



September 1, 2006

The FDA Commissioner  
c/o Division of Dockets Management  
5630 Fishers Lane  
Room 1061 (HFA-305)  
Rockville, MD 20852

Re: Docket No. 2006P-0124

Dear Commissioner:

This correspondence is in reference to Docket No. 2006P-0124 entitled "Stay any approvals of an Abbreviated New Drug Application (ANDA) for Vancocin® Capsules."

To introduce myself, Joseph S. Bertino Jr., Pharm.D., I am a Clinical Pharmacologist and the Scientific Director of the Ordway Research Institute Drug Development Center ([www.oriddc.org](http://www.oriddc.org)), a not for profit research organization. I have served as a member of the FDA Antiinfective and Antiviral Advisory Committees and currently I am a Special Government Employee. I currently have no financial interest (either grants, stock or otherwise) in ViroPharma Inc., the manufacturer of Vancocin ® Capsules.

I understand that the Office of Generic Drugs (OGD) has suggested that generic versions of oral vancomycin capsules can be approved with *in vitro* data only rather than with clinical trial data. This is of concern to me.

*C. difficile* infection continues to be a problem with an ever increasing incidence and severity of disease. While metronidazole (which is not labeled for treatment) has remained the mainstay for initial treatment, the use of oral vancomycin has increased due to lack of response to metronidazole treatment and increasing severity of infection. My concerns with the proposal to not require *in vivo* efficacy and pharmacokinetic data have their basis in a number of areas.

First, the change by OGD to allow application of the biopharmaceutics classification system (BCS) guidelines has not been intended to be applied to locally acting drugs such as oral vancomycin. The BCS, by its own terms, applies to drugs that are highly soluble, highly permeable, and rapidly dissolving. Oral vancomycin does not possess these characteristics. The approval of a rapidly dissolving generic form of vancomycin may result in similar findings to the Vancocin® oral solution that was previously approved in the U.S. for use, lack of bioequivalence. This product was eventually removed from the U.S. marketplace. Dissolution studies are at best, problematic given the difficulty in determining *in vitro* to *in vivo* correlations. As I was unable to find any written documentation to support application of the BCS guidelines to oral vancomycin (in lieu of clinical trials), this decision is extremely unclear and confusing. From a scientific standpoint, it would be helpful to all for FDA to elucidate the rationale behind this decision.

Secondly, in the 1990's the FDA required *in vivo* efficacy studies of another locally acting drug, sucralfate when Teva requested approval of a generic version. Sucralfate acts locally in peptic ulcer disease by binding to damaged tissue. *C. difficile* infection is as important a disease state as peptic ulcer disease and thus, I question why clinical studies were required for generic sucralfate but may not be required for generic oral vancomycin. The rule requiring *in vivo* studies for



sucralfate was not only upheld for Teva's generic form, but again when another company, RatioPharm brought a generic sucralfate product to market.

Finally, my concern from a clinical standpoint has to do with the potential for therapeutic failures. Without clinical studies as a requirement for approval of a generic oral vancomycin, could failures of therapy be pinpointed to the product, resistance, recurrence or reinfection? *C. difficile* is often seen in debilitated patients and I do not believe that the risk involved with failure is in the best interest of the patient. Comparative clinical trials (which include pharmacokinetic sampling), would help to resolve the question of generic oral vancomycin versus the branded form.

I respectfully request that the FDA reconsider the ANDA for generic equivalence to oral Vancocin®. I believe that the precedent for poorly absorbed, slowly soluble drugs is the combination of *in vitro* studies as well as *in vivo* clinical trials (as evidenced by the sucralfate example cited above). I realize that this is a complex issue with a complex drug and ask that the more conservative approach be considered in the interest of the patient.

Sincerely,

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and

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