06-2431

03-17-06 P05:23 IN

397 Eagleview Boulevard
Exton, PA 19341
Phone (610) 458-7300
Fax (610) 458-7380

VIA HAND DELIVERY

Andrew C. von Eschenbach, M.D.
Acting Commissioner of Food and Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA No. 50-606 (Vancocin® (vancomycin hydrochloride) capsules)

Dear Commissioner von Eschenbach:

I write you on a matter of urgent concern. It appears that FDA's Office of Generic Drugs (OGD) may permit the substitution of potentially non-bioequivalent vancomycin solid oral dosage forms for our product, Vancocin® (vancomycin hydrochloride) capsules. This risk leads us to petition (copy attached) your Office to stay any contemplated approvals of such products until they are shown to be truly bioequivalent to Vancocin.

The only way to demonstrate such bioequivalence is through comparative clinical trials. This is FDA's policy for non-systemically absorbed drugs like Vancocin in the absence of appropriately validated *in vitro* methodology demonstrating that dissolution provides an adequate surrogate for levels of the drug at the site of action and their related clinical effect. ViroPharma is unaware of any such validation studies that would support a finding of bioequivalence for a generic vancomycin based on *in vitro* dissolution testing. We learned yesterday, however, that Dale Conner, an OGD pharmacist, apparently seeks to overturn this longstanding policy as it regards Vancocin capsules. Mr. Conner advises that generic pills are equivalent to Vancocin if 12 of them dissolve in solution the same way 12 Vancocin pills do (see attached letter).

Mr. Connor's approach radically restricts the data on which FDA would make vancomycin capsule bioequivalence decisions. Despite some twenty years of capsule formulation experience with vancomycin, Mr. Connor did not ask us to share the implications of that experience for his proposed dissolution bioequivalence approach. In fact, based on that experience, we believe Mr. Connor's approach is so narrow that it would be incapable of detecting bioinequivalent generic versions of Vancocin. Vancomycin is a large molecule that experience demonstrates can be substantially

affected by the capsule formulation process. This can render the vancomycin bioinequivalent, but in ways a dissolution assay will not detect. Using Mr. Connor's approach, FDA will have failed to meet its statutory obligation to approve only generic drugs that are truly equivalent to the listed drugs they reference.

Furthermore, Vancocin's place in the antibiotic armamentarium makes it particularly ill-suited to being the test case for the abandonment of clinical bioequivalence in favor of dissolution testing. Vancocin capsules are the last line of defense against life-threatening colitis associated with clostridium difficile and staphylococcus aureus. In particular, increased incidence and virulence of c. difficile infections have been extensively reported in the lay press and the clinical literature; according to the Centers for Disease Control, there is an epidemic. (McDonald, L.C., et al. 2005. An epidemic, toxin gene-variant strain of Clostridium difficile. N. Engl. J. Med. 353:2433-41.) To combat a disease that can kill so quickly, the uncertainties of dissolution-only bioequivalence are simply unacceptable.

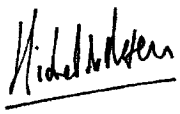
The pattern of behavior exhibited by OGD that allowed it to determine that simple *in vitro* dissolution data provides sufficient information to establish bioequivalence for a new vancomycin product could seriously undermine the scientific credibility of the Division and erode consumers' trust in the safety and efficacy of generic drugs. The fact that OGD undertook this significant shift in thinking regarding data needs in the absence of any public discussion or comment or input from FDA's own expert Advisory Committees does not suggest a thoughtful or public health protective approach to this issue. A review of transcripts from recent Advisory Committee meetings and FDA briefing documents reveals that the level of uncertainty associated with *in vitro* bioequivalence testing for this class of drugs supports the Agency's original position requiring clinical data or validated *in vitro* testing methods. The sudden change in thinking in the absence of data or discussion does not appear consistent with a scientifically justified, evidence-based approach to decision-making at OGD. Consequently, our petition for stay also asks FDA to remedy these substantial procedural shortcomings.

We regret the urgency of this communication. We feel it necessary, however, to address immediately the potential approval of generic vancomycin capsules of unproven bioequivalence. Over the next several weeks, we will submit for FDA's review the evidence supporting what we have outlined above. We also request the opportunity to meet with the Agency on these issues. To this meeting we propose to bring experts on our formulation experience with Vancocin, as well as pharmaceutical science experts. At the conclusion of this process, we believe that FDA will concur that the dissolution approach is insufficient to ensure bioequivalence of vancomycin capsules, and instead re-affirm the Agency's longstanding policy of clinical bioequivalence for non-systemically

absorbed products like vancomycin. In the interim, we respectfully request that FDA not approve any generic capsule versions of vancomycin based on any bioequivalence standard other than comparative clinical trials.

Thank you very much for your consideration. Please contact me if you would like to discuss this matter further, (610) 321-6289.

Very truly yours,



Michel de Rosen
Chief Executive Officer, ViroPharma Incorporated

cc: Janet Woodcock, M.D., Deputy Commissioner for Operations
Steven K. Galson, M.D., M.P.H. Director, CDER
Robert Temple, M.D., Associate Director for Medical Policy
Mark J. Goldberger, M.D., M.P.H., Director, Office of Antimicrobial Products
Gary J. Buehler, Director, Office of Generic Drugs
Anthony Fauci, M.D., Director, NIAID
Allan M. Fox, FoxKiser

VIROPHARMA
INCORPORATED

397 Eagleview Boulevard
Exton, PA 19341
Phone (610) 458-7300
Fax (610) 458-7380

March 17, 2006

VIA HAND DELIVERY
Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

PETITION FOR STAY OF ACTION

ViroPharma Incorporated respectfully submits this petition pursuant to 21 CFR 10.35 requesting the Food and Drug Administration immediately stay the effective date of the following matter:

DECISION INVOLVED

For the reasons described below, ViroPharma requests a stay of any Agency action that would result in the approval of an Abbreviated New Drug Application (ANDA) referencing Vancocin® (vancomycin capsules) as its reference listed drug (RLD). ViroPharma requests such stay of action in the absence of evidence that the Agency has established and applied appropriate standards for approving a generic vancomycin capsule product.

ACTION REQUESTED

ViroPharma will shortly submit scientific evidence to present to the FDA formally requesting that the Agency:

(a) Require using the most rigorous scientific method that will demonstrate a rate and extent of drug release to the site of action consistent with good medicine and science;
(b) Require a demonstration that the stability of a generic vancomycin product is at least as good as the RLD;

(c) Require the ANDA applicant relying on Vancocin to provide evidence that its product is bioequivalent to Vancocin along the entire gastrointestinal tract
(d) Convene a joint meeting of the Advisory Committee for Pharmaceutical Science and the Advisory Committee for Anti-infective Drug Products, with industry participation, to examine the relevant data and information relating to vancomycin delivery to the GI tract for the purpose of developing appropriate and consistent standards for the approval of new products by generic applicants;
(e) Validate with both the FDA Medical Policy Coordinating Committee and the FDA Biopharmaceutics Coordinating Committee the scientific and medical appropriateness of the approval standards for a generic locally acting vancomycin capsule product.
(f) Provide an opportunity for public review and comment on the appropriate approval standards for a generic locally acting vancomycin capsule product.

STATEMENT OF GROUNDS

The agency should grant ViroPharma's Petition for Stay of Action because it satisfies the criteria set forth in 21 CFR 10.35(e).

The public interest would be served by the Agency establishing standards for the approval of a locally acting vancomycin capsule product, a product that is used for treating serious, life threatening infections. For safety and reliability purposes, FDA should not apply unsubstantiated and potentially inadequate bioequivalence standards for such a serious drug.

Approving a generic vancomycin capsule product relying on Vancocin as the RLD based on inadequate demonstration of bioequivalence, has the potential of causing ViroPharma irreparable harm. If the composition of a generic vancomycin capsule raises safety issues, or its local release cannot be effectively measured to show therapeutic equivalence the reputation and goodwill that ViroPharma has established in this field may be destroyed.

ViroPharma respectfully requests that the Agency stay approval of a generic vancomycin capsule in good faith and for non-frivolous reasons. ViroPharma believes the FDA must define a bioequivalence standard in order to ensure the approval of safe and efficacious new products. Standing alone, matching *in vitro* release cannot demonstrate bioequivalence for non-systemically absorbed products like Vancocin. For a drug used for life threatening infections, this is particularly inappropriate.

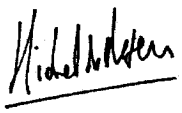
Sound public policy supports a stay in this case. In addition to medical and scientific arguments for establishing bioequivalence standards, the public has an interest in requiring an agency such as FDA to act lawfully, to fulfill obligations under its governing statutes and implementing regulations and to treat regulated parties fairly and equally.

Vancocin, the RLD that a generic vancomycin capsule would rely on in its ANDA, is safe and efficacious for patients. The approval process for an ANDA, however, must be in a manner in which the public can place their confidence. Thus, any delay resulting from a stay would not be outweighed by other interests. Although there is a public interest in lawful generic competition, there is a greater interest in ensuring that generic drugs meet the fundamental statutory and regulatory requirements for approval, i.e., are truly the same as the reference listed drugs to which they claim to be equivalent.

CONCLUSION

For the foregoing reasons this Petition for Stay of Action should be granted.

Respectfully submitted,



Michel de Rosen
Chief Executive Officer
ViroPharma Incorporated

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Infinium Capital Corp.
Attention: Bernadine Leung, Ph.D.
67 Yonge St., Suite 602
Toronto, Ontario, Canada
M5E 1J8

MAR 0 1 2006

Reference Number: OGD #06-0200

Dear Dr. Leung:

This letter is in response to your correspondence dated February 3, 2006. You request that the Office of Generic Drugs (OGD) provide bioequivalence recommendations regarding Vancomycin Hydrochloride Capsules, 125 mg and 250 mg. OGD provides the following comments:

1. Vancomycin is a highly soluble drug and the reference listed drug (RLD) product is rapidly dissolving. Waivers of *in-vivo* bioequivalence testing can be requested in abbreviated new drug applications (ANDAs), provided that the test product is rapidly dissolving at the conditions specified in the guidance *Waiver of in vivo BA and BE studies for IR solid oral dosage forms based on a biopharmaceutics classification system (BCS Guidance)*. Dissolution data in various media on 12 dosage units each of test and reference products (for both strengths) should be provided as follows:

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
Sampling times:	5, 10, 15, 20, 25, 30, and 40 minutes or as needed for profile comparison

2. In addition, please conduct dissolution testing using the USP 29 method for your stability and quality control programs.

If you have any questions, please call Christina Thompson, Pharm.D., Project Manager, Division of Bioequivalence at (301) 827-5847In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OGD # 06-0200