December 21, 2006

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

RE: Docket No. 2006P-0124

My name is Reza Fassihi. I am a Professor of Biopharmaceutics and Industrial Pharmacy, at Temple University in Philadelphia, PA and a fellow of the American Association of Pharmaceutical Scientists (AAPS). My research focuses on drug product design, formulation and development of conventional and modified drug dosage forms, intrinsic permeability of the intestinal wall and drug transport, biopharmaceutical aspects of drug delivery, and the in vitro and in vivo evaluation of pharmaceuticals. This letter is in reference to the above captioned docket number entitled "Stay any approval of an Abbreviated New Drug Application (ANDA) for Vancocin® Capsules".

It has come to my attention that the Office of Generic Drugs (OGD) will evaluate ANDAs for Vancocin Capsules based only on *in vitro* dissolution testing using the Biopharmaceutics Classification System (BCS) framework in lieu of conducting a clinical trial. I am opposed to this proposition as Vancocin Capsules do not meet the criteria for a BCS class I drugs as outlined in the guidances provided by FDA, in that they are not highly permeable and / or highly soluble to fit the specifics of BCS class-I requirements. Therefore, Vancocin Capsules should not be subject to a waiver of clinical bioequivalence when the therapeutic objectives of the drug are considered.

The foundation of the BCS system is that agents that are highly permeable and rapidly dissolving (defined as 85% dissolution in 30 minutes) form a drug solution in the stomach (so-called BCS class I drugs). They therefore enter the small intestine as a solution. Therefore, systemic absorption in the small intestine is not limited by dissolution or gastric emptying and bioequivalence can be considered "self-evident". Vancocin Capsules are not systemically absorbed and do not meet the definition of a rapidly dissolving solid dosage form. In addition, they produce their clinical effect locally in the colon of patients with either *Clostridium difficile* colitis or *Staphylococcus aureus* colitis. Therefore, this agent is clearly not a BCS class I compound and more appropriately belongs to the group of locally-acting gastrointestinal tract agents such as sucralfate or anti-inflammatory drugs that are used in treating ulcerative colitis or inflammatory bowl syndromes. Drugs reaching the lower part of the gut are exposed to the metabolic effect of the microflora in various sites of colonization in the host and will be affected by the complex nature of intestinal motility in relation to drug disposition.

As noted above, because Vancocin Capsules are neither absorbed nor rapidly dissolving, the BCS framework does not apply to the product. Nonetheless, if one were compelled to apply the BCS to categorize Vancocin Capsules, it is my opinion that it would best fit as a Class 3 compound. Class 3 compounds clearly have greater variability regarding dissolution and the most appropriate definition of rapidly dissolving Class 3 agent would be 85% dissolution in 15 minutes or 90% in 30 minutes.

To utilize *in vitro* dissolution testing as the means to determine bioequivalence one must have a thorough and in depth understanding of the *in vivo* environment of patients most likely to receive the product. In the case of Vancocin Capsules, the standard dissolution conditions recommended by the OGD are unlikely to be representative of the gastrointestinal physiology in patients with CDAD as they are based on healthy volunteer studies. To my knowledge, no *in vitro: in vivo* correlation (IVIVC) has been established for Vancocin Capsules on which to provide guidance for the suggested *in vitro* testing. Adding further uncertainty is that Vancocin Capsules are not a simple powder filled capsule. They are manufactured as semi-solid matrix consisting of polyethylene glycol and vancomycin hydrochloride. The interaction of polyethylene glycol and vancomycin hydrochloride as formulated in Vancocin Capsules may be critical to achieve therapeutic concentration within the crypts of the colon where *Clostridium difficile* resides and causes disease. Equivalence based on *in vitro* dissolution in the absence of an IVIVC will not be able to adequately demonstrate the levels that should be achieved at the site of infection, which is heavily colonized by bacterial flora.

In addition, although Vancocin Capsules are poorly absorbed, cases reported in the literature described significant absorption in some patients with *Clostridium difficile* infection and concomitant renal insufficiency. *In vitro* dissolution testing will be unable to assess what impact a new formulation may have on systemic absorption and toxicity. Prior experience with other locally acting gastrointestinal agents such as sucralfate and mesalamine suggest that a conservative approach to locally acting agents is warranted.

In closing, I respectfully request that the OGD reconsider the potential approval of an ANDA of Vancocin Capsules based solely on *in vitro* dissolution testing. This agent is representative of a larger class of locally acting gastrointestinal agents for which the most appropriate means of determining bioequivalence has been debated by experts for several years. Until a better understanding of the relationship between in vitro dissolution and in vivo performance of locally acting agents such as Vancocin capsules is determined, this method to determine bioequivalence is not in the best interest of patients. In the absence of such data, I strongly encourage the OGD to require clinical trials to determine bioequivalence for Vancocin Capsules if the therapeutic objectives are an equivalent clinical response.

Sincerely,

Reza Fassihi, Ph.D., AAPS Fellow
Professor of Biopharmaceutics and Industrial Pharmacy
Temple University School of Pharmacy
Philadelphia, PA 19140
Tel: 215-707-7670
Fax: 215-707-3678
e-mail: reza.fassihi@temple.edu