January 11, 2008

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c124

RE: Docket No. 2006P-1024

Dear FDA:

On March 17, 2006 (as amended March 30, 2006), ViroPharma Incorporated filed a petition seeking to stay approval of any new drug applications filed under Section 505(j) or Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (collectively, "ANDAs") that reference Vancocin® (vancomycin hydrochloride capsules) and rely on a new *in vitro* bioequivalence test emanating from FDA's Office of Generic Drugs ("OGD") (FDA Docket Number 2006P-0124, the "Vancocin docket"). ViroPharma has filed to this docket a number of supplements and amendments to its petition since that date.

On August 29, 2007, ViroPharma filed to FDA Docket Number 2007D-0168 comments on the Draft Guidance for Industry on Bioequivalence Recommendations for Specific Products (the "Draft BE Guidance").

On January 7, 2007, ViroPharma, certain of its advisors, and subject matter experts met with representatives of FDA's Office of Pharmaceutical Sciences (OPS), Office of Generic Drugs (OGD) and FDA legal counsel. During this meeting, ViroPharma provided a variety of information to FDA, including a discussion of procedural deficiencies noted by ViroPharma related to OGD's bioequivalence recommendation for Vancocin. This discussion referenced the comments made by ViroPharma on the Draft BE Guidance.

In the meeting, FDA confirmed that transparency and process were important to its mission, and FDA counsel requested that ViroPharma file the above-referenced comments on the Draft BE Guidance to the Vancocin docket. Accordingly, those comments are attached hereto for filing to this Docket Number 2006P-0124.

Respectfully submitted,

Thomas F. Doyle
Vice President, Strategic Initiatives
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August 29, 2007

Division of Dockets Management (HFA-305)
Food and Drug Administration
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Rockville, MD 20852

RE: Docket No. 2007D-0168

Draft Guidance for Industry on Bioequivalence Recommendations for Specific Products

Dear FDA:

We would like to take this opportunity to comment on the Draft Guidance for Industry on Bioequivalence Recommendations for Specific Products (the "Draft BE Guidance")[1] recently issued by FDA's Office of Generic Drugs (OGD). ViroPharma Incorporated is a biopharmaceutical company dedicated to the development and commercialization of products that address serious infectious diseases, with a focus on products used by physician specialists or in hospital settings.

We applaud OGD's attempt to make its decisions and decision-making process more open to the industries, academia and the public. Through the Draft BE Guidance OGD acknowledges that it is extremely important to provide a meaningful opportunity for the public to consider and comment on product-specific BE study recommendations. The proposal to issue notice in the *Federal Register* (FR) announcing availability on the FDA Web site of new product-specific draft and final BE recommendations is endorsed and commended. The Draft BE Guidance is a positive first step toward ensuring protection of the public health based upon strong science and open public process.

Unfortunately, as its accompanying product-specific draft Guidances[2] make clear, under the Draft BE Guidance OGD's issuance of BE recommendations will only recite, but not explain, bioequivalence testing methods recommended by OGD for particular products. OGD claims this will be sufficient to "provide a meaningful opportunity for the public to consider and comment" on proposed BE recommendations.[3]

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[1] Draft Guidance for Industry on Bioequivalence Recommendations for Specific Products, 72 FR 30388 (May 31, 2007).
[2] Draft Guidances for Industry Describing Product-Specific Bioequivalence Recommendations, 72 FR 30386 (May 31, 2007).
[3] 72 FR at 30387, 30389.

It is difficult to comment meaningfully on draft BE recommendations of unidentified origin which are unaccompanied by supporting data or explanation.[4] For these reasons, the Draft BE Guidance violates principles of good science and the requirements of the law, as explained more fully below. The Draft BE Guidance should not be finalized and OGD should not approve any products based on unsubstantiated BE recommendations until the sources, supporting data, and rationale for those recommendations have been made public, the public has had a chance to comment on them, and FDA has reviewed and responded to the comments received.

Undisclosed Science

Undisclosed science is the first flaw in the Draft BE Guidance. Science does not progress without transparency. The draft recommendations published by OGD leave undisclosed what, if any, data or scientific rationale led OGD to make them, and thus require the public to take on faith whatever bioequivalence tests OGD chooses to recommend. OGD must be transparent. It must disclose the scientific basis for its BE recommendations to permit a meaningful review by interested third parties in order to ensure that the best possible science is brought to bear in this important area.

Abdicating Public Health Role

The Draft BE Guidance also shifts the burden of validating generic drug standards from OGD to members of the public. Rather than meeting its burden to regulate only based on data and science it has demonstrated are valid, the Draft BE Guidance permits OGD to make unsubstantiated proposals, leaving it to others to generate the data and science to show that those proposals are incorrect. If none care to comment, OGD's draft proposals presumably will become final without ever having been demonstrated to be scientifically valid. Comments that are submitted will be unable to critique meaningfully the science behind OGD's recommendations because OGD will not have disclosed it. OGD is abdicating FDA's duty as a public health agency by acting without demonstrating a valid basis for doing so, and then shifting the burden to others to detect flaws in OGD's unsubstantiated actions.

For example, there has been little scientific data presented to date supporting bioequivalence recommendations for most locally acting products. Particularly for drug products used to treat life-threatening conditions, it is imperative that the data supporting BE recommendations be disclosed because the use of a non-equivalent product could cause significant harm, including death to patients.

OGD Must Explain Itself

By not requiring draft product-specific BE Guidances to include any explanation of their scientific basis, the Draft BE Guidance also violates the Administrative Procedure Act. Agencies that fail to explain their actions violate the APA's admonition against arbitrary

[4] ViroPharma speaks from experience on this issue. See ViroPharma Incorporated, Petition for Stay of Approval, Docket No. 2006P-0124.

and capricious conduct. 5 U.S.C. § 706(2)(A). For a more fulsome discussion of this topic, *see* ViroPharma Incorporated, Supplement 1 to Petition for Stay of Approval, May 31, 2006, 9-12, FDA Docket No. 2006P-0124.

OGD Must Identify Its Sources, Including Supporting Data and Models

The Draft BE Guidance should also be amended to ensure that product-specific BE Guidances are issued in compliance with the Data Quality Act. The Data Quality Act requires administrative agencies to maximize the quality, objectivity, utility, and integrity of the information that they disseminate. Pub. L. No. 106-554, § 515 Appendix C, 114 Stat. 2763A-153 (2000). Under the Data Quality Act, OGD must:

> identify the sources of [its BE recommendations] (to the extent possible, consistent with confidentiality protections) and, in a scientific, financial, or statistical context, the supporting data and models, so that the public can assess for itself whether there may be some reason to question the objectivity of the sources. 67 FR 8459 (Feb. 22, 2002).

The Draft BE Guidance violates this provision because it does not require OGD to identify the sources of its BE recommendations, which, because they are made in a scientific context, should also be accompanied by their supporting data and models. To bring the Draft BE Guidance into compliance with the Data Quality Act, OGD needs to (A) determine how it will identify the sources of its BE recommendations; (B) in a manner consistent with confidentiality protections; such that (C) the public can assess for itself whether there may be some reason to question the objectivity of OGD's sources.

As the developer of BE recommendations, OGD should have little trouble identifying its sources each time it issues a draft BE Guidance for a particular drug product. OGD has already identified in the Draft BE Guidance the four general sources on which its BE recommendations are based: (1) FDA's understanding of the characteristics of the listed drug; (2) published literature; (3) agency research; and (4) OGD consults with other CDER offices.[5] Thus, when issuing a new draft BE Guidance, OGD should identify which particular sources within each of these general categories it relied on.

To the extent any such sources are not publicly available, OGD should disclose them, consistent with confidentiality protections. Protection of confidentiality is not an issue regarding published literature, so it should not be a problem for OGD to list citations to any literature sources a draft BE recommendation relies on. Agency research and OGD consults with other CDER offices may raise confidentiality concerns, and FDA's understanding of the characteristics of the listed drug presumably will be based strongly on the innovator's file. Thus, for these three categories OGD will need to develop a

[5] Draft BE Guidance at 2.

process for determining whether there are trade secrets or confidential commercial information which cannot be disclosed.[6]

By identifying and disclosing its sources when it issues a draft BE Guidance for a particular drug, OGD will permit the public to assess for itself whether there may be some reason to question the objectivity of OGD's sources. This approach will enhance confidence in generic drugs, as OGD recently reiterated:

> Methods for equivalence based on sound science build the confidence of health care providers, patients, and the public that generic products are equivalent to innovator products.[7]

Sound science is a product of OGD transparency not only about what it does (i.e., the BE tests it recommends), but also how and why OGD arrived at its recommendation (i.e., the data and science which led OGD to make a particular draft BE recommendation).[8] Disseminating this information and receiving back public input on it are critical to achieving FDA's mission to promote and protect the public health.[9]

In Vitro-In Vivo Correlation

The Proposed BE Guidance also fails to underscore an important requirement for in-vitro assessments: the correlation of in-vitro studies with important in-vivo effects. FDA's previously issued 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. Correlation of in-vitro results to in-vivo performance is also required pursuant to 21 C.F.R. § 320.22(d)(3) (*in vivo*

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[6] To the extent confidentiality concerns would prevent sufficient explanation of a draft BE recommendation under the APA, then issuance of such a recommendation might be precluded as arbitrary and capricious under the APA, as discussed above.

[7] OGD, Critical Path Opportunities for Generic Drugs, May 1, 2007, at 2.

[8] "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." *HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public* in October 2002, at F.

[9] "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. Moreover, For BE standards for drugs selling more than $100 million per year, OGD must disseminate sufficient information to ensure that third parties can accurately reproduce OGD's results. Id. at F.VII.A-B.

bioequivalency testing cannot be waived unless the *in vitro* test "has been correlated with *in vivo* data".) The Draft BE Guidance must ensure compliance with this regulation.

Conflict with BE Regulations

The Draft BE Guidance and each of the draft product-specific Guidances state that they are nonbinding and that "[y]ou can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations". They further state that, once finalized, the Guidances will represent the Agency's current thinking.

The "alternative approach" language is indeed puzzling. This standard Guidance boilerplate seems inapplicable to product-specific bioequivalence recommendations. Once OGD has recommended a particular BE approach for a specific product, there can be no "alternative approach[es]" that will satisfy the requirements of FDA's bioequivalence regulations. Those regulations require that "[a]pplicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available . . .". 21 CFR 320.24(a).

By recommending a particular BE approach, OGD is selecting that approach among the available options. Because the regulation permits only one (the most accurate, sensitive, and reproducible) approach for a given product, OGD's recommendation becomes that one approach. The other options are no longer available because, by virtue of the fact that OGD did not choose them, they are not "the most" accurate, sensitive and reproducible. The regulation does not permit OGD to select an option that is less accurate, sensitive and reproducible than the others, and OGD presumably would not want to do so in any event.

Before finalizing the Draft BE Guidance, OGD will need to consider the conflict between this categorical aspect of FDA's bioequivalence regulations and its interaction with product-specific BE recommendations promulgated pursuant to the Draft BE Guidance that ostensibly permit other, "alternative approach[es]" to also be used.

Conclusion

Before it is finalized the Draft BE Guidance should be amended to:

1. Require FDA to explain clearly and unambiguously the data and rationale for each draft BE recommendation (including the presentation of relevant data generated by FDA in support of the proposed BE approach) and include this information as part of the posting of the draft recommendation to FDA's Website;

2. Include a procedure for appropriately addressing confidentiality protections;

3. Provide a reasonable period for interested members of the public to review and respond to draft BE recommendations;

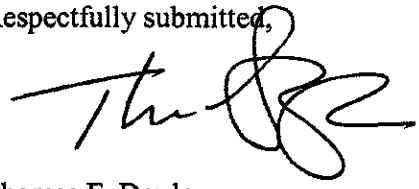
4. Require FDA to respond to comments received with respect to any product specific bioequivalence recommendation before using any such recommendation in the review or approval of a generic drug application;

5. Reiterate the requirement that proposed in-vitro BE tests must be correlated with in-vivo results;

6. Require that, before any BE recommendation for products that treat a serious or life-threatening disease is posted to the FDA's Website, all data purporting to correlate in-vitro tests with in-vivo results be subject to the prior review and approval of a Scientific Advisory Committee convened and requested to provide input to such matters; and

7. Be brought into compliance with FDA's existing bioequivalence regulations.

Respectfully submitted,



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