Minutes of Meeting
FDA/ViroPharma Regarding Vancomycin Hydrochloride
January 7, 2008
White Oak, Building 21, Room 2560

ViroPharma Attendees:

Thomas Doyle, ViroPharma
Steven Gelone, Pharm.D., ViroPharma
Allan Fox, FoxKiser
Ken Wilmarth, Ph.D., M.S.P.H., FoxKiser
Matthew Peterson, FoxKiser
Diane Robertson, Ph.D., FoxKiser
Antony Weaver, FoxKiser
Dale Gerding, M.D., Loyola School of Medicine/Hines VA Medical Center
Thomas Foster, Pharm.D., University of Kentucky

FDA Attendees:

Liz Dickinson, Office of Chief Counsel, Food and Drug Administration (FDA)
Nam Kim, Office of Regulatory Policy, Center for Drug Evaluation and Research (CDER), FDA
Helen N. Winkle, Director, Office of Pharmaceutical Science (OPS), CDER, FDA
Keith Webber, Ph.D., Deputy Director, OPS, CDER, FDA
Ted Sherwood, Special Assistant to the Director, OPS, CDER, FDA
David Read, Regulatory Counsel, OPS, CDER, FDA
Lawrence Yu, Ph.D., Director for Science, Office of Generic Drugs (OGD), OPS, CDER, FDA

I. Introductions

II. Docket Reminder – FDA indicated that they will submit the minutes of this meeting and all supporting materials to the FDA Docket No. 2006P-0124 (the number was changed to FDA-2006-P-0007 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008). ViroPharma confirmed that it understood this requirement.

III. Presentation by ViroPharma Attendees (multiple) made the following points, as described in the attached slide presentation:

1. Vancocin® (vancomycin hydrochloride capsules, USP) is a locally acting gastrointestinal drug product, a class of compounds explicitly excluded from consideration in the Biopharmaceutics Classification System (BCS).
2. Vancocin is the only FDA-approved agent for the treatment of *C. difficile* infection (CDI), an acute, life-threatening disease. A hypervirulent *C.*

difficile strain now epidemic in the US is characterized by more rapid disease progression and increased serious morbidity and mortality (6-7%). Treatment guidelines indicate Vancocin as first line therapy for severe CDI.

3. CDI is an infection of the gastrointestinal tract associated with profound structural and functional changes in diseased patients. The GI tract of CDI patients is not 'normal' or well understood, unlike the healthy GI tract on which the BCS model assumptions are based.
4. Historically, FDA required clinical endpoint studies to demonstrate bioequivalence of generic products to Vancocin.
5. Without public process or announcement, instead of clinical endpoint studies for generic products to demonstrate bioequivalence to Vancocin, OGD began recommending a BCS-based waiver of *in vivo* bioequivalence testing intended and validated for use with rapidly dissolving BCS-1 drugs.
6. OGD selectively disclosed its policy change to certain private parties, one of whom made the change public.
7. The new BE method OGD began recommending for Vancocin was in fact developed as part of a model for predicting the *in vivo* behavior of *systemic* agents using two key properties of the drug: solubility and permeability. Extrapolation of this method to Vancocin (which is in a class of drugs explicitly excluded from consideration in developing the BCS model) requires a determination that the model remains valid when one of the two principal components (high permeability) that define the model is removed from consideration. This is a significant departure from how the method was intended to be used, and with respect to its use with Vancocin should be viewed as an untested and unvalidated hypothesis. Given the seriousness of the disease being treated, the lack of concordance of GI conditions in patients being treated with model assumptions, and the validity of the model when its fundamental underpinning is modified, this method as applied to Vancocin does not represent the application of good science.
8. Available clinical data are not consistent with the hypothesis underlying OGD's new BE method. Dissolution data submitted by ViroPharma do not support FDA's statement that Vancocin is rapidly dissolving per FDA's criteria.
9. Given the acute, severe nature of CDI, bioinequivalent generics approved based on OGD's untested hypothesis would pose severe risk to patients. OGD currently does not, but should consider this risk, consistent with FDA policy.
10. *In vitro* dissolution cannot address safety issues associated with systemic absorption of vancomycin in CDI patients.
11. Absence of public process increases the risk OGD might be wrong, risks loss of public confidence in generic drugs, and fails to comply with multiple legal requirements.

12. Until a robust alternative method can be developed in a data-driven public process that complies with the law, clinical endpoint studies are the only established method available for the demonstration of bioequivalence of generic products to Vancocin.
13. ViroPharma is prepared to assist the Agency in developing a process that will result in scientifically sound alternatives to clinical trials.

IV. General Discussion

1. FDA reaffirmed the Agency's commitment to transparency and public process.
2. FDA described the dated approval of the vancomycin new drug application.
3. ViroPharma indicated that clinical endpoint studies were conducted with vancomycin capsules, but the studies may not have been submitted to the Agency.
4. FDA indicated that sound science is the principle that OGD uses to establish bioequivalence methodologies.
5. FDA expressed its appreciation of the materials presented and subsequent discussion.

V. Action Item – ViroPharma will submit a corrected version of slides to remedy a typo. (Done on January 7, 2008.)

VI. Followup – ViroPharma sent a January 30, 2008 letter to FDA (copy attached), addressing a couple of issues raised by FDA in the discussion at the end of the meeting. Regarding alternatives to clinical endpoint bioequivalence studies for Vancocin, FDA indicated that the next step would be an opportunity for public input.

VII. Annotations for slides 8-10 – as they have no text explanation in the slide deck, Dr. Gerding suggested the following annotations for slides 8-10:

Slide 8: Post-mortem gross specimen of cecum showing confluent pseudomembranes.
Slide 9: Histologic view of pseudomembrane erupting from inflamed mucosa in pseudomembranous colitis.
Slide 10: Histologic view of marked inflammation, mucosal necrosis and pseudomembrane in pseudomembranous colitis.

Minutes prepared by FDA (T. Sherwood), with modifications submitted by ViroPharma.