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VIA HAND DELIVERY
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Food and Drug Administration
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Re: Docket No. 2006P-0124 (FDA-2006-P-007)

Dear FDA:

ViroPharma Incorporated ("ViroPharma") hereby supplements and amends the above-referenced petition.

In light of recent statements by FDA, in this submission ViroPharma explains (I) the *in vivo* bioequivalence requirement of FDA's bioequivalence regulations; (II) recent attempts by FDA's Office of Generic Drugs to circumvent FDA's regulation permitting waiver of the *in vivo* bioequivalence requirement; (III) why OGD cannot circumvent the *in vivo* bioequivalence waiver regulation; (IV) the relevant provision of the *in vivo* bioequivalence waiver regulation under which generic applicants seeking to copy Vancocin® (vancomycin hydrochloride capsules) might seek a waiver of the requirement of *in vivo* bioequivalence; (V) the importance of correlating alternative bioequivalence methods with patient outcomes; and (VI) how currently there are no pharmacokinetic or pharmacodynamic tests to support a finding of bioequivalence to Vancocin in the absence of clinical endpoint data. In light of the above, section (VII) amends the actions requested in this petition.

I. The *In Vivo* Bioequivalence Requirement

Recent OGD citizen petition responses regarding bioequivalence for drugs that act locally in the GI tract have resuscitated and expanded flawed interpretations of FDA's bioequivalence (BE) regulations.[1] In brief, OGD has begun to assert a breadth of discretion regarding bioequivalence policy which strays far beyond what FDA's regulations allow. This section explains how FDA's regulations require validated science-based methodology—not simply untested hypotheses—to support waiver of the requirement that bioequivalence must be demonstrated with evidence obtained *in vivo*.

FDA's bioequivalence regulations begin, after a section on definitions, by enumerating several "[r]equirements for submission of in vivo bioavailability and bioequivalence data." 21 C.F.R. § 320.21. The requirements for *in vivo* BE data include one for new drug applications (NDAs), one for abbreviated new drug applications (ANDAs), one for supplemental applications, and one allowing FDA to approve NDAs and supplemental applications based on an applicant's

[1] *See, e.g., infra* notes 6 and 28 and accompanying text.

agreement to submit data at some later date. 21 C.F.R. §§ 320.21(a)-(d). To satisfy these requirements of *in vivo* BE data, § 320.21 further provides that applicants must use one of the approaches specified in § 320.24:

> Evidence measuring the in vivo bioavailability and demonstrating the in vivo bioequivalence of a drug product shall be obtained using one of the approaches for determining bioavailability set forth in § 320.24.

21 C.F.R. § 320.21(e).

Each of the requirements for *in vivo* BE data also permits an exception, whereby an applicant may request waiver of the *in vivo* BE requirement. 21 C.F.R. §§ 320.21(a)-(d). For ANDA applicants, waiver of the *in vivo* bioequivalence requirement can be requested by submitting in an ANDA:

> Information to show that the drug product is bioequivalent to the reference listed drug which would permit FDA to waive the submission of evidence demonstrating in vivo bioequivalence as provided in paragraph (f) of this section.

21 C.F.R. § 320.21(b)(2). Paragraph (f), in turn, provides that applicants seeking a waiver of *in vivo* BE must meet the criteria of § 320.22:

> Information to permit FDA to waive the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence *shall meet the criteria set forth in § 320.22.*

21 C.F.R. § 320.21(f) (emphasis added).

In summary, FDA's bioequivalence regulations create a general rule in 21 C.F.R. § 320.21 that to demonstrate bioequivalence ANDA sponsors must submit information obtained *in vivo*, unless a sponsor can meet the criteria for waiver set forth in 21 C.F.R. § 320.22.[2]

[2] In addition to the plain language of the regulations described above, FDA's 1992 final rule implementing bioequivalence regulations also affirmed the existence of a general rule requiring submission of data obtained *in vivo* unless a waiver was obtained pursuant to § 320.22. *See e.g., Abbreviated New Drug Application Regulations,* 57 Fed. Reg. 17950, 17975 (Apr. 28, 1992) ("[T]he regulation does permit applicants to request a waiver of the requirement for the submission of evidence in the form of in vivo bioavailability or bioequivalence data *provided the product meets the criteria in § 320.22.*") (emphasis added).

II. OGD's Recent Willingness to Circumvent 21 C.F.R. § 320.22.

The *in vitro* Vancocin BE method set forth in OGD's March 2006 letters[3] is invalid because OGD failed to demonstrate how that method would meet the criteria set forth in § 320.22. As ViroPharma has previously explained,[4] OGD's letters simply stated that "[w]aivers of *in-vivo* bioequivalence testing can be requested" by generic applicants seeking to copy Vancocin.[5]

Recent OGD statements regarding products other than Vancocin indicate that OGD may seek to address this problem by resurrecting an argument it has flirted with in the past: that the *in vivo* BE requirement can be waived by some means other than § 320.22. In particular, OGD may seek to convert the listing of BE methods in § 320.24 into an independent authority for using *in vitro* data in lieu of *in vivo* data to establish bioequivalence.

Two recent citizen petition responses illustrate OGD's recent attempts to circumvent § 320.22.[6] In response to a petition regarding the locally acting GI drug acarbose, OGD offered a materially incomplete summary of FDA's bioequivalence regulations in order to claim a broader measure of "flexibility" regarding BE methods than the regulations actually permit.[7] Most saliently, OGD quoted § 320.21(b)(2), which sets up the possibility for ANDAs to receive waivers of the *in vivo* BE requirement, but omitted the part of that regulation which conditions such waivers on compliance with paragraph (f) of § 320.21.[8] Paragraph (f), as explained above, requires compliance with the waiver criteria set forth in § 320.22. By omitting the paragraph (f) reference, the Acarbose Petition Response short-circuited discussion of § 320.22 waivers and particularly of the provision for *in vitro* testing found at § 320.22(d)(3) requiring *in vitro* tests to be correlated with *in vivo* data. Instead, OGD highlighted the § 320.24 list of BE methods as if that list provided independent authority to waive the *in vivo* BE requirement.[9] Only at the end of its assertion of regulatory authority did OGD even mention § 320.22, and then only as a supplemental source generally supporting OGD's purported flexibility regarding BE, rather than the regulation which must be complied with in order to obtain a waiver of the *in vivo* BE requirement.[10]

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[3] *See* ViroPharma, Supplement 1 to Petition for Stay of Action, Docket No. 2006P-0124/SUP1 (May 31, 2006), at Tabs 1-2.

[4] *Id.* at 18-19, 21.

[5] *See, e.g.*, Letter from Dale P. Conner, Pharm.D., to Infinium Capital Corp. (Mar. 1, 2006), at 1 (attached as Tab 1 to ViroPharma, Supplement 1 to Petition for Stay of Action).

[6] FDA Citizen Petition Response regarding Precose® (acarbose), Docket No. FDA-2007-P-0418 (May 7, 2008) (hereinafter Acarbose Pet'n Resp.); FDA Citizen Petition Response regarding Balsalazide Disodium Drug Products, Docket No. 2005P-0146 (Dec. 28, 2007) (hereinafter Balsalazide Pet'n Resp.).

[7] Acarbose Pet'n Resp. at 3-4.

[8] *Id.* at 4.

[9] *Id.*

[10] *Id.* The particular provision of § 320.22 cited by OGD was the so-called "good cause" waiver at § 320.22(e). As discussed below, the good cause waiver was narrowly tailored to ensure continued marketing of medically important drug products, not approvals of copycat generic drugs, and moreover is invalid because it was never properly promulgated. Thus, by citing § 320.22 OGD was correct insofar as § 320.22 waivers are the only way an applicant may obtain a waiver of the *in vivo* BE requirement, but the specific waiver OGD cited – the good cause waiver – did not support OGD's decision regarding BE methods for generic copies of acarbose.

OGD's response to the balsalazide petition was worse, making no attempt to explain why the regulations permitted alternatives to clinical endpoint studies to demonstrate BE for generic versions of balsalazide disodium. OGD merely cited the BE definition at § 320.1 and the list of BE methods at § 320.24(b).[11]

In support of its general claims of discretion regarding BE methods (including in its recent response to the acarbose petition[12]), OGD has occasionally cited dicta in certain cases[13] from the mid-1990's stating that Hatch-Waxman did not change FDA's discretion regarding BE. None of these cases, however, held that FDA's discretion regarding BE methods allows it to ignore § 320.22(d)(3)'s provision that to waive the *in vivo* BE requirement in favor of an *in vitro* test, the *in vitro* test must have "been correlated with in vivo data."[14] Also, as ViroPharma has explained elsewhere, even if OGD's assertions of independent authority outside of § 320.22(d)(3) were valid, the fact that OGD changed its interpretation of its BE regulations with respect to Vancocin without notice-and-comment rulemaking makes OGD's new *in vitro* BE test for Vancocin invalid.[15]

Unlike the overbroad assertions of authority in OGD's citizen petition responses and litigating positions, FDA guidances have been more respectful of the plain requirement of the Agency's BE regulations that waivers of the *in vivo* requirement must comply with § 320.22. Thus, the broad, generally applicable *Guidance for Industry: Bioavailability and Bioequivalence for Orally Administered Drug Products—General Considerations* (2003), cites a number of provisions of FDA's BE regulations, but never claims that provisions other than § 320.22 could support waiver of the *in vivo* BE requirement for non-DESI oral drugs.[16] Another FDA guidance, the BCS

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[11] Balsalazide Pet'n Resp. at 3-4.

[12] Acarbose Pet'n Resp. at 4-5.

[13] *See, e.g.*, Schering Corp. v. FDA, 51 F.3d 390 (3d Cir. 1995); Fisons Corp. v. Shalala, 860 F. Supp. 859 (D.D.C. 1994); Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212 (D.D.C. 1996) ("BMS").

[14] Only one district court case came near this issue, concluding, based on an FDA litigating position, that regulations other than § 320.22(d)(3) could permit in vitro BE testing when buttressed by sufficient scientific data and rationale. BMS, 923 F. Supp. at 217-20. FDA's own policy statements, however, indicate that the other regulations FDA cited to the BMS court are not additional, independent bases to waive the in vivo BE requirement for ANDAs in favor of in vitro methods. Thus, FDA has stated that § 320.24(b)(5) is for DESI drugs, *see infra* note 18; § 320.33 is similarly for "drugs that are not subject to section 505(j) of the Act," Balsalazide Pet'n Resp. at 16; and § 320.24(b)(6) is for *in vivo* methods, animal models, and isotopically labeled drugs, Bioavailability and Bioequivalence Requirements, 42 Fed. Reg. 1624, 1640-41, 1650 (Jan. 7, 1977). Based on a litigating position at variance with FDA's own policy statements, this case lacks persuasive authority, and, as a district court decision, could not be precedential in any event. *See, e.g.*, In re Executive Office of the President, 215 F.3d 20, 24 (D.C. Cir. 2000) (per curiam) ("District Court decisions do not establish the law of the circuit, nor, indeed, do they even establish 'the law of the district.'") (citations and internal quotation marks omitted).

[15] *See* ViroPharma, Supp. 1 to Petition for Stay of Action, Docket No. 2006P-0124/SUP1 (May 31, 2006), at 22.

[16] *Guidance for Industry: Bioavailability and Bioequivalence for Orally Administered Drug Products—General Considerations* (2003) [hereinafter *Oral Drugs Guidance*]. In addition to § 320.22(d)(3), the *Oral Drugs Guidance* also cites § 320.24(b)(5) and § 320.33. *Id.* at 10. In keeping with the broad scope of this guidance, the reference to § 320.24(b)(5) is understandable because it permits inclusion of the *in vitro* methods for DESI drugs which that provision was designed for (*see infra* note 18). Similarly, the *Oral Drugs Guidance* cites § 320.33 for the proposition that "in vitro approaches to documenting BE for nonbioproblem drugs approved before 1962 remain appropriate (21 CFR 320.33)." *Id.* Indeed, the guidance states that if an *in vitro-in vivo* correlation is available, *in vitro* tests can be used not only as a quality control specification but "also as an indicator of how the product will perform in vivo." *Id.* Notably, the Oral Drugs Guidance published in 2003 modified the original proposed guidance

Guidance, is concerned solely with waivers of the *in vivo* BE requirement, and notably makes no claim to authority beyond § 320.22.[17]

III. OGD Cannot Circumvent 21 C.F.R. § 320.22.

In the case of Vancocin, ViroPharma would advise OGD to reject any impulse to overstep the bounds of the Agency's BE regulations, as OGD has occasionally done in petition responses and litigating positions. Rather, OGD should follow the more considered and circumspect approach illustrated by Agency guidance documents. There are myriad reasons why any alternative to *in vivo* BE testing for Vancocin must meet the requirements of § 320.22.

First, § 320.21 is categorical: an ANDA seeking a waiver of *in vivo* bioequivalence "*shall* meet the criteria set forth in § 320.22." 21 C.F.R. § 320.21(f) (emphasis added). Under FDA's regulations, this path is mandatory to secure a waiver of submission of *in vivo* BE evidence. ViroPharma is not aware of any circumstance in which OGD has tried to explain, let alone satisfactorily explain, how the categorical language of § 320.21(f) would permit waivers of the *in vivo* BE requirement under § 320.24 or some other provision.

Second, § 320.24 (with one exception explained below) neither establishes the *in vivo* BE requirement nor authorizes its waiver. That is the function of §§ 320.21-.22, as seen above. Nowhere does § 320.24 (or any regulation other than §§ 320.21-.22) purport to authorize waiver of the *in vivo* BE requirement.

Third, the only part of § 320.24 authorizing FDA to make or modify a BE requirement not already authorized by § 320.21 does not permit *in vitro* testing. Instead, this exception allows FDA to require *in vivo* BE testing of a product if at any time FDA has evidence of therapeutic inequivalence, bioinequivalence, or greater than anticipated toxicity. 21 C.F.R. § 320.24(c). There is no similar provision in § 320.24 authorizing waiver of *in vivo* testing. The absence of a similar provision is telling. If FDA had intended § 320.24 to expand its authority to waive the *in vivo* BE requirement beyond the narrowly tailored waivers in § 320.22, it could have included a provision, analogous to § 320.24(c), authorizing non-*in vivo* testing methods to establish BE. It did not, because waivers of *in vivo* testing are governed by § 320.22.

Fourth, the inclusion of non-*in vivo* methods in § 320.24 serves several functions, but none of them permit OGD simply to ignore § 320.22. Thus, listing non-*in vivo* methods in § 320.24(a) ensures that § 320.24 fulfills its function of being, as its title states, a complete listing of "[t]ypes of evidence to measure bioavailability or establish bioequivalence"; (b) preserves the possibility of "in vivo or in vitro testing, or both," 21 C.F.R. § 320.24(a); (c) lists non-*in vivo* methods that might become relevant if a waiver of *in vivo* BE is granted pursuant to § 320.22; and (d) in

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published in 2000, which merely cited to § 320.24 instead of the specific provisions found in the 2003 draft. Such a change appears to reflect a considered judgment that § 320.24 does not generally provide a basis to authorize *in vitro* tests in the absence of a § 320.22 waiver.

[17] *Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (2000) [hereinafter *BCS Guidance*], at 1-2.

paragraph (b)(5), addresses *in vitro* testing for certain DESI drugs.[18] Nowhere, however, does § 320.24 somehow nullify the criteria for waiver of *in vivo* BE set forth in § 320.22.

Fifth, 21 C.F.R. § 320.24(b)(6), the provision at the bottom of the § 320.24 hierarchy, is no basis for FDA to waive the requirement of *in vivo* BE without complying with § 320.22. Just as § 320.24(b)(5) was specifically intended for DESI drugs, FDA had a particular intent for § 320.24(b)(6): special *in vivo* situations involving animal models or isotopically labeled drugs.[19] A regulation intended only for *in vivo* situations obviously cannot waive the *in vivo* BE requirement.[20] FDA's *in vivo* intent for § 320.24(b)(6) is further evidenced by the failure of that provision to mention *in vitro* methods, especially given that other provisions of § 320.24(b) do mention *in vitro* methods, demonstrating FDA's capacity to include them when it so intends.

Sixth, the notion that § 320.24 might furnish an independent basis to grant *in vivo* BE waivers does not square with FDA's correction of a typographical error in its BE regulations. Under FDA's bioequivalence rules finalized in 1992, § 320.21 "inaccurately include[d] a reference to criteria set forth in § 320.24 as containing information under which FDA could waive the requirement for submission of evidence demonstrating in vivo bioavailability or bioequivalence."[21] FDA thus proposed to "replace the reference to § 320.24 with § 320.22."[22] FDA finalized this change in 2002.[23] The 1992 reference to § 320.24 was obviously a mistake, but potentially a misleading one that could support an inference that § 320.24 authorized *in vivo* waivers. In sum, FDA's typographical correction underscores that § 320.24 should *not* be

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[18] *See Abbreviated New Drug Application Regulations*, 57 Fed. Reg. 17950, 17977 (Apr. 28, 1992) (stating that § 320.24(b)(5) was "intended for drug products determined to be effective under DESI for at least one indication that contain no active ingredients regarded as presenting either actual or potential bioequivalence problems or drug quality or standards issues" and limiting § 320.24(b)(5) only to *in vitro* tests used for drug products coded "AA" in the Orange Book). Thus, paragraph (b)(5) is the *in vitro* bioequivalence method for nonbioproblem DESI drugs that obtain a waiver pursuant to 320.22(c) and thereby receive an AA therapeutic equivalence code. Notably, FDA added paragraph (b)(5) without giving notice of the addition but instead merely inserted the paragraph "on its own initiative." *Id. See also id.* at 17976 (explaining that the 1977 automatic waiver for pharmaceutical equivalent drug products that referenced an approved drug and met an appropriate *in vitro* test was being removed because "FDA has no evidence to show that in vitro data alone are regularly sufficient to support the bioequivalence of any other drug classes" besides those described in 320.22(c) and 320.22(d)); *id.* at 17975 (explaining that the prior automatic waivers for locally acting topical and gastrointestinal drugs were being removed because waivers for such drugs had to be reviewed on a case by case basis in accordance with the waiver criteria set forth in § 320.22). To construe paragraph (b)(5) as a general authorization enabling FDA to permit any ANDA sponsor to establish bioequivalence through "currently acceptable in vitro tests" without a suitable waiver would, therefore, directly contradict FDA's reasoned basis for removing several automatic waiver categories and restricting waivers to the criteria established in 320.22.

[19] Bioavailability and Bioequivalence Requirements, 42 Fed. Reg. 1624, 1650 (Jan. 7, 1977).

[20] Agencies must interpret their regulations consistent with the plain language of the regulations and their intent at the time they were promulgated. See, e.g., Long Island Care at Home v. Coke, 127 S. Ct. 2339, 2349 (2007); National Ass'n of Home Builders v. Defenders of Wildlife, 127 S. Ct. 2518, 2537-38 (2007); Auer v. Robbins, 519 U.S. 452, 461 (1997); Bowles v. Seminole Rock Co., 325 U.S. 410, 413-414 (1945).

[21] *Bioavailability and Bioequivalence Requirements; Abbreviated Applications; Proposed Revisions*, 63 Fed. Reg. 64222, 64223 (proposed Nov. 19, 1998).

[22] *Id.*

[23] *Bioavailability and Bioequivalence Requirements; Abbreviated Applications; Final Rule,* 67 Fed. Reg. 77668, 77674 (Dec. 19, 2002).

confused with § 320.22, and that the Agency has passed on the opportunity to make § 320.24 an independent basis on which to waive the requirement of *in vivo* bioequivalence.[24]

Seventh, the law requires agencies to interpret their regulations consistent with the plain language of the regulations and their intent at the time they were promulgated.[25] As described above, the plain language of the regulations provides that waivers of *in vivo* evidence to demonstrate bioequivalence may only be granted in accordance with the waiver criteria established in § 320.22. In addition, FDA's explanation of its BE regulations in 1989 and 1992 consistently indicated that *in vivo* evidence was required unless a waiver could be obtained under § 320.22, stating, for example, that "the regulation does permit applicants to request a waiver of the requirement for the submission of evidence in the form of in vivo bioavailability or bioequivalence data *provided the product meets the criteria in § 320.22.*"[26]

Through notice-and-comment rulemaking, of course, FDA could propose to modify its bioequivalence regulations to permit OGD to rely on standalone *in vitro* testing irrespective of

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[24] FDA's correction of this typographical error occurred in the context of a rulemaking addressing its BE regulations. Thus, if FDA had wanted to allow waivers of *in vivo* BE based solely on § 320.24, it had ample opportunity in 1998 to propose revisions that would support such an approach. It did not. *Bioavailability and Bioequivalence Requirements*, 63 Fed. Reg. at 64222. FDA's decision in this rulemaking not to modify the longstanding exclusivity of § 320.22 as the only source of waivers of the *in vivo* BE requirement is further evidence of § 320.22 being the mandatory pathway to waiver of the *in vivo* BE requirement.

[25] *See, e.g.,* Long Island Care at Home v. Coke, 127 S. Ct. 2339, 2349 (2007); National Ass'n of Home Builders v. Defenders of Wildlife, 127 S. Ct. 2518, 2537-38 (2007); Auer v. Robbins, 519 U.S. 452, 461 (1997); Bowles v. Seminole Rock Co., 325 U.S. 410, 413-414 (1945).

[26] *Abbreviated New Drug Application Regulations*, 57 Fed. Reg. 17950, 17975 (Apr. 28, 1992). *See also id.* at 17976 ("In general, the submission of in vivo data is required to support a new product unless there is a known in vivo/in vitro correlation, in which case in vitro data alone may be sufficient. Section 320.22(d) of this final rule lists certain classes of drug products whose bioavailability or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo. (In addition, FDA continues to waive *in vivo* data for certain drugs determined to be effective for at least one indication under the DESI program.) As FDA has no evidence to show that in vitro data are alone sufficient to support the bioequivalence of any other drug classes, the agency believes that it is inappropriate to retain existing § 320.22(d)(5). Section 320.22(d)(5) is, therefore, removed.") Moreover, FDA expressly clarified that *in vivo* data is required for oral drug products not intended for systemic absorption unless a waiver could be obtained under § 320.22:

> [T]his change [removing the self-evident waiver for non-systemic oral drugs] does not require applicants to submit evidence of in vivo bioavailability or in vivo bioequivalence in every case. The elimination of the automatic waiver for nonsystemically absorbed oral dosage products simply reflects FDA's view that requests for waiver of in vivo bioavailability and bioequivalence for these products need to be reviewed on a case-by-case basis. While the amendments may well increase the number of in vivo studies required, the regulation does permit applicants to request a waiver of the requirement for the submission of evidence in the form of in vivo bioavailability or bioequivalence data *provided the product meets the criteria in § 320.22.*

Abbreviated New Drug Application Regulations, 57 Fed. Reg. at 17975 (emphasis added). FDA said the same thing when proposing these regulations. *See Abbreviated New Drug Application Regulations (Proposed Rule),* 54 Fed. Reg. 28872, 28912 (proposed July 10, 1989).("The agency has no evidence to show that in vitro data alone are regularly sufficient to assure bioequivalence. In vitro testing can be used for drugs where there is a known in vivo/in vitro correlation, and has been used for pre-1962 drugs not suspected of having, or not likely to have, a bioavailability problem. For all other drug products, an in vivo bioequivalence study on the product is required to support at least one strength of the product.")

whether a drug product satisfies the criteria for waiving *in vivo* evidence of bioequivalence. Short of notice-and-comment rulemaking, however, FDA must abide by the plain language of its regulations, consistent with FDA's intent regarding those provisions when they were promulgated—both of which affirm that § 320.22 is the only means to a waiver of the requirement of *in vivo* evidence demonstrating bioequivalence.

Eighth, agency interpretations or applications that break with the plain words and intent of the regulations are not entitled to deference.[27] As just described, FDA's intent as expressed in its regulatory preambles was consistent with the plain wording of its BE regulations that waiver of the *in vivo* BE requirement could only be made pursuant to § 320.22. The BCS Guidance and the cholestyramine petition response stayed true to this intent.[28] Inconsistent FDA petition responses or litigating positions[29] therefore either should not be accorded any weight or should serve only to demonstrate OGD's inconsistent application of FDA regulations and thereby undermine any deference to which FDA might otherwise be entitled.

Ninth, under the established principle of construction that "normally the specific governs the general,"[30] § 320.22, not § 320.24, governs the circumstances for waiving *in vivo* BE testing, because § 320.22 is the more specific regulation. The sole purpose of § 320.22 is waiver of the *in vivo* BE requirement. Section 320.24, by contrast, does not address waiver of the *in vivo* BE requirement at all, but is a list of various BE methods in which both *in vivo* and non-*in vivo* methods appear.

Tenth, as ViroPharma has previously pointed out,[31] well-established rules of construction require that words must be interpreted in context to harmonize the overall statutory and regulatory scheme, and that any interpretation of one regulation that would render another regulation superfluous should be avoided.[32] If OGD could rely on *in vitro* testing any time it wished based

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[27] *See, e.g.*, Standard Oil Co. v. DOE, 453 F. Supp. 203, 211-217 (N.D. Ohio 1978), *aff'd* 596 F.2d 1029 (TECA 1978) (finding that an agency's newly-adopted interpretation of its own regulations was inconsistent with the agency's repeatedly-affirmed prior interpretation); *id.* at 240 ("[A] federal court will not retroactively apply an unforeseeable interpretation of an administrative regulation to the detriment of a regulated party on the theory that the *post hoc* interpretation asserted by the agency is generally consistent with the policies underlying the agency's regulatory program, when the semantic meaning of the regulations, as previously drafted and construed by the appropriate agency, does not support the interpretation which that agency urges upon the court.").

[28] *BCS Guidance, supra* note 17, at 2 ("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))."); FDA, Citizen Petition Response regarding Cholestyramine, Docket No. 93P-0307 (Mar. 8, 1996) [hereinafter Cholestyramine Pet'n Resp.] ("In making the decision that in vivo bioequivalence testing no longer appeared to be necessary for cholestyramine power drug products, FDA relied principally on 320.22(e)."). Indeed, even in its recent Citizen Petition Response regarding Precose® (acarbose) tablets, OGD cited § 320.22(e) as a back-up authority in the event that its novel claim to waiver authority outside of § 320.22 did not pass muster. Acarbose Pet'n Resp. at 6 n.21. While these FDA statements acknowledge the requirement to seek authority for waivers in § 320.22, FDA's reliance on § 320.22(e) is nonetheless invalid for the reasons discussed in the following section.

[29] *See supra* notes 6 and 28.

[30] *See, e.g.*, Long Island Home Care at Home, Ltd. v. Coke, 127 S. Ct. 2339, 2348-49 (2007).

[31] ViroPharma, Supplement 1 to Petition for Stay of Action, at 18-19.

[32] *See, e.g.*, FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 133 (2000) ("It is a 'fundamental canon of statutory construction that the words of a statute must be read in their context and with a view to their place in the overall statutory scheme.") (quoting Davis v. Michigan Dept. of Treasury, 489 U.S. 803, 809 (1989));

on § 320.24, § 320.22's framework for granting *in vivo* BE waivers in favor of *in vitro* testing would become superfluous. OGD cannot rewrite FDA's regulations in this way. Only notice-and-comment rulemaking could permit the Agency to ignore (by its elimination) § 320.22.

Finally, even assuming § 320.24 provided an independent basis to waive the *in vivo* BE requirement without a § 320.22 waiver, OGD has not explained (and cannot explain) how its proposed *in vitro* BE test for generics seeking to copy Vancocin is consistent with any of the methods identified in § 320.24(b). Section 320.24(a) states that "[a]pplicants shall conduct . . . bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section." However, § 320.24(b) mentions only two *in vitro* tests. The first one is found in § 320.24(b)(1)(ii): "An in vitro test that has been correlated with and is predictive of human in vivo bioavailability data." This provision mirrors the *in vitro* waiver found in § 320.22(d)(3). ViroPharma has previously explained that this is the correct standard against which OGD's dissolution test should be measured.[33] To date, however, OGD has failed to provide any data to validate an *in vivo in vitro* correlation for its Vancocin *in vitro* BE test.

The other *in vitro* provision in § 320.24 is § 320.24(b)(5): "A currently available in vitro test acceptable to FDA (usually a dissolution rate test) that ensures human in vivo bioavailability." It is not surprising that OGD has not cited this provision in support of its *in vitro* dissolution BE test for Vancocin. As explained above,[34] FDA inserted paragraph (b)(5) specifically for DESI drugs, and expressly limited it to DESI drugs, rendering it inapplicable to Vancocin. Because agencies are bound by their clearly-expressed intent at the time regulations are promulgated, OGD cannot now claim that paragraph (b)(5) is generally applicable to a non-DESI drug like Vancocin.

In sum, there is no basis, whether in § 320.24 or any other part of FDA's BE regulations, for OGD to ignore § 320.21's categorical requirement that applications that do not contain evidence of *in vivo* BE must meet the waiver criteria of § 320.22.

IV. *In Vivo* BE Waivers for Generic Drugs Seeking to Copy Vancocin

There are several types of BE waivers set forth in 21 C.F.R. § 320.22. The only waiver conceivably relevant to the *in vitro* test in OGD's March 2006 letters regarding methods for generic applicants to demonstrate BE to Vancocin provides that:

> FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of the drug product if . . . [t]he drug product is, on the basis of scientific evidence submitted

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Edmonds v. Hammett (In re Estate of Covington), 450 F.3d 917 (9th Cir. 2006) ("Our task is to interpret the regulation as a whole, in light of the overall statutory and regulatory scheme, and not to give force to one phrase in isolation. . . . When interpreting a regulation, we must avoid an interpretation that would render another regulation superfluous.") (internal citations and quotations omitted).

[33] ViroPharma, Supplement 1 to Petition for Stay of Action, *supra* note 3, at 18-19.

[34] *See supra* note 18.

in the application, shown to meet an in vitro test that has been correlated with in vivo data.

21 C.F.R. § 320.22(d)(3).[35] Thus, to obtain a waiver of evidence of *in vivo* BE, a generic vancomycin capsule product must be shown to meet, through scientific evidence, an *in vitro* test that has been correlated with *in vivo* data. OGD, however, has never sought to advance any data in support of its *in vitro* BE test for Vancocin, let alone data purporting to correlate that test with *in vivo* data from patients that Vancocin treats.

In fact, as discussed in previous ViroPharma submissions to this docket, OGD's new *in vitro* BE test for Vancocin is legally invalid for a number of reasons, including: (1) it was not properly promulgated or disclosed; (2) it was never explained; (3) OGD offered no regulatory basis for it; and (4) the only authority cited by OGD, the BCS Guidance, does not apply to Vancocin.

ViroPharma welcomes FDA's recent concession of this last point. In its Acarbose Petition Response, FDA acknowledged that "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)."[36] The BCS Guidance, of course, was the only authority cited in OGD's March 2006 letters disclosing OGD's new *in vitro* BE test for generics seeking to demonstrate BE to Vancocin. Having conceded that its only possible authority for the new *in vitro* BE test for Vancocin does not apply to Vancocin, OGD should concede publicly that its new *in vitro* BE test for Vancocin is invalid.

Should OGD wish at some point to repromulgate its *in vitro* test for Vancocin, it would need to do so pursuant to § 320.22(d)(3) and demonstrate that the *in vitro* test correlates with *in vivo* results in Vancocin patients. OGD, however, may be tempted to sidestep § 320.22(d)(3) and instead claim that § 320.22(e) provides an additional basis to waive the *in vivo* BE requirement in favor of an *in vitro* test. The law does not permit such a maneuver.

First, § 320.22(e) does not apply to Vancocin. As ViroPharma has previously explained,[37] FDA's original explanation for the "good cause" waiver was that it was necessary to ensure the "continued marketing of medically important drug products while adequate methodology is being developed or bioavailability studies are being conducted."[38] Vancocin is a critically-

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[35] The requirement that an *in vitro* test be correlated with *in vivo* results is longstanding. *See, e.g.*, Letter from Harry M. Meyer, Jr., M.D., Director, Center for Drugs and Biologics, to Sir or Madam (Nov. 16, 1984), *in* GENERIC DRUGS: A GUIDE TO FDA APPROVAL REQUIREMENTS (2d ed. 1989), at 362-63 ("*In vivo* data will be required for single-source and post-1962 drugs until such time as a correlation between *in vivo* and *in vitro* standards can be established for individual drugs."); *Abbreviated New Drug Application Regulations (Proposed Rule),* 54 Fed. Reg. 28872, 28912 (proposed July 10, 1989) ("The agency has no evidence to show that in vitro data alone are regularly sufficient to assure bioequivalence. In vitro testing can be used for drugs where there is a known in vivo/in vitro correlation, and has been used for pre-1962 drugs not suspected of having, or not likely to have, a bioavailability problem. For all other drug products, an in vivo bioequivalence study on the product is required to support at least one strength of the product."); *Abbreviated New Drug Application Regulations*, 57 Fed. Reg. 17950, 17976 (Apr. 28, 1992) ("In general, the submission of in vivo data is required to support a new product unless there is a known in vivo/in vitro correlation, in which case in vitro data alone may be sufficient.").

[36] *See* Acarbose Pet'n Resp., *supra* note 6, at 6.

[37] ViroPharma, Supplement 1 to Petition for Stay of Action, *supra* note 3, at 17-19.

[38] *Bioavailability and Bioequivalence Requirements,* 42 Fed. Reg. at 1642.

needed medicine, but its continued marketing is not endangered by the unavailability of a bioequivalence method or a wait for bioavailability study results. Moreover, § 320.22(e) plainly states that each "good cause" waiver must be "compatible with the protection of the public health," a showing that OGD has thus far neglected to make in this case. Because the law requires agencies to interpret their regulations consistent with the plain language of the regulations and their intent at the time they were promulgated,[39] and OGD's *in vitro* dissolution test for Vancocin is consistent with neither the wording nor the intent of § 320.22(e), OGD's test cannot be based on that regulation. Finally, as ViroPharma has also addressed previously,[40] OGD cannot use § 320.22(e) to waive the *in vivo* BE requirement and replace it with an *in vitro* method because that would render § 320.22(d)(3), which specifically provides for *in vivo* waivers in favor of *in vitro* methods, superfluous. Simply put, the "good cause" waiver cannot operate as *carte blanche* authority for OGD to do whatever it feels most expedient.

Second, even if § 320.22(e) could be appropriately applied to Vancocin, OGD would need to repromulgate § 320.22(e) because it was never properly promulgated in the first place. FDA failed to give proper notice regarding the § 320.22(e) "good cause" waiver and instead inserted it into a final rule "on [FDA's] own initiative."[41] There was nothing in FDA's proposed rule[42] of which the "good cause" waiver could be considered the "logical outgrowth."[43] This renders it invalid.[44] Moreover, FDA gave its regulation an interpretation when inserting it in the final rule 30 years ago, asserting it was intended to ensure the continued marketing of medically important drug products. This interpretation cannot be modified without notice-and-comment rulemaking.[45] Since then, however, FDA has never proposed[46] for notice and comment the possibility of expanding its interpretation of the "good cause" waiver to include allowing ANDAs to be approved based on *in vitro* dissolution testing for which no *in vivo in vitro* correlation has been established. For this additional reason FDA would also need to repromulgate § 320.22(e) if it wanted to use that regulation to support OGD's *in vitro* dissolution test as a means to waive the requirement of *in vivo* BE for generics seeking to copy Vancocin.

In conclusion, if OGD chooses to claim that § 320.22(e) could permit a waiver of *in vivo* BE testing for generic versions of Vancocin, OGD must first: 1) repromulgate § 320.22(e); 2) describe with sufficient specificity the standards for establishing "good cause" to permit waiver of the requirement of *in vivo* bioequivalence; 3) set forth what showing will be required to

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[39] *See supra* notes 25 and 26 and accompanying text.

[40] ViroPharma, Supplement 1 to Petition for Stay of Action, at 18-19.

[41] *Bioavailability and Bioequivalence Requirements*, 42 Fed. Reg. at 1642.

[42] *Procedures for Determining the In Vivo Bioavailability of Drug Products,* 40 Fed. Reg. 26157 (June 20, 1975).

[43] Envt'l. Integrity Project v. Envt'l. Protection Agency, 425 F.3d 992, 996 (DC Cir 2005).

[44] *See, e.g.,* 5 U.S.C. § 553(b)(3); Long Island Home Care at Home, Ltd. v. Coke, 127 S. Ct. 2339, 2351 (2007); Envt'l. Integrity Project, 425 F.3d at 996.

[45] Envtl. Integrity Project, 425 F.3d at 995.

[46] FDA's failure to conduct the necessary notice-and-comment rulemaking to permit § 320.22(e) to be used to permit waiver of the *in vivo* BE requirement in favor of *in vitro* tests uncorrelated with *in vivo* results stands in contrast to the notice-and-comment rulemaking FDA has engaged in when modifying its BE regulations. *See Bioavailability and Bioequivalence Requirements; Abbreviated Applications*, 63 Fed. Reg. 64222 (proposed Nov. 19, 1998); *Bioavailability and Bioequivalence Requirements; Abbreviated Applications*, 67 Fed. Reg. 77668 (Dec. 19, 2002). FDA's decision not to revise its regulations despite ample opportunity to do so further undermines any potential claim that § 320.22(e) could be the regulatory basis for OGD's new *in vitro* test for Vancocin.

ensure, as § 320.22(e) currently provides, that "good cause" waivers are "compatible with the protection of the public health"; and 4) tailor the "good cause" waiver so that it does not overlap with and thus render superfluous any of the other waivers enumerated in § 320.22, e.g., the requirement of *in vitro-in vivo* correlation in § 320.22(d)(3). Alternatively, OGD could abandon § 320.22(d)(3)'s requirement of *in vitro-in vivo* correlation, but the modification of that regulation would likewise require notice-and-comment rulemaking. Only if OGD follows one of these approaches to modifying FDA's regulations in a manner consistent with administrative law will it be in a position to consider waivers of the *in vivo* BE requirement for generic versions of Vancocin based on the *in vitro* method outlined in OGD's March 2006 letters, or any other non-*in vivo* method that has not been correlated with outcomes in patients.

V. The Need to Correlate Alternative BE Methods With Patient Outcomes

Even if OGD claims it can ignore FDA's *in vivo* BE waiver regulation and instead use some other regulation to waive the requirement of *in vivo* BE, OGD has advanced no evidence for doing so. If OGD were to claim it had evidence for some alternative to *in vivo* BE, it would need to show why that evidence is sufficient to predict *in vivo* outcomes—what happens in patients. This is good science, and what consumers and practitioners expect of generic drugs. Consequently it is also prudent regulation, and therefore written as a requirement into both the FFDCA (BE methods for locally acting drugs must be "scientifically valid") and FDA's regulations (*in vitro* methods must correlate with *in vivo* data).

Clinical endpoint studies measure patient outcomes, so assuming they are properly conducted (e.g., with appropriate design and sufficient statistical power) the answers about safety and effectiveness obtained in clinical trials speak for themselves. Other methods that do not directly measure clinical safety and effectiveness can be used as surrogates of safety and effectiveness, but only if they are scientifically valid and can be expected to assess whether a generic drug is the same as the reference listed drug. 21 U.S.C. § 355(j)(8)(C). If not, the alternate method is not scientifically valid, and cannot answer whether a test drug will work the same in patients as the reference product.

A key issue, then, is how to assess whether a proposed alternative to clinical endpoint studies is scientifically valid.[47] The authors of FDA's bioequivalence regulations understood this, and crafted the regulations to minimize the risk of FDA approving generic drugs that in fact are not bioequivalent to the brands they purport to copy. Consequently, the regulations provide that in order to secure a waiver of the *in vivo* BE requirement for post-1962 drugs, an *in vitro* test must be correlated with and predictive of human *in vivo* data.[48]

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[47] A recent OGD publication reminds us that developing alternatives to clinical endpoint studies is a "scientific challenge[]" for locally acting drugs. OGD, *Critical Path Opportunities for Generic Drugs* (May 1, 2007), at 4.3. In light of this challenge, few alternatives to clinical endpoint BE for locally acting drugs have been developed over the years.

[48] As previously noted by ViroPharma, in the case of two other locally acting GI drugs, cholestyramine and mesalamine, OGD approved generic drugs based on BE methods other than clinical endpoint BE measures only after many years of public discussion of drug-specific data. Letter from ViroPharma, Inc. to Helen Winkle, Director of the Office of Pharmaceutical Science (Jan. 30, 2008) (copy attached as Ex. 1).

It would be wrong for OGD to retreat from this requirement simply to avoid the additional work required to correlate *in vitro* methods with *in vivo* data. Put another way, OGD's recent pronouncements seem to indicate that OGD may let this carefully developed regulatory requirement fall into disuse, and instead claim the "flexibility"[49] to approve generics as bioequivalent based on other regulatory provisions that do not require correlation with what happens in patients. In addition to the legal invalidity of such a maneuver (explained above), the lack of science associated with such an approach would be disturbing, all the more so with a drug like Vancocin, where treatment failures associated with bioinequivalence risk acutely worse patient outcomes, including death. It is a short road from "flexibility" to expediency, at the cost of patient safety and the public's confidence in generic drugs.

It remains unclear how OGD could have met this burden of validation for Vancocin by sole reliance on scientific principles and historical data sets derived from validation of highly soluble, highly permeable systemic drugs. As discussed in this and previous ViroPharma submissions to this docket, there remains significant uncertainty associated with the *in vivo* conditions in the GI tract of patients who receive Vancocin. By recommending its new *in vitro* BE test for generic copies of Vancocin, OGD seems to assert that it has an understanding of these conditions beyond the little that is available in the open literature. Such an understanding would be requisite to reaching a determination (as FDA asserted for the proposed method as applied to the healthy gut) that OGD's proposed *in vitro* testing conditions provide an adequate representation of the *in vivo* environment in patients who take Vancocin.

VI. No Pharmacokinetic or Pharmacodynamic Tests Exist to Support a "Portfolio" BE Approach for Vancocin.

In light of OGD's recent reliance[50] on a multi-test ("portfolio") approach to BE for some other locally acting GI drugs, it bears reiterating that such a portfolio approach—without a clinical endpoint component—is inadequate to assure bioequivalence of generic versions to Vancocin. A pharmacokinetic endpoint study can help ensure that generic vancomycin capsules will not cause greater systemic exposure than Vancocin, but has not been validated as a BE method for this agent. Moreover, unlike the skin blanching effect of corticosteroids, no relevant pharmacodynamic endpoint has been identified as a surrogate measure of Vancocin's local delivery to the GI tract. The only currently available *in vivo* method that is "sufficiently accurate for . . . demonstrating bioequivalence" of Vancocin, an "oral dosage form[] not intended to be absorbed," is a clinical endpoint study.[51] Nevertheless, because OGD has placed renewed emphasis on portfolio approaches in this area, and a recent submission to this Docket mistakenly mentions fecal recovery,[52] ViroPharma below also expands on its previous discussion[53] of fecal recovery of vancomycin.[54]

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[49] Acarbose Pet'n Resp., *supra* note 6, at 3.

[50] *See, e.g.*, Balsalazide Pet'n Resp., *supra* note 6.

[51] 21 C.F.R. § 320.24(b)(4).

[52] Mylan Pharmaceuticals Inc., Response to Petition for Stay of Action by ViroPharma Inc., Docket No. 2006P-0124 (June 13, 2008), at 3.

[53] ViroPharma, Supplement 4 to Petition for Stay of Action, Docket No. FDA-2006-P-0007-0013 (May 17, 2007), at 11.

[54] Of course, OGD could not add another method to its BE approach for Vancocin until it rectifies the many procedural failings in its current approach. *See generally* ViroPharma, Supplement 1 to Petition for Stay of Action,

A. OGD Has Explicitly Disavowed Use of Vancomycin Fecal Measurements in the Evaluation of Bioequivalence

Over two years ago, OGD specifically addressed whether fecal recovery of vancomycin could be used for Vancocin bioequivalence:

> OGD is not recommending the use of vancomycin fecal measurements in the evaluation of bioequivalence.[55]

Since this statement was made in March 2006, OGD has not announced any change in BE methods for generic applicants seeking to demonstrate bioequivalence to Vancocin. Thus, OGD's current bioequivalence policy for Vancocin does not contemplate fecal recovery of vancomycin.

Were OGD to consider adding fecal recovery to its bioequivalence approach for Vancocin, it could do so only pursuant to a legally sufficient process, a topic ViroPharma has addressed in previous filings to this docket.[56] Moreover, if OGD were to engage in such a process, OGD would need to advance sufficient data to demonstrate that fecal recovery of vancomycin is a "scientifically valid measurement" that will "reflect the rate and extent to which [vancomycin] becomes available at the site of action" and "detect a significant difference between the drug and [a generic vancomycin capsule] and [Vancocin] in safety and therapeutic effect." 21 U.S.C. § 355(j)(8)(A)(ii);(C).

B. Fecal Recovery of Vancomycin Has Not Been Validated to Reflect the Rate and Extent of Vancomycin Availability at Vancocin's Site of Action or to Detect Significant Differences Between Generics and Vancocin in Safety or Therapeutic Effect

ViroPharma is unaware of any data validating quantitation of residual drug in feces as sufficiently accurate, sensitive, and reproducible to reflect the rate and extent to which vancomycin becomes available at the site of action or to detect clinically significant differences in the safety and therapeutic effect of different formulations of vancomycin hydrochloride capsules. Moreover, it is unlikely that fecal recovery could ever be demonstrated to be a "scientifically valid" measure of either safety or therapeutic effect.

First, at best, fecal recovery measures an integrated luminal sample of drug available *downstream* from Vancocin's site of action in the colon. Consequently, though fecal drug measurement can show how much drug is excreted in stool after a vancomycin capsule travels through the gastrointestinal tract, it does not address whether there are significant differences between formulations in drug concentration and pharmacological effect *at the relevant site(s) of*

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supra note 3. Assuming those failings are addressed, OGD would then be in a position to consider adding additional methods to create a portfolio approach, but, again, could only do so pursuant to a legally valid procedure.

[55] FDA, Letter from Dale Conner, Pharm.D., to Mintz Levin (Mar. 8, 2006) (attached at Tab 2 to ViroPharma, Supplement 1 to Petition for Stay of Action, *supra* note 3).

[56] *See* ViroPharma, Supplement 1 to Petition for Stay of Action, *supra* note 3.

action within the gastrointestinal tract. This is further complicated by the fact that Vancocin's site(s) of action have not been adequately characterized.

Second, differences in safety due to variable systemic absorption of oral vancomycin would be difficult to detect via fecal recovery of vancomycin. Although oral vancomycin is not absorbed from the healthy human gut, it is well documented that patients with *Clostridium difficile* infection (CDI) may experience systemic absorption of vancomycin after oral administration, and that such absorption has been associated with a number of adverse events.[57] The impact of any differences in formulation of a vancomycin capsule on systemic absorption is not known. Thus, were FDA, in order to meet the requirements of 21 U.S.C. § 355(j)(8)(A)(ii);(C), to seek to demonstrate the scientific validity of fecal recovery of vancomycin as a BE method, substantial data would need to be generated.

C. Demonstration of Safety and Efficacy via Fecal Recovery of Vancomycin Would Not Permit ANDA Approvals

FDA distinguishes between clinical studies conducted for the purpose of demonstrating bioequivalence, and studies conducted for the purpose of demonstrating that a drug is safe and effective. ANDAs are generally reserved for a "*duplicate* of a previously approved drug that contains information to show that the proposed product is identical in active ingredient(s), dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product, and *for which clinical studies are not necessary to show safety and effectiveness.*"[58] Where clinical endpoint studies are used to demonstrate bioequivalence in accordance with 21 C.F.R. § 320.24, the studies are conducted only to show that the test product is the *same* as the reference product, not to show that the test drug is, on its own, *safe and effective.* Conversely, if "clinical studies are necessary to demonstrate safety and/or effectiveness"[59] for a drug that references a listed drug, the proposed drug cannot be approved in an ANDA.

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[57] Vancocin® HCl Capsules label at 2, available at http://www.viropharma.com/docs/RM-0085.00%20(OSG00521_1365)%20Website.htm ("Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of vancomycin and, therefore, may be at risk for the development of adverse reactions associated with the parenteral administration of vancomycin," including ototoxicity and renal dysfunction). *See also, e.g.*, Sangita Aradhyula et al., *Significant Absorption of Oral Vancomycin in a Patient with Clostridium difficile Colitis and Normal Renal Function*, 99 S. MED. J. 518, 518-20 (2006); Luc Bergeron & François D. Boucher, *Possible Red-Man Syndrome Associated with Systemic Absorption or Oral Vancomycin in a Child with Normal Renal Function*, 28 ANNALS PHARMACOTHERAPY 581, 581-84 (1994); Deas M Brouwer et al., *Systemic Absorption of Low-Dose Oral Vancomycin*, 35 J. PHARMACY PRAC. & RES. 222, 222-23 (2005); Sumio Hirata et al., *Elevated Serum Vancomycin Concentrations after Oral Administration in a Hemodialysis Patient with Pseudomembranous Colitis*, 34 JPN. J. CLIN. PHARMACOL. THER. 87, 87-90 (2003); Aaron D. Killian et al., *Red Man Syndrome after Oral Vancomycin*, 115 ANNALS INTERNAL MED. 410, 410-11 (1991); G.R. Matzke et al., *Systemic Absorption of Oral Vancomycin in Patients with Renal Insufficiency and Antibiotic-Associated Colitis*, 9 AM. J. KIDNEY DISEASE 422-25 (1987); P Barclay & P O'Connell, *Therapeutic Serum Levels Achieved with Oral Vancomycin*, 25 AUSTRL. J. HOSP. PHARMACY 125, 125 (1994); C.M. Thompson Jr. et al., *Absorption of Oral Vancomycin—Possible Associated Toxicity*, 4 INT'L J. PEDIATRIC NEPHROLOGY 1, 1-4 (1983).

[58] FDA, Citizen Petition Response, Docket Nos. 2001P-0323, 2002P-0447, and 2003P-0408 (Oct. 14, 2003), at 2-3 (emphasis added).

[59] *Id.* at 15.

Therefore, regardless of whether it could become possible to use fecal recovery of vancomycin to support an independent finding of safety and effectiveness, an ANDA referencing Vancocin could only be approved based on fecal recovery if fecal drug levels were validated as a surrogate for clinical endpoints in Vancocin patients, and pursuant to such a validated methodology the ANDA product was shown to produce the *same* fecal drug levels as those observed with Vancocin within an appropriately-defined equivalence range. ViroPharma is unaware that any party has produced the data to validate such a method.

D. Vancocin NDA History Does Not Support Use of Fecal Recovery as a BE Method

Data submitted as part of the Vancocin capsule NDA included clinical efficacy data following administration of a vancomycin hydrochloride solution and a study that compared plasma, urine, and fecal recovery of vancomycin following oral administration of a Vancocin solution or Vancocin capsules. The NDA sponsor (Eli Lilly) asked FDA to approve Vancocin capsules based on the demonstrated safety and efficacy associated with vancomycin hydrochloride solution and the comparative solution/capsule study, asserting that the solution and the capsule had the same bioavailability or were bioequivalent.

A review of the record shows that FDA did not agree with the sponsor's interpretation of these data and that the solution/capsule study did not demonstrate bioequivalence. FDA's understanding of these data is clarified by discussion of the proposed Vancocin labeling where the Agency asked the sponsor to delete the following sentence due to a lack of evidence: "In comparative bioavailability of the pulvule and oral solution, there were no significant differences in serum or fecal concentrations." Further, the Vancocin approval letter states that the basis for approval was a demonstration of safety and efficacy, not bioequivalence to a vancomycin solution.

The comparative bioavailability study contained in the Vancocin NDA was published in the year following FDA review and approval of Vancocin.[60] Discussion in this paper is wholly consistent with the FDA's position that the data did not provide a demonstration of bioequivalence between solution and capsule, but rather provided the Division of Anti-Infective Drug Products with sufficient evidence of safety and efficacy to support the approval of Vancocin. In the paper, the authors discuss how the objectives of the study "differed from those of a standard bioavailability trial" and that a definitive study of vancomycin availability following oral dosing would require use of an approach "outside the scope" of the present study.[61] The authors state that parameters such as fecal volume and fluid content would be expected to differ between patients receiving treatment and the healthy subjects included in this study and that it would be of interest to compare their findings to those observed in CDAD patients receiving Vancocin.[62]

It is clear from both the Vancocin NDA and the subsequent publication of these data that neither the FDA nor the researchers who conducted the study viewed fecal recovery of vancomycin in healthy volunteers as a validated approach for establishing bioequivalence for this drug

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[60] R. A. Lucas, et al., *Disposition of Vancomycin in Healthy Volunteers from Oral Solution and Semi-Solid Matrix Capsules,* J. CLIN. PHARM. & THER. (1987) 12, 27-31.

[61] *Id.* at 29.

[62] *Id.*

following oral administration. In fact, the authors raise serious questions regarding the appropriateness of the healthy volunteer model given known differences between patients and normals with respect to important parameters of GI function and a lack of any comparison of findings from healthy subjects with results in patients.[63] Consequently, if a sponsor wishes to market a generic vancomycin hydrochloride capsule and submits to FDA fecal recovery data for review, these data could not be used to establish bioequivalence.

The use of fecal recovery data to support a demonstration of bioequivalence for generic vancomycin hydrochloride capsules to Vancocin would require that OGD address the uncertainties previously identified in the Vancocin NDA and publication. Data would need to be generated that validate the use of a healthy patient model and would require a correlation study with patients receiving drug. Further, the nature and clinical relevance of variable recovery would need to be fully discussed and a consensus reached before this method could be used to approve generic versions of an antibiotic such as Vancocin.

E. Fecal Drug Recovery as a BE Method Comparing an ANDA Drug to an Innovator Drug Would Set an Unwarranted New Precedent

It appears there is only one instance in which FDA has allowed use of fecal recovery to demonstrate BE of a drug that acts locally within the GI tract. Xenical® (orlistat) is an oral capsule drug that is minimally absorbed and exerts its therapeutic activity in the gastrointestinal (GI) tract.[64] In the course of the Clinical Pharmacology and Biopharmaceutical Review of Xenical's New Drug Application seeking FDA approval for the indication of long-term weight control, FDA accepted fecal excretion of fat (not the active ingredient) "as a pharmacodynamic endpoint for bioequivalence studies of the clinical and to-be-marketed formulations."[65]

To our knowledge, there is no parallel pharmacodynamic marker of the action of vancomycin in the GI tract. No similar data exists for Vancocin that would withstand rigorous scientific scrutiny correlating diminished levels of *Clostridium difficile* bacteria, spores or another potential pharmacodynamic marker recovered in feces with the clinical endpoint of cessation of diarrhea in patients afflicted with *Clostridium difficile*. It bears further noting that even in the case of Xenical, the formulations of the drug product being compared were both from the same sponsor and the FDA clarified that "whether or not fecal fat excretion is a valid surrogate marker for clinical efficacy (i.e. weight loss) is unknown" and stressed that "its utility in testing the bioequivalence of generic, or other, formulations of orlistat remains dubious."[66]

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[63] In its recent filing to this docket, Mylan Pharmaceuticals Inc. makes no attempt to refute the fact that this publication did not establish a validated BE method for Vancocin. Mylan Pharmaceuticals Inc., Response to Petition for Stay of Action by ViroPharma Inc., Docket No. 2006P-0124 (June 13, 2008), at 3.

[64] Xenical ® Capsules label at 1 & 3, available at http://www.fda.gov/cder/foi/label/2007/020766s022lbl.pdf.

[65] Clinical Pharmacology and Biopharmaceutical Review of Xenical, March 21, 2007 at 1 & 8, available at http://www.fda.gov/cder/foi/nda/99/020766a.htm.

[66] *Id.*, at 9, 19.

VII. Amended Actions Requested

In light of the foregoing, ViroPharma hereby amends the actions requested in this petition to include the following:

- FDA should publicly disavow the *in vitro* dissolution test for generic copies of Vancocin outlined in OGD's March 2006 letters because the only authority they cite is the BCS Guidance and FDA has now publicly conceded that the BCS does not apply to drugs like Vancocin.
- FDA should withdraw 21 C.F.R. § 320.22(e) and re-promulgate a proposed rule that explicitly sets forth the criteria and standards according to which FDA may establish "good cause" to grant a biowaiver beyond the criteria established in 21 C.F.R. § 320.22(b)-(d) and determine that such a waiver is "compatible with the public health."
- FDA should withdraw the 2000 BCS guidance because the authority upon which it relies, 21 C.F.R. § 320.22(e), is invalid.

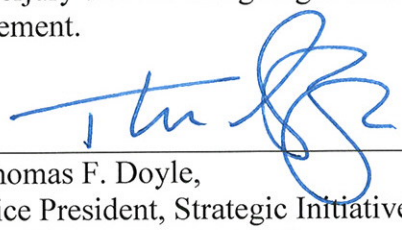
VIII. CONCLUSION

In March 2006 ViroPharma learned from a Canadian stock analyst that OGD had abandoned clinical endpoint bioequivalence in favor of an *in vitro* dissolution method for generic companies seeking to copy ViroPharma's only marketed product, Vancocin. This petition was filed because FDA would not acknowledge, let alone explain, OGD's policy change. FDA's failure to explain OGD's action continues to date, forcing ViroPharma to speculate as to OGD's bases for its *in vitro* dissolution method. The instant filing refutes positions taken by OGD in recent responses to other petitions because OGD may be considering similar action regarding Vancocin.

However, the preferred approach as both a matter of law and science would be for OGD to begin by explaining itself publicly in a process permitting interested members of the public like ViroPharma and the many consumers, scientists, and clinicians who have written to FDA protesting OGD's action to review the full bases for OGD's new *in vitro* approach, including all data on which FDA purports to base this approach, before it is used to review or approve potentially inequivalent generic versions of a life-saving antibiotic. The Agency would then review comments received, Advisory Committee experts would also be consulted, and neutral decisionmakers would make the ultimate decision as to whether OGD's new *in vitro* test will ensure patients get the same safe and effective treatment as they currently get with Vancocin. This has been ViroPharma's request from the beginning, and ViroPharma respectfully reiterates this request today.

Verification

Although not legally required, I certify, that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about the time subsequent to the filing of the instant Petition*. I further certify that neither I nor ViroPharma received or expects to receive any cash payments or other consideration to file this Petition or any of the information contained herein other than compensation paid to me as an employee of ViroPharma. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this Petition Supplement.



Thomas F. Doyle,
Vice President, Strategic Initiatives
ViroPharma Incorporated

* As explained herein, this document was filed in response to recent statements made by FDA and others (e.g., FDA's Acarbose and Balsalazide citizen petition responses, and Mylan Pharmaceuticals' June 13, 2008 filing to this docket).