates several distinct datasets that are required for an applicant that wishes to request a BCS-based waiver of *in vivo* bioequivalence. Sponsors are asked to submit:

(1) "Data Supporting High Solubility" (test methods, drug substance, test results, graphic representation of mean pH-solubility profile)
(2) "Data Supporting High Permeability" (study designs, list of selected model drugs, including data used to establish suitability of method, permeability classes of model drugs, etc.)
(3) "Data Supporting Rapid and Similar Dissolution" (drug product statistics, dissolution data from 12 units of test and reference drug using methods recommended in section III.C of the Guidance, data supporting similarity of dissolution profiles, using the f2 metric)
(4) "Additional Information" (manufacturing process, excipients)

BCS Guidance at 10.

OGD's letters request only the dissolution data in number (3). Nowhere, however, does the BCS Guidance, the product of years of scientific inquiry and open scientific debate, suggest that the model it describes can be broken apart into components to allow OGD or an applicant to "pick and choose" the data to be submitted. Rather, all data described by the BCS Guidance are required to be submitted. Thus, the OGD letters do not in fact outline BCS-based waivers of *in vivo* BE, but something less complete, based on only one BCS component in isolation, and scientifically unproven. OGD's unscientific dissection of the Guidance is particularly troubling given that it took place behind closed doors, with no open scientific debate, or even the announcement of a statement of grounds on which OGD might claim its actions are justified.

In sum, OGD's new dissolution test is based solely on the BCS Guidance, which therefore is the only basis on which it might be upheld. State Farm, 463 U.S. 29, 50 (1983). OGD's action was arbitrary and capricious because OGD failed to consider that the BCS Guidance does not apply to drugs like Vancocin, and OGD made no attempt to justify its extraction of only one part of the BCS for use with respect to Vancocin. 5 USC 706(2)(A); D&F Afonso Realty Trust, 216 F.3d at 1195 ("we must strike down agency

action if the agency failed to consider relevant factors or made a clear error of judgment"); JSG Trading, 176 F.3d at 544 (agency "obligated to articulate a principled rationale for departing from [prior] test"); A.L. Pharma, 62 F.3d at 1491 ("an agency must cogently explain why it has exercised its discretion in a given manner" (quoting State Farm, 463 U.S. at 48)); Drug Plastics, 44 F.3d at 1022 (agency failure to explain departure from precedent resulted in invalidated agency action).

Accordingly, for this additional reason, OGD's new dissolution test for ANDA copies to demonstrate BE to Vancocin is unlawful and must be set aside.

D. FDA's Bioequivalence Waiver Regulations Do Not Support OGD's New Test

The failure of either the BCS Guidance or the "good cause" waiver to authorize OGD's action here may cause OGD to seek to justify its new dissolution test on one of the other waivers in FDA's *in vivo* BE waiver regulation. 21 C.F.R. § 320.22. The only waiver that might arguably bear this burden[12] has already been mentioned: 21 C.F.R. § 320.22(d)(3) permits *in vitro* dissolution instead of *in vivo* testing if "[t]he drug product is, on the basis of scientific evidence submitted in the application, shown to meet an *in vitro* test that has been correlated with *in vivo* data". Of course, having already relied on other grounds for its vancomycin capsules dissolution test, OGD cannot simply change horses in the middle of the regulatory stream, but would need notice-and-comment rulemaking to use a different regulation such as this as authority for its new test. (See section II.F. below.)

Such a rulemaking, however, would encounter at least two problems. First, the regulation requires an ANDA to contain scientific evidence correlating the *in vitro* test with *in vivo* data. 21 C.F.R. § 320.22(d)(3). OGD's letters, by contrast, merely require the ANDA to provide "dissolution data in various media on 12 dosage units each of test and reference product". Correlation of the *in vitro* test in OGD's letters with *in vivo* data would be necessary before OGD's test could meet the regulation.

Second, there is no evidence of any *in vitro* BE test for Vancocin capsules for which an *in vivo* correlation has been established. Indeed, if OGD had data establishing such a correlation, that fact would presumably have been mentioned in OGD's letters. One is left to conclude that OGD has advised ANDA applicants to conduct *in vitro* tests that have not been correlated with *in vivo* data. Thus, in addition to being unsupported by either the BCS Guidance or the "good cause" regulation, OGD's new *in vitro* dissolution test fails FDA's *in vitro* dissolution waiver regulation as well. In other words, there are no valid regulatory options to justify OGD's new *in vitro* dissolution test for use in demonstrating bioequivalence of ANDA products to Vancocin.

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[12] The other waivers do not apply to Vancocin, but address different types of drugs: (1) those (solutions, inhaled gases, skin products, tinctures, etc.) for which BE may be considered self-evident; (2) non-bioproblem DESI drugs; (3) same dosage form but different strength versions of already-approved products; (4) reformulations of approved drugs that only change colors, flavors, or preservatives that could not affect bioavailability or BE. 21 C.F.R. § 320.22 passim.

E. FDA May Not Change Its Interpretation of Its BE Regulations as Applied to Vancomycin Capsules Without Notice and Comment Rulemaking

Having interpreted its BE regulations to require clinical testing for ANDA copies to demonstrate BE to Vancocin, FDA can only abandon clinical testing through notice and comment rulemaking. See, e.g., Environmental Integrity Project v. Environmental Protection Agency, 425 F.3d 992, 997-98 (D.C. Cir. 2005) (having interpreted its regulation a particular way, EPA could not adopt a different interpretation without notice-and-comment rulemaking); Alaska Professional Hunters Ass'n v. FAA, 177 F.3d 1030, 1034 (D.C. Cir. 1999) ("When an agency has given its regulation a definitive interpretation, and later significantly revises that interpretation, the agency has in effect amended its rule, something that it may not accomplish without notice and comment."); Paralyzed Veterans of America v. D.C. Arena, 117 F.3d 579, 586 (D.C. Cir. 1997) ("Once an agency gives its regulation an interpretation, it can only change that interpretation as it would formally modify the regulation itself: through the process of notice and comment rulemaking.").

Regarding bioequivalence standards for vancomycin capsules, OGD had given its bioequivalence regulations a definitive and consistent interpretation until it reversed course earlier this year without notice or an opportunity for public comment. As set forth above, OGD has reiterated on multiple occasions its interpretation that the regulatory requirement for establishing BE to Vancocin requires an *in vivo* demonstration via a clinical study. Indeed, ViroPharma relied upon this longstanding interpretation in its decision to acquire, market, and continue investing in Vancocin. Consequently, the Agency: "can only change that interpretation as it would formally modify the regulation itself: through notice and comment rulemaking." Paralyzed Veterans, 117 F.3d at 586. *See also, e.g.,* Tripoli Rocketry Assoc. v. ATF, 337 F. Supp. 2d 1 (D.D.C. 2004) (ATF reversal of the applicability of an exemption from a regulatory requirement invalid without notice and comment rulemaking); Mercy Medical Skilled Nursing Facility v. Thompson, 2004 U.S. Dist. LEXIS 27365, 9 (D.D.C. 2004) (no requirement that Agency's prior interpretation had been subject of formal adjudication or official announcement); Torch Operating Co. v. Babbitt, 172 F. Supp. 2d 113, 126 (D.D.C. 2001) (same).[13]

[13] The Paralyzed Veterans line of cases also renders inapposite earlier caselaw that allowed OGD to change its interpretations of its BE regulations without notice and comment rulemaking. Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212 (D.D.C. 1996); Schering Corp. v. Sullivan, 782 F. Supp. 645 (D.D.C. 1992), vacated as moot sub nom, Schering v. Shalala, 995 F.2d. 1103 (D.C.Cir. 1993). In addition, unlike Vancocin, the drugs involved in these cases were not for life-threatening diseases; one drug lowered cholesterol (Bristol-Myers Squibb), the other treated asthma (Schering).

III. No Vancomycin Capsule ANDA Approvals Until Risk of BE Fraud Has Been Eliminated

In 1993 FDA proposed regulations to avoid a problem that has plagued generic drugs for some time: ANDA applicants not submitting failed BE studies. Generally, ANDA applicants only submit BE studies that "pass":

> "ANDA applicants that have conducted multiple studies on a final formulation producing passing and nonpassing results have generally not submitted the results of the nonpassing study or studies to FDA. . . . As a result, FDA only infrequently sees data from additional studies and is generally unaware of the existence of such studies."

Requirements for Submission of In Vivo Bioequivalence Data; Proposed Rule, 68 Fed. Reg. 61640, 61641 (Oct. 29, 2003).

As FDA concedes, the failure to submit failed BE studies is a significant problem, because "information from additional BE studies conducted on a product can be important in assessing bioequivalence for that product." Id. For a life-saving drug like Vancocin, it is particularly unnerving to contemplate that an ANDA might be approved as a "generic equivalent" to Vancocin based on one passing *in vitro* dissolution BE test, when in fact the ANDA product failed that test on its first three or four (or more) attempts. The fact that FDA itself concedes that it "is generally unaware of the existence of such [failed] studies" only increases the alarm.

FDA's proposed regulation that would require submission of failed studies has not been finalized. Until it has been, and until there is certainty that all failed studies have actually been submitted to FDA from ANDA applicants seeking to copy Vancocin, FDA cannot approve such products because it cannot be certain that they are truly bioequivalent to Vancocin.

A similar problem has afflicted the retention of BE test samples for ANDA products. In 1993, after the Generic Drug Scandal of the late 1980's, FDA finalized regulations requiring retention for a specified period of reserve samples of drug products used to conduct BE studies for ANDA submissions. FDA did this in response to fraud by generic drug applicants:

> "This action is intended to help ensure bioequivalence between generic drugs and their brand-name counterparts and to help the agency investigate more fully instances of possible fraud in bioavailability and bioequivalence testing."

Retention of Bioavailability and Bioequivalence Testing Samples, Final Rule, 58 Fed. Reg. 25918 (April 28, 1993).

Later in the rule's preamble FDA explained the type of fraud the rule was designed to eliminate:

> "The purpose of this requirement is to eliminate the possibility for sample substitution by the study sponsor or to preclude a study sponsor from altering a reserve sample from a study conducted by a contract research organization prior to release of the reserve sample to FDA. In several instances, FDA has found that a study sponsor provided the contract testing facility with disguised innovators' products rather than its own proposed product as the test product in certain bioequivalence studies."

Id. at 25921.

Unfortunately, ten years later, OGD has still not gotten a handle on this problem. Dale Conner, the Director of OGD's Division of Bioequivalence, gave a presentation in June 2003 which included a slide stating that "Reserve Sample Retention . . . Continues to be a problem". Bioequivalence Review Issues, GPhA/OGD Joint Meeting, June 26, 2003. The context was a joint meeting between OGD and the Generic Pharmaceutical Association. Mr. Conner's slide appears to have been exhorting the assembled generic drug executives to do a better job of retaining their reserve samples. In other words, whether the generic industry will comply with FDA's reserve retention rules seems to be up to the industry, not FDA.

In light of known instances of fraud in the past, it seems likely that voluntary efforts like the proposed regulations to require submission of failed BE studies or the enacted but unpoliced reserve sample retention regulations will be insufficient to eliminate bioequivalence fraud. The implications for important drugs like Vancocin are chilling. In essence, OGD does not have the capacity to truly confirm that any given ANDA product is actually bioequivalent to Vancocin. Because this failure precludes the statutorily required finding of bioequivalence, no ANDA copies of Vancocin can be approved until the situation has been resolved.

CONCLUSION

In conclusion, OGD's new bioequivalence standard for ANDA copies of Vancocin is fatally flawed. By law, it should not have come about without prior public process, its announcement should have been better explained, and to all at once rather than a select few, and its record should now be available to interested members of the public. Each of these failures individually suffices to invalidate OGD's action. Together, they are a devastating indictment of OGD itself. 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.

Furthermore, as explained above, what little is known of OGD's decision to permit *in vitro* bioequivalence testing for Vancocin exemplifies the flawed results that occur when

administrative agencies go underground. The obvious inapplicability to Vancocin of the BCS, the invalidity of the BCS Guidance itself, and OGD's failure to comply with FDA's own regulations each trigger disturbing questions about the quality controls, or lack thereof, in OGD's secret process.

Finally, the extent to which OGD is unaware of failed bioequivalence studies and reserve sample fraud renders it impossible for OGD to certify any purported ANDA as having truly demonstrated bioequivalence to Vancocin. Given the life-threatening nature of the disease that Vancocin treats, anything less than 100% assurance of bioequivalence is simply unacceptable.

There is more to be said on these issues, and ViroPharma intends to say it, at a minimum in additional filings to the present docket. This will include a demonstration that, based only on what is publicly known about OGD's action, it is scientifically flawed, in addition to the legal infirmities identified above.

FDA, however, need not wait. Recognizing the myriad legal infirmities that afflict OGD's decision, the Agency should rescind that decision now.

For the foregoing reasons, ViroPharma's Petition for Stay of Action should be granted.

Respectfully submitted,

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