administered as an oral solution daily for 16 days in five anephric patients with no inflammatory bowel disease. Vancomycin could not be detected in blood in 3/5 patients, and in 2/5 patients, blood concentrations were hardly measurable (0.66.µg/mL). With doses of 2 g daily (oral solution), very high drug concentrations were found in faeces (>3100 mg/kg) and very low concentrations (<1µg/ml) was found in the serum of patients with normal renal function who have pseudomembranous colitis. Orally administered Vancomycin does not usually enter the systematic circulation even when inflammatory lesions are present. After multiple-dose of oral administration of vancomycin, measurable serum concentration may infrequently occur in patients with active *C. difficile* induced pseudodomembranous colitis, and, in the presence of renal impairment, the possibility of accumulation exists.[9]

Vancomycin Hydrochloride Capsule at a glance

Vancomycin Hydrochloride (figure no. 1) has molecular formula $C_{66}H_{75}N_9O_{24}$.HCl with about 1485.71 molecular mass. The CAS No. of Vancomycin Hydrochloride is 1404-93-6. According to Merck Index (2006), Vancomycin Hydrochloride has more than 100 mg solubility in per ml of water, but according to ViroPharma Incorporated, Vancomycin Hydrochloride cannot be considered as highly soluble compound.[12,13] FDA's laboratory conducted studies to determine the aqueous solubility of Vancomycin under conditions prescribed in the FDA's guidance.[15] The results of the FDA studies showed that Vancomycin HCl is highly soluble.[16] The FDA defines a drug substance as highly soluble when the highest strength is soluble in 250 ml or less of aqueous media over the pH range of 1.0-7.5.[17]

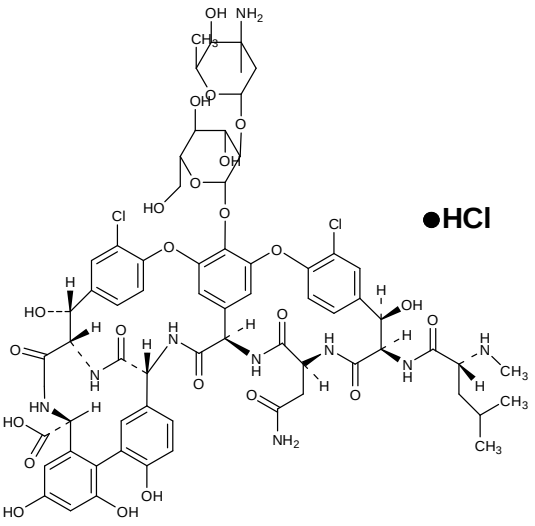

Figure 1: Structure of Vancomycin Hydrochloride

The FDA's laboratory performed studies to resolve the dissolution characteristics of Vancocin® HCl Capsules. Figure 2 shows dissolution profiles of Vancocin® HCl Capsule (Lot. No.-200240). The conclusion of FDA's dissolution study showed that all lots and strengths of Vancocin® HCl Capsules met FDA's description of a rapidly dissolution drug product at pH 1.2. At pH 4.5, Vancocin® HCl Capsule usually dissolves more than 85 % in 45 minutes. It requires 60 minutes for Vancocin® HCl Capsules to dissolve more than 85% at pH-6.8.[17]

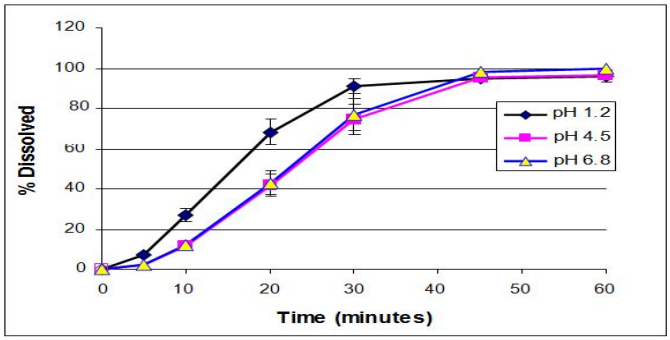

Figure 2: Dissolution Profiles of Vacocin® HCl Capsules (Lot No. 200240)

Regulatory history of Vancomycin HCl capsule

Vancomycin has been in use for the systematic treatment of resistant staphylococcal infections since 1956.[18] First time, Vancocin® HCl injection was approved under New Drug Application (NDA) 60-180 on November 6, 1964. No clinical data were submitted with NDA 60-180; the approval judgment was based on case reports and literature references.[19] A new approval was made on July 13, 1983 of Vancocin Solution for oral use, for the treatment of pseudomembranous colitis caused by *C. Difficile*. Both Vancocin® HCl Injection and Vancocin® Solution has been removed from market. Lilly Research Laboratories submitted NDA 50- 606, TO FDA on March 15, 1985.[20] The submission was made on the basis of two bioavailability studies. In the first Study, Vancomycin was not detected in the blood, and mean urine recovery did not exceed 0.1% of the dose. In the second study, Vancomycin was not detected in the blood, and mean urine recovery did not exceed 0.76% over the treatment period. The biopharmaceutics Division, which reviewed the bioavailability studies, recommended waiving the requirement for *in vivo* bioequivalence studies based on acceptable dissolution characteristic of the capsule. Therefore, clinical safety and efficacy studies of Vancocin® in HCl Capsules were not carried out for application NDA 50-606.[20]

On October 20, 2004, FDA's Advisory Committee for Pharmaceutical Science met and discussed Bioequivalence of locally acting gastrointestinal drugs. The concluding report of the committee concluded, '*in vitro* is good if there is control over the test' and 'in order to prove bioequivalence in vitro dissolution along with pharmacokinetics should be acceptable'. Even though Vancomycin was not discussed at this meeting, the symposium of potential waivers for high solubility GI acting drugs triggered activity by potential ANDA sponsors.[22]

Vancocin® acquired by ViroPharma in November 2004.[21] Before 2006, the OGD suggested bioequivalence studies with clinical endpoints in patients for Vancocin® HCl

Capsules. The prime Reason for this recommendation was that oral Vancomycin is poorly absorbed.[9]

On March 1, 2006, OGD revised the bioequivalence recommendations for generic products referencing Vancocin® HCl Capsules and recommended that bioequivalence can be demonstrated by comparative in vitro dissolution with the RLD. Pursuant to FDA's standard procedure at that time, anyone who had written to the OCD requesting information about bioequivalence recommendations for Vacomycin HCl Capsules received a letter describing these recommendations. Once the RLD sponsor (ViroPharma Incorporated) became aware of the new recommendations, and immediately filed a Citizen's Petition asking for discloser of data that supported this novel approach, and asked that no approval be made on the basis of this new method until the OGD presented its data outside experts, including clinicians experienced in treating the disease.[13] The request was ignored.

FDA's dissolution data suggested that Vancocin® Capsules would not meet the BCS Guidance definition of rapidly dissolving, the OGD decided that this finding would not have a bearing on the proposed in vitro bioequivalence approach for Vancomcyin HCl Capsules.[17] This is because the use of 30 minutes in the BCS definition is generally considered as conservative among academic, industry, and regulatory scientists is that it should be 60 minutes.[15,23] Further, as Vancomycin is poorly absorbed and acts primarily in the lower GI tract, a longer time for complete dissolution is justified. In addition, equivalent dissolution profiles at pH 1.2, 4.5 and 6.8 media ensure that generic and RLD products will have equivalent even in patients with GI transit times, pH, or fluid volumes different from those in healthy subjects.

OGD released its revised BE recommendations in December 2008. AT this time, OGD also released the reports of the FDA laboratory dissolution and solubility studies. Pursuant to the FDA's current procedure, the December 2008 recommendations were realised as draft with a public comment period. Moreover, guideline was open for public comments until Marh 19, 2009.[11]

Draft Guidance on Vancomycin Hydrochloride Capsule:[11]

- *In Vitro* Option:

If the test product formulations are qualitatively (Q1) (i.e., contain all of the same inactive ingredients) and quantitatively (Q2) the same as the reference listed drug (RLD) with respect to inactive ingredients, bioequivalence (BE) of all capsule strengths may be established based on comparative dissolution.

For test product formulations that are Q1 and Q2 the same as the RLD, dissolution data in each specified medium should be provided for 12 capsules each of test and reference products, as table 1.

An f2 test should be performed using mean profiles to ensure comparable test (T) and reference (R) product drug release under a range of pH conditions. The f2 test comparing T vs. R in each medium should be between 50 and 100. Dissolution profiles may be compared using the following equation that defines a similarity factory (f2):

$$f2 = 50 \text{ LOG } \{[1+1/n \Sigma nt=1 (Rt-Tt)2]-0.5 \text{ x } 100\}$$

Where Rt and Tt are the percent dissolved at each time point. An f2 value between 50 and 100 suggests the two dissolution profiles are similar.

Table 1: FDA recommended dissolution parameters for Vancomycin HCl Capsule

Apparatus	USP Apparatus 1
(basket) Rotation speed	100 rpm
Medium	0.1N HCl (or 0.1N HCl with NaCl at pH 1.2), pH 4.5 Acetate buffer, And pH 6.8 Phosphate buffer.
Volume	900 mL
Temperature	37°C
Sample times	5, 10, 20, 30, and 45 minutes or as needed for profile comparison

- *In Vivo* Option:

If the test product formulations are not Q1 and Q2 the same as the RLD with respect to inactive ingredients, BE should be established by conducting an *in vivo* study, recommend that any sponsor choosing this option submit their protocol to the OGD clinical review team for review and concurrence prior of initiating the study.

- Dissolution testing for stability and quality control: USP method

DISCUSSION

ViroPharma Incorporated filed petition on March 17, 2006 with following basis:[13]

ViroPharma believed the recommendation required scientific validity. This is because potential risk associated with a perceptible decision by OGD. It requires clinical demonstration of bioequivalence to approve generic version of Vancomycin in Hydrochloride Capsule. ViroPharma state, FDA considered Vancocin® Capsule as rapidly dissolving Capsule (BCS class 1) but on the basis of the information provided by ViroPharma, Vancocin® capsule cannot be considered as rapidly dissolving capsule and the pharmaceutically active ingredient vancomycin is large, complex, biologically- derived antibiotic peptide, that is poorly absorbed. Until March 17, 2006 no generic have approved on the bases on in vitro dissolution test in the place of clinical bioequivalence study since 1984.

ViroPharma believed that the scientific basis for extrapolating in vitro test results to predict how generic forms of Vancocin® Capsules would perform therapeutically, has not been validated and it is unknown

whether clinically relevant differences in performances can be discerned through *in vitro*-testing. Further, the impact of the proprietary Vancocin® Capsule formulation on delivery of Vancomycin to the site of infection is not fully characterized.

FDA stands over this:[11]

As Vancomycin solubility is high at all pH values that could be encountered in the GI tract and is not extensively absorbed. All Vancomycin that is released from the drug product, should be available at the site of action. Therefore, dissolution of the drug product is directly related to rate and extent to which the active ingredient becomes available at the site of action and represents the most significant potential difference between generic Vancomycin HCL Capsule and RLD. Any difference between the dissolution of the generic and the RLD products would likely be due to a difference in the formulation's pharmaceutical properties such as particle size, crystal habits, formulation and processing variables, or excipient grades. It is well established that, especially for highly soluble drugs, in vitro dissolution tests are much more sensitive to these potential difference between products than any in vivo tests. Therefore, the OGD believes that the most suitable approach for determining bioequivalence is an in vitro comparison, in which the dissolution rate of a test Vancomycin HCl Capsule is compared to that of the Vancocin® HCl Capsule at a range of pH values representative of conditions in the GI tract.

Similar dissolution profiles also ensure that generic and RLD products will have equivalent effectiveness in patients with infections at any location in the GI tract or patients with different transit times. FDA's laboratory study showed that Vancomycin HCl Capsules within one hour are at least 95% dissolved at pH 1.2 and 4.5, and at least 85% dissolved in pH 6.8. This is rapid enough for complete dissolution before reaching the site of action in colon in patients with normal GI transit times.

In-vitro dissolution testing across physiologic conditions provides a high level of assurance that a proposed generic product would complete solubilisation prior to reaching the site of action within the GI tract. In theory, FDA's recommendation that generic Vancomycin capsule products have dissolution profiles matching those of Vancocin® ($f2 \geq 50$) is overly restrictive and could be broadened to permit f2 values below 50 if the generic product dissolves at least as fast as Vancocin®.

Present Status

Draft guideline has been accepted and three generic version of Vancomycin Hydrochloride capsule by different manufacture (Akom, Strides Arcolabs Ltd, and Watson Pharmaceuticals) has been approved in September 2010 on the basis of in Vitro dissolution bioequivalence.

FDA's response (to comments on guideline and petition by Viro Pharma) provides numerous insights into FDA's decision-making process for bioequivalence determination in addition to FDA's affirmation of its draft generic Vancocin® recommendation as "scientifically sound" and "the most accurate, sensitive, and reproducible approach for demonstrating bioequivalence for generic vancomycin capsules." For generic Vancocin® FDA will continue to permit *in vitro* dissolution data alone to demonstrate bioequivalence for generic Vancocin® Capsule versions that contain the same active and inactive ingredients in the same amounts ("Q1/Q2"). Non-Q1/Q2 formulations must perform clinical endpoint studies in patients with *Clostridium defficile* associated diarrhea.[25]

CONCLUSION

ANDA applicants may only use the in vitro approach to determine bioequivalence of Vancomycin HCl Capsules if the generic Formulation is Q1 and Q2 as same as Vancocin® HCl Capsules. For Vancomycin HCl Capsule with respect to inactive ingredients, meet currently accepted standards for assay, potency, purity, and stability (equivalent to those in place for Vancocin® HCl capsules), and are manufactured according to cGMP regulations. Any potential differences in manufacturing, *in vitro* dissolution testing will be expected to be due to differences in manufacturing. *In vitro* dissolution testing will ensure that generic Vancomycin HCl Capsules have equivalent release properties to Vancocin® HCl Capsules. As a result, generic Vancomycin HCl Capsules that meet the above criteria and have comparable dissolution profiles as set forth in FDA's 2008 draft recommendation would be expected to be therapeutically to Vancocin® HCl Capsules and there is no reason to believe that they will perform differently in patients.

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