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Dear Dr. Winkle,

I wanted to take the opportunity to thank you again for having us to FDA to discuss bioequivalence method development for Vancocin® (vancomycin hydrochloride capsules). Your comments reaffirming the central role of transparency and public process as part of FDA's approach to ensuring public health protective, science-based regulation were greatly appreciated. This letter follows up on a couple of the issues raised by FDA during discussion at the end of the meeting.

First, Liz Dickinson asked whether Vancocin was discussed at the October 2004 meeting of FDA's Advisory Committee for Pharmaceutical Sciences (ACPS). As we said when we met with you, the only mention of Vancocin at that meeting was Dr. Yu's statement reiterating that clinical endpoint studies are the bioequivalence (BE) method for Vancocin. We would add that in the background materials provided to Committee members prior to the meeting FDA wrote that "application of the scientific basis of the BCS would suggest that a high solubility drug in a rapidly dissolving formulation . . . may be eligible for a biowaiver". This statement of hypothesis was never discussed at the meeting in the context of method development for any locally-acting GI drug. We can also add that having spent some two years reviewing the available public records, we have found no reference to OGD's new *in vitro* dissolution BE method for Vancocin prior to its March 2006 disclosure by the Canadian stock analyst. Further, based on our attendance at the relevant scientific meetings and workshops for the past two years, we are aware of only one FDA statement regarding OGD's new method. It was never written on a slide (we have yet to find mention of vancomycin BE method development on any FDA slide deck), but, as more fully explained in our petition papers, was made as an aside by Dr. Yu during a presentation at the Crystal City dissolution conference in May 2006.

Dr. Yu's single, conclusionary statement, after OGD had already adopted its new *in vitro* BE method, that evidence and science support the use of an *in vitro* dissolution BE test for Vancocin contrasts sharply with the public process OGD has engaged in to develop alternatives to clinical endpoint BE for other locally acting GI drugs. For cholestyramine, OGD first presented an abstract of work "designed to perform preliminary experiments toward developing an in vitro bioequivalence test for cholestyramine which could be used for the determination of therapeutic bioequivalence of a generic product in a process to approve it for marketing" at the November 1991 meeting of the American Association of Pharmaceutical Scientists. (Notably, this abstract came only after some three years of internal scientific work on the issue by FDA and certain outside consultants.) A year later, at the November 1992 AAPS meeting, OGD presented another abstract described as a "continuation of our efforts to develop *in vitro* bioequivalence test for cholestyramine drug products". In July 1993 OGD published an Interim

Guidance Cholestyramine Powder In Vitro Bioequivalence which further cited as references four academic papers as well as data obtained by and on file at FDA. In June 1994 FDA prepared a synopsis entitled "The Raw Data Behind Cholestyramine Interim Guidance". After this public process starting in 1991, the Interim Guidance's new *in vitro* BE method was not used to approve generic cholestyramine products until February 1996.

For mesalamine, another locally acting GI drug, FDA began presenting data regarding the possibility of an alternative to clinical endpoint BE studies at least as early as the October 2004 ACPS meeting that Liz Dickinson asked about. At that meeting, Gordon Amidon presented a background on the 'scientific principles' of the BCS and how they might be applied to thinking about locally acting GI products, using mesalamine as his primary example. OGD's Robert Lionberger gave a presentation titled "Bioequivalence of Locally Acting GI Drugs", the bulk of which related to the role of PK studies as a measure of formulation performance for this class of drugs and used mesalamine data as the basis for discussion. Subsequent to the October 2004 ACPS meeting and until the recent (December 2007) approvals of generic versions of the mesalamine prodrug balsalazide disodium, alternatives to clinical trial BE studies for mesalamine were widely discussed at a number of FDA and AAPS sponsored meetings and workshops.

In sum, use of BE methods other than clinical endpoint bioequivalence for these other locally acting GI drugs occurred only after several years of public process that, importantly, began with proposal and discussion of drug-specific data. The absence to date of any public process regarding OGD's new *in vitro* BE method for Vancocin would thus seem to indicate that the next step for FDA is to commence a public process like that used for cholestyramine and mesalamine. Abstracts, AAPS and FDA meetings, and FDA Advisory Committee meetings will all provide opportunities for experts and others to assess OGD's proposal and either give it their endorsement or critique any failings they might see. In this way, for Vancocin OGD will engage in at least the same level of process and scientific discussion it has previously afforded locally acting GI drugs used to treat far less serious disease where the consequences associated with getting it wrong do not pose as great a risk to patients. Open process and public discussion will also make BE method development for Vancocin consistent with OGD's recent Critical Path document identifying the development of BE methods for locally acting drugs as a scientific challenge needing "additional discussion and collaboration about the science".

The second issue I wanted to follow up on was consideration of patient risk when OGD determines appropriate use of biowaivers. As we discussed at the meeting, fundamental principles of risk assessment, which FDA has explicitly stated it employs in assessing the use of biowaivers for generic drugs, include two key factors: (1) likelihood of occurrence of bioinequivalence; and (2) severity of consequences if bioinequivalence occurs. Vancocin is a drug where the second factor weighs more heavily than with most drugs, because Vancocin is indicated to treat an acute, life-threatening infection. Treatment failure in these patients may result in severe morbidity including loss of the colon or death. You will recall that in our presentation we cited examples of how the biowaiver monographs for WHO's essential drugs overtly consider the "severity of consequences" in a discussion of the risk to patients associated with bioinequvalence and we critiqued how OGD apparently does not consider this factor when it makes biowaiver decisions for generic drugs.

Toward the end of the meeting, Dr. Yu acknowledged that the WHO monographs consider patient risk associated with bioinequivalence but asserted that most of these monographs are for BCS Class III drugs for which OGD does not allow biowaivers and that all OGD decisions regarding use of biowaivers are scientifically appropriate. Dr. Yu thus seems to suggest two reasons why analysis of patient risk associated with bioinequivalence is not needed when biowaivers are recommended by OGD: (1) OGD's science is just too good to be wrong; and (2) unlike the WHO monographs, OGD has not extended biowaivers beyond rapidly dissolving, BCS-I drugs where the data and experience base is strong.

It is true that OGD has not extended the use of biowaivers to BCS Class III drugs. Indeed, while the concept has been a topic of active research and open discussion for over a decade, the conclusion to date has been that there is insufficient basis to permit biowaivers beyond BCS-I drugs. At the same time, Dr. Yu apparently sees no issue with extrapolation of this same biowaiver – absent any apparent data or public discussion – for use with Vancocin, a non-BCS drug, one used to treat a life-threatening disease. It is difficult to understand why Dr. Yu would not think this extrapolation of a BCS waiver beyond the BCS model and application of an untested hypothesis does not create a level of uncertainty sufficient to overtly consider the risk of bioinequivalence and the severity of the consequences bioinequivalence poses to patients receiving the drug.

Before adoption of alternatives to clinical endpoint bioequivalence for cholestyramine or mesalamine, and before expansion of BCS-based biowaivers beyond BCS-I drugs, FDA has previously engaged in data-driven, public process. Whether or not these precedents would meet the legal standards we have also raised with the Agency is not a subject of this letter. They do, however, establish a minimum of open scientific consideration that OGD has yet to engage in with respect to Vancocin. As stated in OGD's Critical Path document, "[m]ethods 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". We submit that as a science-based agency FDA should make its development of bioequivalence methods for Vancocin more consistent with the open, data-driven, scientific approach it has, to its credit, previously engaged in on similar issues.

Very truly yours,

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