

# VIROPHARMA INC

## FORM 8-K (Current report filing)

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**UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION**

**Washington, D.C. 20549**

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**FORM 8-K**

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**CURRENT REPORT**

**PURSUANT TO SECTION 13 OR 15(d) OF THE  
SECURITIES EXCHANGE ACT OF 1934**

**Date of Report (Date of Earliest Event Reported): January 3, 2012**

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**V I R O P H A R M A I N C O R P O R A T E D**

**(Exact Name of Registrant as Specified in its Charter)**

**DELAWARE**  
**(State or Other Jurisdiction of  
Incorporation or Organization)**

**0-021699**  
**(Commission  
File Number)**

**23-2789550**  
**(I.R.S. Employer  
Identification Number)**

**730 STOCKTON DRIVE, EXTON, PENNSYLVANIA 19341**  
**(Address of Principal Executive Offices including Zip Code)**

**(610) 458-7300**  
**(Registrant's Telephone Number, Including Area Code)**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
  - Soliciting material pursuant to Rule 14a-12 under the Exchange Act(17CFR240.14a-12)
  - Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act(17CFR240.14d-2(b))
  - Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act(17CFR240.13e-4(c))
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**Item 5.02 Departure of Directors or Certain Officers; Election of Directors; Appointment of Certain Officers; Compensatory Arrangements of Certain Officers.**

On January 3, 2012, the Board of Directors (the “Board”) of ViroPharma Incorporated (the “Company”), based upon the recommendation of the Board’s Nominating and Corporate Governance Committee, appointed Julie McHugh to serve on the Company’s Board of Directors as a Class II director. In connection with the appointment, the Board expanded the size of the Board to eight directors. Ms. McHugh will serve for a term expiring at the Company’s annual meeting of stockholders in 2013 and until her successor shall have been elected and qualified or until her earlier resignation or removal.

Ms. McHugh, age 47, is currently the chief operating officer of Endo Pharmaceuticals (“Endo”), a U.S.-based, specialty healthcare solutions company. Prior to joining Endo, Ms. McHugh was chief executive officer of Nora Therapeutics, Inc., (“Nora”) a biotech company focused on the treatment of infertility disorders. Prior to joining Nora Therapeutics, Ms. McHugh was company group chairman for Johnson & Johnson’s (“J&J”) Worldwide Virology Business Unit and prior to this role she served as president of Centocor, Inc., a J&J subsidiary. Ms. McHugh received a Bachelor of Science degree from Pennsylvania State University and a Masters of Business Administration degree from St. Joseph’s University. She currently serves on the Board of Visitors for the Smeal College of Business of the Pennsylvania State University. Ms. McHugh also currently serves on the Board of Directors of Biotechnology Industry Association (BIO), New England Health Institute (NEHI) and the Nathaniel Adamczyk Foundation. Ms. McHugh served in 2009 as Chairman of the Board of Directors for the Pennsylvania Biotech Association.

There is no agreement or understanding between Ms. McHugh and any other person pursuant to which Ms. McHugh was appointed to the Board. Ms. McHugh is not a party to any transaction, or series of transactions, required to be disclosed pursuant to Item 404(a) of Regulation S-K.

The Board is in the process of determining which committees Ms. McHugh shall serve upon, if any. Ms. McHugh shall receive compensation for serving on the Board pursuant to the Board compensation plan that was previously disclosed in the Company’s filings with the Securities and Exchange Commission.

On January 3, 2012, the Company issued a press release announcing the appointment of Ms. McHugh to the Board. A copy of this press release is attached as Exhibit 99.1.

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**Item 8.01 Other Events.**

Following the approval by the U.S. Food and Drug Administration (“FDA”) of a supplemental new drug application to modernize the labeling for Vancocin® (vancomycin hydrochloride, USP) Capsules (“sNDA”), on December 22, 2011, the Company supplemented its citizen petition to provide additional information to the FDA regarding the Company’s belief that attempting to omit Vancocin labeling changes protected by exclusivity would render generic versions of Vancocin less safe and effective. A copy of the supplement to its citizen petition regarding Vancocin is attached as Exhibit 99.2.

**Item 9.01 Financial Statements and Exhibits.**

The following exhibits are attached to this Form 8-K:

(d)	<u>Exhibit No.</u>	<u>Description</u>
	99.1	Press release dated January 3, 2012 announcing the appointment of Julie McHugh to the Board of Directors.
	99.2	ViroPharma supplement to its citizen petition regarding Vancocin.

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**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

**V I R O P H A R M A I N C O R P O R A T E D**

Date: January 4, 2012

By: /s/ J. Peter Wolf

J. Peter Wolf

Vice President, General Counsel and Secretary



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**VIROPHARMA ANNOUNCES APPOINTMENT OF JULIE H. MCHUGH  
 TO BOARD OF DIRECTORS**

**Exton, PA, January 3, 2012** — ViroPharma Incorporated (Nasdaq: VPHM) today announced the appointment of Julie H. McHugh to its board of directors.

Ms. McHugh brings a wealth of pharmaceutical and health care industry experience and leadership to ViroPharma's Board of Directors. She is currently the chief operating officer of Endo Pharmaceuticals, a U.S.-based, specialty healthcare solutions company. Prior to joining Endo, Ms. McHugh was chief executive officer of Nora Therapeutics, Inc., a biotech company focused on the treatment of infertility disorders. Prior to joining Nora Therapeutics, she was company group chairman for Johnson & Johnson's Worldwide Virology Business Unit and prior to this role she served as president of Centocor, Inc., a J&J subsidiary.

Ms. McHugh received a Bachelor of Science degree from Pennsylvania State University and a Masters of Business Administration degree from St. Joseph's University. She currently serves on the Board of Visitors for the Smeal College of Business of the Pennsylvania State University. Ms. McHugh also currently serves on the Board of Directors of Biotechnology Industry Association (BIO), New England Health Institute (NEHI) and the Nathaniel Adamczyk Foundation. Ms. McHugh served in 2009 as Chairman of the Board of Directors for the Pennsylvania Biotech Association.

"We are very enthusiastic about the addition of Julie to our board," commented Vincent Milano, president and chief executive officer of ViroPharma. "Julie's experience and insight gained from years of pharmaceutical leadership at a number of successful organizations will play a critical role in helping guide our company through our next levels of growth and achievement."

"I am excited to have the opportunity to serve on the board of directors of ViroPharma; I am impressed by the success that the company has achieved and look forward to taking part in guiding the company towards future growth and successes in the years ahead," commented Ms. McHugh.

***About ViroPharma Incorporated***

ViroPharma Incorporated is an international biopharmaceutical company committed to developing and commercializing novel solutions for physician specialists to address unmet medical needs of patients living with diseases that have few if any clinical therapeutic options, including C1 esterase inhibitor deficiency, treatment of seizures in children and adolescents, adrenal insufficiency, and *C. difficile* infection (CDI). Our goal is to provide rewarding careers to employees, to create new standards of care in the way serious diseases are treated, and to build international partnerships with the patients, advocates, and health care professionals we serve. ViroPharma's commercial products address diseases including hereditary angioedema (HAE), seizures in children and adolescents, and CDI; for

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full U.S. prescribing information on our products, please download the package inserts at <http://www.viopharma.com/Products.aspx>; the prescribing information for other countries can be found at [www.viopharma.com](http://www.viopharma.com).

ViroPharma routinely posts information, including press releases, which may be important to investors in the investor relations and media sections of our company's web site, [www.viopharma.com](http://www.viopharma.com). The company encourages investors to consult these sections for more information on ViroPharma and our business.

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December 22, 2011

**Submitted Electronically**

Division of Dockets Management (HFA-305)  
 Food and Drug Administration  
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RE: Docket Nos. FDA-2006-P-0007 (formerly 2006P-0124) & FDA-2008-D-0626

**Implications of New Vancocin® Labeling for Generic Vancomycin Products**

The Food and Drug Administration (FDA) recently approved a supplemental New Drug Application (sNDA) for Vancocin® (vancomycin hydrochloride capsules). The changes approved in the sNDA were based on new clinical safety and efficacy data to which ViroPharma Incorporated, Vancocin's sponsor, has exclusive rights. As explained below, for the three year period expiring December 15, 2014, generic vancomycin capsule products that omit the new labeling changes should not be approved, because such omissions would render the generic products less safe or effective than Vancocin.

**I. Vancocin Labeling History**

On December 14, 2011, FDA approved a supplemental new drug application (sNDA) that fundamentally changed the labeling for Vancocin (vancomycin hydrochloride capsules). Like many older drugs originally approved years ago, the evidence supporting Vancocin's old labeling was lacking. Vancocin's new sNDA approval changed the Vancocin labeling, for the first time, based on data from controlled clinical safety and efficacy studies in patients taking Vancocin capsules. Entirely new sections on Clinical Studies, Adverse Reactions: Clinical Trials, Nephrotoxicity, and Geriatric Use were added to Vancocin's labeling based on the new data. The new Vancocin labeling also modified Vancocin's indication and for the first time specifies a recommended dosing regimen.

Generic products that do not carry these critical sections in their labeling would be less safe and effective than Vancocin and thus should not be approved until the 3 year exclusivity period protecting Vancocin's new labeling expires.

**A. Old Vancocin Labeling: Paucity of Clinical Safety & Efficacy Data**

Vancocin capsules (at the time called "pulvules") were first approved in 1986. <sup>1</sup> The application contained "no specific clinical data." <sup>2</sup> In briefing materials for a 2009 Advisory Committee meeting, FDA reiterated that it had not approved Vancocin capsules based on "a clinical safety and efficacy study." <sup>3</sup> During the course of the Committee meeting, FDA reemphasized the lack of any clinical safety and efficacy data supporting approval of Vancocin capsules. <sup>4</sup>

<sup>1</sup> FDA approved NDA 50-606 for Vancocin Pulvules® on April 15, 1986. Letter from Edward Tabor, Dir. Division of Anti-Infective Drug Products, FDA to Glenn L. Cooper, Medical Advisor, Lilly Research Laboratories, Approval Letter (Apr. 15, 1986). *Attached*.

<sup>2</sup> Letter from Robert A. Browne, Med. Advisor, Lilly Research Laboratories to FDA Center for Drugs and Biologics, Initial Form 5, Pulvules® Vancocin® HCl, Vancomycin Hydrochloride, USP (Mar. 15, 1985). *Attached*.

<sup>3</sup> FDA CENTER FOR DRUG EVALUATION AND RESEARCH, Briefing Materials, Advisory Committee for Pharmaceutical Science and Clinical Pharmacology Meeting to Discuss Bioequivalence Recommendations for Oral Vancomycin Hydrochloride Products, 12 (Aug. 4, 2009).

<sup>4</sup> FDA CENTER FOR DRUG EVALUATION AND RESEARCH, Meeting Transcript, Advisory Committee for Pharmaceutical Science and Clinical Pharmacology Meeting to Discuss Bioequivalence Recommendations for Oral Vancomycin Hydrochloride Products, 51 (Aug. 4, 2009) [hereinafter *Vancocin Advisory Committee*] (statement of Robert Lionberger, FDA) ("[A] common theme here is that this initial approval was supported by case reports and literature references, but no controlled clinical studies.").

Vancocin capsules were developed in response to patient dissatisfaction with the foul taste of the predecessor oral solution formulation. Like the capsule, the oral solution was approved without any clinical safety or efficacy data.<sup>5</sup> Instead, the oral solution was a repackaged vial of the intravenous form of vancomycin, for which FDA originally had permitted marketing in the 1950s.<sup>6</sup>

Vancocin's old labeling reflected this absence of robust clinical data. It lacked standard prescription drug labeling sections where clinical study results and findings are summarized, such as Clinical Studies and Adverse Events: Clinical Trial Experience. In sum, there was an absence of information based on analysis of safety or efficacy data from controlled clinical studies of Vancocin capsules in treating *Clostridium difficile* - associated diarrhea (CDAD) or enterocolitis caused by *Staphylococcus aureus*.

#### B. The Paucity of Quality Clinical Data on Oral Use of Vancomycin is Reflected in the Literature

Information on older drugs is often limited to small, uncontrolled studies and sporadic case reports. This paucity of data hinders physicians who must make clinical decisions about the use of older medications based on limited labeling information developed in an absence of robust clinical data. For older antibiotics the problem is further exacerbated by changes that occur over time in susceptible populations and microbial strains. Vancocin is an older antibiotic, and until last week's sNDA approval suffered from these same problems.<sup>7</sup>

The lack of clinical data in the old Vancocin labeling is reflected in the scientific and clinical literature. Most of the literature regarding the use of oral vancomycin in the treatment of CDAD is of marginal quality, as reported in a 2011 Cochrane Review.<sup>8</sup> In April 2011, FDA also reviewed the literature and similarly concluded that:

[T]here is limited information on effect of vancomycin compared to placebo for treatment of CDAD. The Cochrane review (Nelson 2007) identified only two randomized studies comparing vancomycin to placebo for treatment of *C. difficile* infection: Keighley 1978 and Johnson 1992. Johnson's 1992 study is not appropriate ... because while the patient population in that trial was stool positive for *C. difficile*, they did not have diarrhea and diarrhea is an important symptom of CDAD.<sup>9</sup>

<sup>5</sup> Vancocin Oral Solution was approved as an antibiotic in 1972. Letter from Merle L. Gibson, Dir. Office of Scientific Evaluation, Bureau of Drugs, FDA to Eli Lilly and Company, Approval Letter Form 6 #61-667 (Jul. 24, 1972). *Attached*.

<sup>6</sup> Donald P. Levine, *Vancomycin: A History*, 42 *J. CLINICAL INFECTIOUS DISEASES* S5, S6 (2006). *Attached*.

<sup>7</sup> See, e.g. Centers for Disease Control and Prevention, *Severe Clostridium difficile-associated disease in populations previously at low risk—four states*, 54 *MORBIDITY & MORTALITY WEEKLY REPORT* at 1201 (2005); See also Ed J. Kuijper et al., *Clostridium difficile* Ribotype 027, Toxinotype III, the Netherlands, 12 *EMERGING INFECTIOUS DISEASES* at 827 (2006). *Attached*.

<sup>8</sup> R.L. Nelson et al., *Antibiotic treatment for Clostridium difficile-associated diarrhea in adults (Review)*, 9 *COCHRANE REVIEW* at 1 (2011). *Attached*.

<sup>9</sup> FDA CENTER FOR DRUG EVALUATION AND RESEARCH, Briefing Information, Anti-Infective Drugs Advisory Committee, Appendix A, 41 (Apr. 5, 2011) [hereinafter *FDA Fidaxomicin Briefing Information*].

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FDA then assessed the one study of potential relevance, Keighley's 1978 study,<sup>10</sup> and found it lacking:

First, susceptible populations to CDAD and *C. difficile* strains have changed over time (see Aslam et al 2005), so results from Keighley 1978, a > 30 year old study, may not apply to the current CDAD population. Moreover, Keighley's 1978 design varied substantially from current CDAD trials with the most important difference being the duration of treatment of vancomycin (4 times a day for 5 days compared to 4 times a day for 10 days in current trials). Additionally, there are several major quality concerns with this study including inadequate follow-up, and mislaid or missing specimens. When the poor quality of the trial and the small size are taken into consideration, the study results should be used with caution.<sup>11</sup>

For staphylococcal enterocolitis, there are no properly conducted modern trials demonstrating the safety and effectiveness of Vancocin capsules for this use. What evidence does exist is older, not robust, of variable quality, and inconsistent with respect to findings.<sup>12</sup>

Rather than assess whether therapies such as Vancocin might be safe and effective against staphylococcal enterocolitis, recent studies mentioning enteric *S. aureus* disease are typically stool sample analyses, which consistently note that *S. aureus* is rarely a cause of antibiotic-associated diarrhea. For example, based on screening several thousand fecal samples, a 2006 British study found that "[f]or every 10 cases of *C. difficile* AAD, we identified ... 0.17 cases of *S. aureus* AAD."<sup>13</sup> With particular respect to methicillin-resistant *S. aureus*, a 2005 American study found that "MRSA has rarely been reported to be a cause of antibiotic-associated diarrhea."<sup>14</sup>

<sup>10</sup> M. R. B. Keighley et al., *Randomised controlled trial of vancomycin for pseudomembranous colitis and postoperative diarrhea*, 2 *B RIT . M E D . J.* at 1667 (1978). *Attached*.

<sup>11</sup> *FDA Fidaxomicin Briefing Information* at 42.

<sup>12</sup> See, e.g., Mohammed Y. Khan & Wendell H. Hall, *Staphylococcal Enterocolitis: Treatment with Oral Vancomycin*, 65 *A NNALS I NTERNAL M E D .* at 1 (1966). *Attached*.

<sup>13</sup> N. J. Asha et al., *Comparative Analysis of Prevalence, Risk Factors, and Molecular Epidemiology of Antibiotic-Associated Diarrhea Due to Clostridium difficile, Clostridium perfringens, and Staphylococcus aureus*, 44 *J. C LINICAL M ICROBIOLOGY* 2785, 2787 (2006). *Attached*.

<sup>14</sup> John M. Boyce & Nancy L. Havill, *Nosocomial Antibiotic-Associated Diarrhea Associated with Enterotoxin-Producing Strains of Methicillin-Resistant Staphylococcus aureus*, 100 *A M . J. G ASTROENTEROLOGY* 1828 (2005); See also, e.g., Zheng Lin et al., *Staphylococcal Enterocolitis: Forgotten but Not Gone?*, 55 *D IGESTIVE D ISEASES & S CI .* at 1200 (2010); Shyam Thakkar & Radheshyam Agrawal, *A Case of Staphylococcus Enterocolitis: A Rare Entity*, 6 *G ASTROENTEROLOGY & H EPTOLOGY* 2 at 115 (2010). *Attached*.

Indeed, following identification of *C. difficile* as the major cause of antibiotic-associated diarrhea, many experts apparently assumed that *S. aureus* enterocolitis was simply unrecognized *C. difficile* -related disease.<sup>15</sup> The stool studies cited above indicate that this is not entirely true, but do consistently show that *S. aureus* enterocolitis is rare as compared to *C. difficile* -related disease.<sup>16</sup> This has also been reflected in the literature, as one commentator noted last year:

[I]n the mid-1970s, *Clostridium difficile* and its toxins were implicated in the pathogenesis of antibiotic-associated, pseudomembranous colitis. Since that time, much more attention has been given to *C. difficile* -associated diarrhea (CDAD), and studies of *S. aureus* -related diarrhea have almost disappeared from the medical literature.<sup>17</sup>

In sum, other than the data in the new Vancocin sNDA, there is a paucity of well-controlled clinical evidence for the safety and efficacy of Vancocin capsules in the treatment of CDAD and staphylococcal enterocolitis.

#### C. The Two New Randomized, Double-Blind, Controlled Vancocin Capsule Studies on Which the New Vancocin sNDA was Based

As noted above, FDA's April 2011 review of available evidence found "limited information on effect of vancomycin compared to placebo for treatment of CDAD."<sup>18</sup> FDA ultimately identified only two relevant trials. Those studies are the very same studies that formed the basis for Vancocin's recently approved sNDA. As FDA explained, these "two large randomized, double blind, and controlled studies" demonstrat[ed] the "superiority of vancomycin to tolevamer," a "putative placebo."<sup>19</sup>

ViroPharma obtained these studies only through substantial investment, in the tens of millions of dollars. The studies were originally designed to test tolevamer, a novel CDAD therapy, against Vancocin. Tolevamer failed, so its sponsor, Genzyme Corporation, was in a position to grant ViroPharma an exclusive license.

ViroPharma acquired exclusive rights to these studies because (1) including robust, randomized clinical trial data in a label where previously there were none provides important information to prescribers and patients; (2) Congress amended the Federal Food, Drug, and Cosmetic Act to permit 3 year exclusivity for "old" antibiotics like Vancocin;<sup>20</sup> and (3) the absence of clinical

<sup>15</sup> Boyce, *supra* note 14 at 1828 (2005) ("Following the discovery of the role of *C. difficile* in causing pseudomembranous colitis and antibiotic-associated diarrhea, *S. aureus* enterocolitis was assumed by most experts to have represented unrecognized *C. difficile* -related disease, and *S. aureus* was discounted as a cause of antibiotic-associated diarrhea."). *Attached* .

<sup>16</sup> Indeed, IMS data indicate 99.85% percent of oral capsule vancomycin prescriptions are written for *C. difficile* disease, and only .15% percent for *S. aureus* . *Projected Vancomycin Usage for intestinal infections due to C. Diff. vs. Staphylococcus 9/2010 to 8/2011* , CDM Inpatient/Outpatient Hospital Discharge, IMS Health®. (Data on file at ViroPharma Incorporated).

<sup>17</sup> Zheng, *supra* note 14 at 1200 (2010). *Attached* .

<sup>18</sup> *FDA Fidaxomicin Briefing Information* at 42.

<sup>19</sup> *Id* . at 41-42.

<sup>20</sup> Congress expanded the 3 and 5 year exclusivity provisions available under 21 U.S.C. § 355 of the Federal Food, Drug, and Cosmetic Act to older antibiotics in the QI Program Supplemental Funding Act of 2008, Pub L. No. 110-379, § 4 (2008). Consistent with the new law, the new Vancocin sNDA has changed Vancocin's labeling with extensive new "conditions of use" as described in Section I(D) below.

data from Vancocin’s labeling – pointedly reiterated by FDA, the medical community, and generic drug companies at FDA’s August 2009 Vancocin Advisory Committee meeting <sup>21</sup> – meant that the 3 year exclusivity would provide a meaningful three year period during which ViroPharma could recoup its investment in these studies.

The studies submitted in the Vancocin sNDA included 260 Vancocin-treated patients in two multicenter, randomized, double-blind, double-dummy active controlled parallel-design trials. Trial subjects were enrolled if they had CDAD in the 24 hours before enrollment. For the purposes of the study, CDAD was defined as more than two loose or watery bowel movements 24 hours before enrollment and a positive *C. difficile* toxin assay or pseudomembranes on endoscopy within 72 hours prior to enrollment. <sup>22</sup> Patients received Vancocin 125 mg q.i.d. for 10 days. <sup>23</sup>

Patients were deemed a clinical success if by Day 10, their diarrhea had resolved and they did not have severe abdominal discomfort. <sup>24</sup> This unique co-primary endpoint was incorporated in the study protocols at the request of FDA. Diarrhea resolution was defined as two consecutive days of hard or formed bowel movements. <sup>25</sup>

The two trials demonstrated that 125 mg q.i.d. dosing led to a clinical success rate for patients of all disease severities of between 80.8% and 81.3%. <sup>26</sup> The data also revealed a longer median time to resolution in geriatric patients. <sup>27</sup>

#### D. The New Studies Modernized the Vancocin Labeling with Fundamental, Extensive Labeling Changes

The new studies submitted in the Vancocin sNDA transformed the old Vancocin labeling into modern, evidence-based, data-driven information useful to physicians who prescribe and patients who take this important antibiotic. The changes were extensive, with entirely new sections – like Clinical Studies and Adverse Reactions: Clinical Trial Experience – added for the first time to Vancocin’s labeling because there were now data to support them. Similarly, other sections – like Nephrotoxicity and Geriatric Use – were wholly rewritten based on the new data.

ViroPharma’s analyses of the data also led to new findings about Vancocin therapy, like the need to monitor renal function in all patients, and for clinicians to be aware of the importance of not prematurely discontinuing Vancocin treatment in the elderly. Indeed, ViroPharma’s indication itself was changed based on the new data, and now includes a new recommended dose of 125 mg q.i.d., the dose demonstrated to be safe and effective in the new studies.

<sup>21</sup> See, e.g., *Vancocin Advisory Committee* at 51 (statement of Robert Lionberger, FDA, “[A] common theme here is that this initial approval was supported by case reports and literature references, but no controlled clinical studies.”); *Id.* at 185 (statement of Russell J. Rackley, Mylan Pharmaceuticals) (“[N]o control studies are known to have been sponsored by ViroPharma or included in a study other than as a comparator; thus, no clinical endpoint studies are known to have ever been conducted, primarily for vancomycin capsules.”).

<sup>22</sup> Vancocin® Package Insert, §14.1: Clinical Studies, Diarrhea Associated with *Clostridium difficile* (Dec. 2011).

<sup>23</sup> Vancocin® Package Insert, §14.1: Clinical Studies, Diarrhea Associated with *Clostridium difficile* (Dec. 2011).

<sup>24</sup> Vancocin® Package Insert, §14.1: Clinical Studies, Diarrhea Associated with *Clostridium difficile* (Dec. 2011).

<sup>25</sup> Vancocin® Package Insert, §14.1: Clinical Studies, Diarrhea Associated with *Clostridium difficile* (Dec. 2011).

<sup>26</sup> Vancocin® Package Insert, §14.1: Clinical Studies, Diarrhea Associated with *Clostridium difficile* (Dec. 2011).

<sup>27</sup> Vancocin® Package Insert, §14.1: Clinical Studies, Diarrhea Associated with *Clostridium difficile* (Dec. 2011).

In sum, Vancocin’s labeling was fundamentally and extensively changed in the new sNDA with numerous new conditions of use. Details of some of these major changes include:

- **CLINICAL STUDIES.** This section of the labeling did not exist prior to the recent Vancocin sNDA (because there were no clinical studies). Hence this entire section is wholly based on the new clinical data submitted in the sNDA. It recites the unique entry criteria and efficacy endpoint used in the submitted studies, as well as specific study results, e.g., clinical success rates generally, clinical success rates in patients with the epidemic, hypervirulent BI strain, median time to resolution of diarrhea (and how that differed between elderly and non-elderly patients), recurrence rates, the number of subjects in the Full Analysis Set, demographic characteristics of those subjects, how many suffered from severe disease, and how many were previously treated for CDAD, among other information.
- **ADVERSE REACTIONS: Clinical Trial Experience.**<sup>28</sup> This section, like the Clinical Studies section, did not previously exist in the Vancocin labeling because there were no clinical studies from which adverse reaction data could be reported. Based on the new studies submitted in the Vancocin sNDA, specific adverse reaction data are now reported in the Vancocin labeling. After describing the mean duration of treatment and the median age, age range, race, and gender of study subjects, this section reports adverse reactions seen in — 10% of study subjects, includes a table ranking twelve adverse reactions seen in — 5% of study subjects, reports nephrotoxicity rates generally as well as median day of nephrotoxicity onset, breaks out nephrotoxicity rates for elderly and non-elderly, and lists nine additional adverse reactions which occurred at a greater frequency in patients > 65 years of age.
- **NEPHROTOXICITY.** Vancocin’s old labeling stated that “[w]hen patients with underlying renal dysfunction or those receiving concomitant therapy with an aminoglycoside are being treated, serial monitoring of renal function should be performed.”<sup>29</sup> Based on the studies submitted in the new Vancocin sNDA, this precaution was wholly rewritten and expanded. It now warns that “[n]ephrotoxicity (e.g., reports of renal failure, renal impairment, blood creatinine increased) has occurred following oral VANCOCIN therapy in randomized controlled clinical studies, and can occur either during or after completion of therapy. The risk of nephrotoxicity is increased in patients >65 years of age .... In patients >65 years of age, including those with normal renal function prior to treatment, renal function should be monitored during and following treatment with VANCOCIN to detect potential vancomycin induced nephrotoxicity.”<sup>30</sup>
- **HIGHLIGHTS: Nephrotoxicity.** Vancocin’s new Highlights section summarizes the “most clinically significant information,”<sup>21</sup> C.F.R. § 201.57(a)(10), from the nephrotoxicity subsection. In three separate warnings, the labeling directs clinicians to “[m]onitor renal function”; warns that “[n]ephrotoxicity has occurred following oral VANCOCIN therapy and can occur either during or after completion of therapy”; and highlights that nephrotoxicity “risk is increased in geriatric patients.”<sup>31</sup>

<sup>28</sup> Vancocin® Package Insert, §6.1: Adverse Reactions, Clinical Trial Experience (Dec. 2011).

<sup>29</sup> Vancocin® Package Insert, Precautions (Jan. 2010).

<sup>30</sup> Vancocin® Package Insert, §5.3: Warnings and Precautions, Nephrotoxicity (Dec. 2011).

<sup>31</sup> Vancocin® Package Insert, Highlights (Dec. 2011).

- GERIATRIC USE. Also wholly rewritten based on the new data submitted by ViroPharma, this subsection now lists the percentage of patients in the new studies who were >65, between >65 and 75, and >75, the increased risk of nephrotoxicity in geriatric patients seen in the new studies, and the associated instruction that renal function should be monitored in all elderly both during and following treatment. This section further notes that the new studies showed geriatric patients may take longer to respond to therapy, and as a result advises that “[c]linicians should be aware of the importance of appropriate duration of VANCOCIN treatment in patients >65 years of age and not discontinue or switch to alternative treatment prematurely.”<sup>32</sup>
- INDICATIONS AND USAGE. Vancocin’s previous *C. difficile* indication was changed based on the new studies, such that Vancocin is now “indicated for the treatment of *C. difficile* -associated diarrhea.”<sup>33</sup> Vancocin’s new Clinical Studies section explains what is meant by “*C. difficile* -associated diarrhea” in the new studies that led to this changed indication, as well as the efficacy endpoint by which resolution of CDAD was measured,<sup>34</sup> and the new recommended Vancocin dose based on these studies is recited in the Dosage and Administration section.<sup>35</sup> In light of the two new CDAD studies, the Indications and Usage section was also modified to reflect the relative absence of data for *S. aureus* enterocolitis, which is no longer referred to as an indication.
- DOSAGE AND ADMINISTRATION. The new Vancocin studies led to the significant modification of Vancocin’s previously labeled “usual” 500 mg to 2 g CDAD daily dosing range. For the first time Vancocin is now labeled with a “recommended” CDAD dose: 125 mg four times daily for ten days,<sup>36</sup> based on the dose used in the two new studies submitted in the Vancocin sNDA, which also removed the word “usual”<sup>37</sup> from the *S. aureus* dosing range due to data insufficiency concerns.

As a result of these extensive changes based on new clinical safety and efficacy data, the recent Vancocin sNDA was a “Prior Approval” efficacy supplement.<sup>38</sup> Accordingly, the Vancocin labeling was required to be brought into compliance with FDA’s Physician Labeling Rule (PLR). 21 C.F.R. § 201.56(b)(iii). Thus, in addition to the changes just discussed, the Vancocin sNDA also rewrote all of Vancocin’s labeling to comply with the PLR.

<sup>32</sup> Vancocin® Package Insert, §8.5: Use in Specific Populations, Geriatric Use (Dec. 2011).

<sup>33</sup> Vancocin® Package Insert, §1: Indications and Usage (Dec. 2011).

<sup>34</sup> As explained above, both the definition of CDAD and the efficacy endpoint used in the two new studies that formed the basis for the recent Vancocin sNDA were unique to those studies.

<sup>35</sup> Vancocin® Package Insert, §2: Dosage and Administration (Dec. 2011).

<sup>36</sup> Vancocin® Package Insert, §2.1: Dosage and Administration, Adults (Dec. 2011).

<sup>37</sup> Vancocin® Package Insert, §2.1: Dosage and Administration, Adults (Dec. 2011).

<sup>38</sup> See Letter from Katherine A. Laessig, FDA to ViroPharma, Inc., Approval of sNDA, NDA 50-606/S-028 at 1 (Dec. 14, 2011) (“This ‘Prior Approval’ efficacy supplemental new drug application provides for updates to the prescribing information for VANCOCIN with clinically relevant new safety and efficacy information.”). *Attached*.

## II. FDA Recognizes the Need for Modern Antibiotic Studies and Labeling

Antibiotics are a critical public health resource and unique among drug products. Their intended effect is to kill pathogenic organisms (i.e., bacteria) that cause harm in the human body. Bacteria evolve over time (i.e., develop resistance), and antibiotics that are effective upon approval may become less so over time due to the emergence of resistant strains. Therefore, updated labeling based on modern, relevant safety and efficacy data is especially important for antibiotics.

In light of the special nature of antibiotics, Congress, FDA, the Infectious Diseases Society of America (IDSA), and other public health advocates have urged the creation of incentives for pharmaceutical companies to invest in antibiotic research. As FDA Commissioner Dr. Margaret Hamburg said earlier this year, the unique economic challenges facing antibiotic companies have “led to important discussions of the types of economic policies and incentives that recognize the unique value of these products.”<sup>39</sup> ViroPharma believes that ensuring generic sponsors must carry a complete label consistent with ViroPharma’s extensive, new, modernized labeling will recognize the unique value of antibiotics and promote further investment.

Unfortunately, as FDA’s Dr. Janet Woodcock testified to Congress in 2010, “[t]he [antibiotic] pipeline is diminishing at a time when the need could not be greater.”<sup>40</sup> This highlights the need for good stewardship of existing antibiotics through, among other things, updating labeling information to ensure safe and effective use against new bacterial strains and, for many older antibiotics, adding safety and efficacy data where previously there were none. There is broad agreement among public health officials and experts in the field that multiple approaches are needed to solve the serious public health problem presented by the limited numbers of effective antibiotics, old or new, in the midst of growing antimicrobial resistance.

In the original passage of the 3 year exclusivity provisions and subsequent laws ensuring this incentive applied to antibiotics, the intent of Congress was to incent continued research and development with the goal of important changes to the drug label.<sup>41</sup> It is notable that Congress passed the 2008 law ensuring 3 year exclusivity for old antibiotics at a time of heightened concern regarding antibiotic resistance and the dearth of research into antibiotics. The only logical inference to draw from these facts is that Congress, and stakeholders advocating for these changes to the law, intended that the available incentives be maximally available to antibiotic manufacturers.<sup>42</sup> Recognizing that ViroPharma’s investment in new investigations to update Vancocin’s labeling has earned 3 year exclusivity will help cement this incentive as a means to attract further investment in research on older antibiotics.

<sup>39</sup> Margaret Hamburg, Commissioner, Food & Drug Admin., FDA’s Efforts to Facilitate Antibiotic Development, Remarks at IDSA World Health Day Event (Apr. 7, 2011) available at <http://www.fda.gov/NewsEvents/Speeches/ucm250391.htm>.

<sup>40</sup> *Promoting the Development of Antibiotics and Ensuring Judicious Use in Humans*, Hearing Before the H. Subcomm. on Health, House Energy and Commerce Committee, 111<sup>th</sup> Cong. (2010) (response of Janet Woodcock, Dir., CDER, FDA) as quoted in Julie Steenhuyzen, *Regulators urged to help develop antibiotics*, REUTERS, June 9, 2010, available at <http://www.reuters.com/article/2010/06/09/us-antibiotic-resistance-idUSTRE65865O20100609>.

<sup>41</sup> Senator Hatch was one of the original sponsors of the provision ensuring that 3 year exclusivity applied to old antibiotics, which was initially included in S. 1082, the Food and Drug Administration Revitalization Act. S. 1082, 110<sup>th</sup> Cong. §261 (as passed by Senate, May 9, 2007). During floor debate regarding this provision, Senator Hatch stated: “[I]t is fair to say that major pharmaceutical companies have not been making significant investments in antibiotics....[I]f Congress fails to act, we walk blindly into a future where we must fear basic infections we have long taken for granted are not a problem.” 110 CONG. REC. S5624 (May 7, 2007).

<sup>42</sup> Senator Burr addressed the importance of incentivizing companies to conduct more antibiotic research. 110 CONG. REC. S9638 (daily ed. Sep. 26, 2008) (“[M]any pharmaceutical companies are abandoning or scaling back antibiotic research and development...as market forces that would lead companies to consider investing in new antibiotic development is weak.”).

### III. Changes Approved in the Vancocin sNDA Have Earned 3 Year Exclusivity

The Federal Food, Drug and Cosmetic Act provides that generic applications<sup>43</sup> will not be approved for changes approved in an sNDA for three years from the date of approval of the sNDA if the sNDA contained “reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement.”<sup>44</sup> 21 U.S.C. § 355 (c)(3)(E)(iv); 21 U.S.C. § 355(j)(5)(F)(iv).<sup>45</sup> The recently approved Vancocin sNDA meets each of these three criteria for 3 year exclusivity.

#### A. The New Vancocin Studies are “New Clinical Investigations”

The two studies (of 260 Vancocin patients) submitted in the Vancocin sNDA are new clinical investigations because they:

have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product. 21 C.F.R. § 314.108 (a).

FDA’s approval letter acknowledges that the new Vancocin sNDA included “new clinical investigations” when it describes the sNDA as updating the prescribing information for VANCOCIN with “clinically relevant new safety and efficacy information.”<sup>46</sup> A closer analysis of the regulatory requirement further confirms this conclusion.

Each new Vancocin study was a “new clinical investigation” because FDA never previously relied on either study “to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population.” 21 C.F.R. § 314.108(a). The investigations here have only been relied on by FDA “to demonstrate substantial evidence of effectiveness” and safety of Vancocin, in the Vancocin sNDA. *Id.*

Additionally, the new Vancocin studies do not “duplicate ... another investigation.” *Id.* The new Vancocin studies are unique. As FDA said in April 2011, there is “limited information on

<sup>43</sup> As used herein, the terms “generic applications,” “generic,” etc. mean applications under either 21 U.S.C. § 355(b)(2) or 21 U.S.C. § 355 (j).

<sup>44</sup> Through meeting these three criteria an sNDA sponsor demonstrates that it has made a “considerable investment” in obtaining FDA approval for “important innovations requiring substantial study” and is therefore entitled to 3 year exclusivity. 54 Fed. Reg. 28899.

<sup>45</sup> A separate pair of provisions furnish 3 year exclusivity for “conditions of approval” approved in new drug applications which include a previously-approved active ingredient. 21 U.S.C. § 355(c)(3)(E)(iii); 21 U.S.C. § 355(j)(5)(F)(iii).

<sup>46</sup> Letter from Katherine A. Laessig, FDA to ViroPharma, Inc., Approval of sNDA, NDA 50-606/S-028 at 1 (Dec. 14, 2011). *Attached* .

effect of vancomycin compared to placebo for treatment of CDAD,”<sup>47</sup> none of it as rigorous as the new Vancocin studies. Further, the unique entry criteria and efficacy endpoint used in the new Vancocin studies, and the data that flowed from this unique protocol, do not duplicate any other investigation. Nor could Vancocin’s efficacy against placebo be the subject of another trial’s protocol, as it would be unethical to expose CDAD patients suffering from life-threatening disease to a placebo.<sup>48</sup>

B. The New Vancocin Studies were “Essential to the Approval” of the New Vancocin sNDA

The two new studies were essential to approval of the new Vancocin sNDA because “there are no other data available that could support approval of the application.” 21 C.F.R. § 314.108(a). Vancocin labeling previously contained no clinical data. As explained above, the new clinical safety and efficacy data submitted in the Vancocin sNDA led to extensive, fundamental changes in Vancocin’s labeling. These changes could not have been based on any other data, because no other data set could provide the specific results and analyses from the new Vancocin studies reported in, e.g., Vancocin’s new Clinical Studies, Adverse Events: Clinical Trial Experience, Nephrotoxicity, and Geriatric Use sections. FDA would not have approved these changes if ViroPharma had requested them in the absence of the specific data sets and analyses submitted in the Vancocin sNDA.

Some might claim the studies conducted in support of Dificid™ (fidaxomicin)<sup>49</sup> are similar to the Vancocin studies in the new sNDA. The Dificid trials, however, could not have supported FDA approval of Vancocin’s new Clinical Studies, Adverse Events: Clinical Trial Experience, Nephrotoxicity, or Geriatric Use sections because those sections are directly based on the specific data from the new Vancocin studies. For example, the Dificid trials could not have been a basis for FDA to approve the data tables in Vancocin’s new labeling which (1) rank order the specific adverse reactions seen in the new Vancocin studies<sup>50</sup> and (2) provide clinical success rates based on the Full Analysis Sets in the two trials.<sup>51</sup> No study other than the new Vancocin studies could have supplied these specific data, and thus the new Vancocin studies were essential to approval.

The new Vancocin studies also modified Vancocin’s indication and for the first time included a recommended dose,<sup>52</sup> as discussed above. The Dificid trials could not have supported these

<sup>47</sup> *Vancocin Advisory Committee* at 46.

<sup>48</sup> Moreover, even if the new Vancocin studies each somehow “duplicated” a previous trial, FDA would have had to rely on each such previous trial “to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.” 21 § C.F.R. § 314.108(a) (emphasis added).

<sup>49</sup> FDA approved Dificid on May 27, 2011. Other than the Dificid trials, the literature contains only (1) results from the tolevamer studies to which ViroPharma has exclusive rights, and (2) the weak evidence base reviewed above, which lacks robust, adequate and well-controlled studies demonstrating the safety and efficacy of Vancocin capsules.

<sup>50</sup> Vancocin® Package Insert, §6.1: Adverse Reactions: Clinical Trial Experience, Diarrhea Associated with *Clostridium difficile*, Table 1: Common (— 5% of VANCOCIN Reported in Clinical Trials for Treatment of Diarrhea Associated with *C. difficile* (Dec. 2011).

<sup>51</sup> Vancocin® Package Insert, §14: Clinical Studies, Diarrhea Associated with *Clostridium difficile*, Table 2, Clinical Success Rates (Full Analysis Set) (Dec. 2011).

<sup>52</sup> Vancocin’s new recommended dosing regimen is protected by Vancocin’s new 3 year exclusivity because it resulted directly from the new studies submitted in the Vancocin sNDA, which removed the former “usual” dosing range and replaced it with 125 mg q.i.d. for ten days. Removal of old labeling statements can be eligible for 3 year exclusivity. See, e.g., Orange Book exclusivity code M-76 – “REMOVAL OF SCREEN REQUIREMENT IN PTS WITH G6PD DEFICIENCY PRIOR TO INITIATING ACZONE TREATMENT; REMOVAL OF BLOOD COUNT & RETICULOCYTE MONITORING DURING TREATMENT IN G6PD DEFICIENT PTS AND IN PATIENTS WITH HISTORY OF ANEMIA.”

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changes because they were different in design, entry criteria, and efficacy endpoint from the new Vancocin studies. Moreover, they were powered to show that Dificid is not inferior to Vancocin, rather than to demonstrate Vancocin efficacy, which was assumed.

The Dificid trials did not replicate the unique result of the new Vancocin studies: demonstration of Vancocin efficacy against a (“putative”) <sup>53</sup> placebo. Due to the severity and life-threatening potential of CDAD and the existence of approved effective therapies, it would be unethical to conduct a placebo-controlled trial for this condition. Given this constraint, tolevamer’s unfortunate efficacy failure provided the closest possible approximation of a placebo-controlled demonstration of Vancocin efficacy – something critically lacking in both Vancocin’s labeling and the literature, as discussed above. Because the Dificid studies were active-controlled, they did not replicate the unique “putative placebo” findings of the studies submitted in the recent Vancocin sNDA.

In addition, the Dificid trials were not designed to yield a statistically significant assessment of Vancocin efficacy (as defined in the tolevamer trials) in the treatment of CDAD (as defined in the tolevamer trials) against placebo, but rather to show Dificid to be noninferior to Vancocin using the Dificid protocol definitions of CDAD and cure.

Moreover, Vancocin’s CDAD indication (defined in Vancocin’s new Clinical Studies section) <sup>54</sup> is different from the Dificid definition of CDAD. In the Vancocin trials, CDAD is defined as three or more loose or watery bowel movements within the 24 hours preceding enrollment, plus the presence of *C. difficile* toxins or pseudomembranes on endoscopy. By contrast, the Dificid trials required four or more unformed bowel movements in the 24 hours before randomization, and the presence of *C. difficile* toxins was required, i.e., could not be replaced by pseudomembranes on endoscopy.

Finally, the efficacy of Vancocin (125 mg q.i.d.) against (the Dificid definition of) CDAD was also assessed differently in the Dificid studies. The Vancocin studies defined treatment success as two or fewer loose or unformed bowel movements and the absence of severe abdominal discomfort due to CDAD, a unique co-primary endpoint requested by FDA. The Dificid studies, on the other hand, did not replicate Vancocin’s co-primary endpoint, but instead defined clinical success as “improvement in diarrhea or other symptoms such that, in the Investigator’s judgment, further CDAD treatment was not needed.” <sup>55 56</sup>

<sup>53</sup> FDA Fidaxomicin Briefing Information at 42.

<sup>54</sup> Vancocin® Package Insert, §14: Clinical Studies, Diarrhea Associated with *Clostridium difficile* (Dec. 2011) (“CDAD was defined as — 3 loose or watery bowel movements within the 24 hours preceding enrollment, and the presence of either *C. difficile* toxin A or B, or pseudomembranes on endoscopy within the 72 hours preceding enrollment.”).

<sup>55</sup> Dificid® Package Insert, §14: Clinical Studies (May 2011).

<sup>56</sup> The studies also vary greatly in the clinical history of the patients and the severity of the disease. Both defined severe CDAD as “10 or more unformed bowel movements per day or a WBC greater than or equal to 15000/mm<sup>2</sup>.” 37% of Vancocin patients in the Dificid studies met this definition, but only 25% did in the Vancocin sNDA studies. Furthermore, 47% of the patients in the Vancocin sNDA studies had previously been treated for CDAD, while only 16% of patients in the Dificid studies had been. This difference in previous occurrence could have a large impact on the clinical success rate.

For each of the above reasons, neither the Difucid trials nor any other studies could be considered as data sets that could have led to approval of Vancocin's new sNDA. The new studies submitted by ViroPharma were essential to the approval of the new Vancocin sNDA, because without them the changes in the sNDA would not have been approved.

C. The New Vancocin Studies were "Conducted or Sponsored by the Applicant"

ViroPharma also meets the third and final criterion for 3 year exclusivity: that the new clinical studies were "conducted or sponsored by the applicant." 21 C.F.R. § 314.108(a).

A study is considered to have been "conducted or sponsored by the applicant" if "the applicant or the applicant's predecessor in interest, provided substantial support for the investigation." *Id.* Genzyme originally provided "substantial support" for the studies, defined as providing more than 50% of their cost. *Id.*

Genzyme is ViroPharma's "predecessor in interest" because ViroPharma obtained exclusive rights to the studies from Genzyme. As the Agency has explained, "FDA interprets the act to allow for exclusivity where the applicant has supported the study by providing more than 50 percent of the funding or by purchasing exclusive rights to the study."<sup>57</sup> While "[p]urchase of non-exclusive rights to a clinical investigation after it is completed is not sufficient to satisfy this definition,"<sup>58</sup> purchase of exclusive rights is sufficient:

FDA agrees that an applicant who has purchased exclusive rights to a study should be able to obtain new drug exclusivity. FDA, therefore, has revised the definition of "conducted or sponsored by the applicant" to state that the purchase of nonexclusive rights to an investigation does not satisfy the definition. FDA emphasizes that the applicant must have exclusive rights to the purchased study in order to be deemed to have sponsored a study.<sup>59 60</sup>

<sup>57</sup> Abbreviated New Drug Application Regulations Patent and Exclusivity Provisions; Final Rule, 59 Fed. Reg. 50338, 50360 (Oct. 3, 1994). A "predecessor in interest" may also be "an entity, e.g., a corporation, that the applicant has taken over, merged with, or purchased, or from which the applicant has purchased all rights to the drug." 21 C.F.R. § 314.108(a).

<sup>58</sup> 21 C.F.R. § 314.108(a).

<sup>59</sup> Abbreviated New Drug Application Regulations Patent and Exclusivity Provisions; Final Rule, 59 Fed. Reg. 50338, 50358 (Oct. 3, 1994). *See also, e.g., id.* at 50359 ("an applicant may purchase an application or rights to data and information in an application (i.e., exclusive rights to a new clinical investigation), from which exclusivity would flow ..."); (FDA construes "a party who has purchased exclusive rights to a study to have 'conducted or sponsored' the study"); FDA, Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity (Jul. 1, 2010) *available at* <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069962.htm> ("An applicant who has purchased exclusive rights to a study should be able to obtain new drug product exclusivity.").

<sup>60</sup> ViroPharma recognizes that vestiges remain of FDA's proposed regulation, which had stated that "[p]urchase of a clinical investigation itself or the rights to an investigation after it is completed is not sufficient to satisfy [the] definition" of "conducted or sponsored by the applicant." (Abbreviated New Drug Application Regulations; Proposed Rule, 54 Fed. Reg. 28872, 28930 (July 10, 1989)). For example, FDA's Exclusivity Summary checklist continues to state that "[p]urchased studies may not be used as the basis for exclusivity." FDA Center for Drug Evaluation and Research, Form OGD-011347, at 7 (May 10, 2004). However, when it finalized this regulation, FDA replaced the sentence disqualifying purchased studies from exclusivity with the new sentence quoted above clarifying that only purchase of non-exclusive rights is ineligible for exclusivity, and made clear in the preamble accompanying the final regulation that "an applicant who has purchased exclusive rights to a study should be able to obtain new drug exclusivity." (Abbreviated New Drug Application Regulations Patent and Exclusivity Provisions, 59 Fed. Reg. 50338, 50358 (Oct. 3, 1994)).

FDA's insistence on purchase of exclusive study rights was motivated by a desire to avoid situations where "[t]he purchase of nonexclusive rights by different parties could result in multiple claims of exclusivity for the same study."<sup>61</sup> Because ViroPharma purchased exclusive rights, this risk is inapplicable here.

In sum, the recently approved Vancocin sNDA meets the criteria for 3 year exclusivity. Exclusivity begins upon sNDA approval. 21 U.S.C. § 355(c)(3)(E)(iv); 21 U.S.C. § 355(j)(5)(F)(iv). Thus Vancocin's 3 year exclusivity began on December 14, 2011, the date the Vancocin sNDA was approved, and will expire on December 15, 2014.

#### IV. Generic Products that Omit Vancocin's New Labeling Would Not Be Approvable

Generic vancomycin capsule products are required to copy Vancocin's labeling. 21 C.F.R. § 314.94(a)(8)(iv). They must also comply with FDA's prescription drug labeling regulations. 21 C.F.R. § 201.57. It will not be possible, however, for generics to fulfill these requirements without including in their labeling the new exclusivity-protected portions of Vancocin's labeling. Thus generic applicants shall have to wait until Vancocin's new 3 year exclusivity expires.

In an effort to circumvent these FDA regulations, generic applicants may argue that they can omit the changes approved in the recent Vancocin sNDA because such omissions would not render their drugs less safe or effective than Vancocin for whatever non-protected conditions of use remain. 21 C.F.R. § 314.127(a)(7).

Such an argument would be misguided. Vancocin's new exclusivity-protected labeling is extensive, and fundamental to the safe and effective use of Vancocin. Excising the protected labeling would remove key required labeling sections – e.g., Clinical Studies, Adverse Reactions: Clinical Trial Experience, Nephrotoxicity, Geriatric Use – in their entirety and thus violate FDA's labeling regulations. Generics also would have no indication, or recommended dosing regimen. The result would be an incoherent patchwork which certainly would not constitute a modern drug label, or even be equivalent to Vancocin's old labeling. Lacking extensive and critical aspects of Vancocin's labeling, generic vancomycin capsule products would be less safe or effective than Vancocin, and thus not approvable.

##### A. If Vancocin Has Clinical Safety and Efficacy Data but Generics Do Not, Generics By Definition Will Be Less Safe and Effective than Vancocin

FDA's prescription drug labeling regulations reflect the pivotal importance of clinical safety and efficacy data in prescription drug labeling. Thus, prescription drug labeling "must contain" enumerated sections of information. 21 C.F.R. § 201.57(c). These include a Clinical Studies section that:

must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively. Ordinarily, this section will describe the studies that support effectiveness for the labeled indication(s), including discussion of study design, population, endpoints, and results ... 21 C.F.R. § 201.57(c)(15).

<sup>61</sup> *Id.* at 50358.

The regulations specify that “any clinical study that is discussed in prescription drug labeling that relates to an indication for or use of the drug must be adequate and well-controlled as described in § 314.126(b) ...” 21 C.F.R. § 201.57(c)(15)(i). Following approval of the new Vancocin sNDA, the Vancocin labeling for the first time includes data-driven clinical efficacy rates.

Similarly, the regulations require an Adverse Reactions section that “must describe the overall adverse reaction profile of the drug based on the entire safety database.” 21 C.F.R. § 201.57(c)(7). With respect to clinical study data, the Adverse Reactions: Clinical Trials Experience section “must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database.” 21 C.F.R. § 201.57(c)(7)(ii)(A). Moreover, if there are any:

adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics... 21 C.F.R. § 201.57(c)(7)(ii)(A).

In the case of Vancocin’s new labeling, these clinically significant reactions based on clinical study data include nephrotoxicity, higher incidences of certain adverse events in geriatric patients, as well as discontinuation rates and their associated adverse events.

Generic vancomycin capsule labeling that omits the changes approved in the Vancocin sNDA would not contain any of these required labeling sections or the clinical safety and efficacy data contained therein. As discussed above, the only vancomycin capsule clinical safety and efficacy data in the Vancocin labeling are the data that were added via the recent Vancocin sNDA, which are protected by 3 year exclusivity.<sup>62</sup> Thus, compared to Vancocin, an omitting generic’s labeling would be starkly silent.<sup>63</sup> Without any clinical data showing it to be safe and effective, a generic product would violate the prescription drug labeling regulations and be less safe or effective than Vancocin, which does have clinical safety and efficacy data.

<sup>62</sup> By contrast, with most other drugs, despite omission of protected labeling, generic labeling would still contain controlled clinical safety and efficacy data, e.g., from the Reference Listed Drug (RLD)’s original NDA data package – something lacking in the case of Vancocin, as explained above.

<sup>63</sup> The extensive ambit of the 3 year exclusivity-protected changes to Vancocin’s labeling also distinguishes Vancocin from previous cases where the scope of protected labeling was narrow because it was based on patents rather than non-patent exclusivity. *See, e.g.*, Letter from Janet Woodcock, FDA to Stephen R. Auten, Sandoz, Response to Citizen Petition, Docket No. FDA-2010-P-0087 at 9 (Jul. 30, 2010) [hereinafter *Lyrica Letter*] (“complete removal of section 5.4 is not necessary to ensure that the protected seizure indication is not disclosed. Rather, selective deletions and *de minimis* modifications in the labeling ... can adequately ensure that the necessary safety information is conveyed without disclosing the patent-protected indication.”); Letter from Janet Woodcock, FDA, to Robert Trainor, Citizen Petition Response on Xyzal, Docket No. FDA-2010-P-0545, at 10 (“selective deletions of the references to allergic rhinitis and *de minimis* modifications in the labeling ... can adequately ensure that the necessary safety information is conveyed without disclosing the patent-protected indications.”).

Indeed, the labeling changes approved in the Vancocin sNDA are at least as extensive as the kinds of changes that FDA has previously determined cannot be carved-out of generic labeling. For example, FDA recently determined that generic products seeking to copy Colcris® (colchicine) could not carve-out protected information where Colcris was the first FDA approval of an old drug.<sup>64</sup> Although literature regarding the use of colchicine existed and formed part of the basis for the Colcris approval, the sponsor had submitted a new clinical study that for the first time established the safety and efficacy of colchicine under modern FDA approval standards, including the establishment of a lower dose of this old drug.<sup>65</sup> Similarly, FDA refused to permit generic copies of Rapamune® (sirolimus) to carve-out “extensive information” included in multiple sections of Rapamune’s labeling.<sup>66</sup>

Like Colcris, the protected Vancocin labeling information derives from new controlled clinical data demonstrating the safety and efficacy of an old drug, as well as a recommended dose for the drug, for which such data previously had been lacking, and did this without (as Colcris had) resort to the literature. And like both Colcris and Rapamune, the new protected Vancocin labeling is extensive, adding new sections and wholly rewriting old sections of the Vancocin labeling, as explained above.

Because a generic drug bereft of any clinical data showing it to be safe and effective would, by definition, be less safe or effective than a drug (Vancocin) with clinical data proving its safety and effectiveness, generic products that omit Vancocin’s protected labeling would be unapprovable.

#### B. Generic Products That Omit Vancocin’s New Renal Function Monitoring Instructions Would Be Unapprovable

Vancocin’s old labeling stated that renal function should be monitored only “[w]hen patients with underlying renal dysfunction or those receiving concomitant therapy with an aminoglycoside are being treated.”<sup>67</sup> Based on the new clinical studies in the Vancocin sNDA, FDA expanded Vancocin’s old, limited renal monitoring labeling to a broad, categorical instruction: “Monitor renal function.”<sup>68</sup>

##### 1. Omission of the Instruction to “Monitor Renal Function” Would Violate FDA’s Labeling Regulations and Render Generic Products Less Safe or Effective

FDA’s labeling regulations provide that prescription drug labeling “must contain”<sup>69</sup> a Warnings and Precautions section which “must describe clinically significant adverse reactions.”<sup>70</sup> Regarding monitoring, “[t]his section must identify any laboratory tests helpful in following the patient’s response or in identifying possible adverse reactions.”<sup>71</sup>

<sup>64</sup> Letter from Janet Woodcock, FDA to Gary L. Veron, Response to Citizen Petition, Docket No. FDA-20100P-0614, at 3 (May 25, 2011) [hereinafter *Colcris Letter*].

<sup>65</sup> *Colcris Letter* at 6-8.

<sup>66</sup> Letter from Steven K. Galson to Wyeth Pharmaceuticals et al. Response to Citizen Petition Docket No. 2003P-0518/CP1, at 2 (Sep. 20, 2004) [hereinafter *Rapamune Letter*].

<sup>67</sup> Vancocin® Package Insert, Precautions (Jan. 2010).

<sup>68</sup> Vancocin® Package Insert, Highlights; §5:Warnings & Precautions (Dec. 2011).

<sup>69</sup> 21 C.F.R. § 201.57(c).

<sup>70</sup> 21 C.F.R. § 201.57(c)(6)(i).

<sup>71</sup> 21 C.F.R. § 201.57(c)(6)(iii).

Generic vancomycin capsule labeling which omits the protected portions of Vancocin’s labeling would not include Vancocin’s categorical and unqualified instruction to “[m]onitor renal function.” Indeed, an omitting generic would lack the entire section on Nephrotoxicity in Vancocin’s new labeling, because that section is wholly based on the new clinical investigations submitted in the Vancocin sNDA.

As a result, such generics would fail to adequately warn clinicians of the risks of nephrotoxicity, the data from Vancocin’s clinical trials regarding nephrotoxicity rate, and, most importantly, would not instruct clinicians, without qualification, to monitor renal function.<sup>72</sup> There can be little doubt that generic products lacking this vital information would be less safe or effective than Vancocin.

## 2. Nephrotoxicity and Renal Function Monitoring Are Not Addressed in Unprotected Sections of the Vancocin Labeling

ANDA applicants may claim that because generic labeling would retain unprotected portions of the Potential for Systemic Absorption section of Vancocin’s labeling, it would not be less safe or effective, despite omitting Vancocin’s Nephrotoxicity section and the instruction in Vancocin’s Highlights section to “[m]onitor renal function.” The unprotected language, however, is not based on controlled clinical data with vancomycin capsules, does not mention renal function monitoring, is optional, not categorical, and does not encompass all patients. Instead, the unprotected language only notes that “some patients” with inflammatory intestinal disorders “may” have systemic vancomycin absorption and “may” risk adverse reactions, and thus “monitoring of serum concentrations of vancomycin *may be appropriate in some instances*, e.g., in patients with renal insufficiency and/or colitis or in those receiving concomitant therapy with an aminoglycoside antibiotic.”<sup>73 74</sup>

<sup>72</sup> Indeed, the only non-exclusivity protected mention of nephrotoxicity that would remain after omitting Vancocin’s protected labeling would be regarding Pregnancy and is based on intravenous vancomycin administration to pregnant drug abusers. “In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin on infants were evaluated when the drug was administered intravenously to pregnant women for serious staphylococcal infections complicating intravenous drug abuse.... No ... nephrotoxicity attributable to vancomycin was noted.... [T]he number of subjects treated in this study was limited ....” Vancocin® Package Insert, §8.1: Use in Specific Populations, Pregnancy (Dec. 2011).

<sup>73</sup> Vancocin® Package Insert, § 5.2: Warnings and Precautions, Potential for Systemic Absorption (Dec. 2011) (emphasis added).

<sup>74</sup> The labeling regulations also require an *Adverse Reactions: Postmarketing Experience* section. In the Vancocin labeling this section is short and based largely on case reports associated with intravenous administration of vancomycin. The labeling statements are old and date from an era when vancomycin was less pure than the Vancocin sold today. Prior to the introduction and refinement of modern manufacturing techniques, intravenous vancomycin contained so many impurities it was referred to as “Mississippi Mud.” See Levine *supra* note 6 at S5; See also , Michael Rybak et al., *Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists* , 66 A M . J . H EALTH -S YST . P HARM . at 82 (2009). The relevance of these reports to adverse events that might be expected with use of higher purity oral Vancocin capsules manufactured with modern techniques developed over several intervening decades of empiric improvements is unclear, and relatively much less informative than the extensive adverse event data collected in the two recent controlled studies submitted in the Vancocin sNDA. *Attached* .

Unlike these qualified, limited, non-categorical statements that do not mention renal monitoring, Vancocin’s protected labeling is universal, categorical, and precise: “Monitor renal function.” Relying on Vancocin’s protected labeling, clinicians will understand that they should monitor renal function for all patients. By contrast, clinicians relying on a generic label that omits these statements will believe only that vancomycin “serum concentration[ ]” monitoring “may be appropriate in some circumstances.” Thus, even if from time to time a clinician were to mistakenly equate monitoring serum vancomycin concentrations with monitoring renal function to detect nephrotoxicity, they “may” only monitor in “some circumstances.” It is clear that renal function monitoring will be less likely in patients whose physicians rely on the generic labeling, an obviously less safe or effective result.

### 3. FDA Has Previously Refused to Allow Carve-Out of Toxicity Warnings

Like Vancocin’s new nephrotoxicity warning, concerns about generics that omit exclusivity-protected adverse event information have in the past led FDA to refuse to allow generic products to “carve-out” the protected information from their labeling. For example, in the case of Colcris, FDA recently considered whether generic products could carve-out labeling protected by 3 year exclusivity based on new clinical data that “improve[d] the safety profile of colchicine.”<sup>75</sup> FDA agreed with the innovator manufacturer that generic labeling would need to include protected information that addressed “drug-drug interactions, including relevant dose adjustments needed to prevent unnecessary toxicity.”<sup>76</sup>

Similarly, for Rapamune, FDA concluded that labeling protected based on a new clinical study showing “that withdrawal of cyclosporine can have a significant impact on the adverse event profile of patients” could not be carved-out.<sup>77</sup> Rapamune had originally been approved only for use in combination with cyclosporine.<sup>78</sup> The drug’s sponsor subsequently submitted an sNDA containing a new clinical study showing cyclosporine should be withdrawn after 2-4 months in most patients.<sup>79</sup> FDA concluded that the protected labeling resulting from the sNDA contained “extensive, critical prescribing information ... that any physician should receive to appropriately determine treatment for all indications of sirolimus.”<sup>80</sup>

Just as Colcris’ protected information was necessary to prevent “unnecessary toxicity,” and Rapamune’s protected withdrawal regimen could have “a significant impact on the adverse event profile” of Rapamune, Vancocin’s new nephrotoxicity warning is critical to the safe and effective use of Vancocin. Generic products that omit Vancocin’s protected labeling would result in fewer patients receiving renal function monitoring. As a result, omission of Vancocin’s protected labeling would render the generic “less safe or effective” than Vancocin.

<sup>75</sup> Colcris Letter at 3.

<sup>76</sup> Colcris Letter at 3.

<sup>77</sup> Rapamune Letter at 3-4.

<sup>78</sup> Rapamune Letter at 1.

<sup>79</sup> Rapamune Letter at 2.

<sup>80</sup> Rapamune Letter at 3.

4. The Elderly Would Be Particularly Vulnerable to Omission of Nephrotoxicity Labeling Information and the Instruction to Monitor Renal Function

Elderly patients in particular would be put at risk by generic products omitting the specific information and instructions regarding this patient population that the recent sNDA added to Vancocin's labeling:

The risk of nephrotoxicity is increased in patients >65 years of age ( see *ADVERSE REACTIONS, Clinical Trial Experience [6.1] and USE IN SPECIFIC POPULATIONS, Geriatric Use [8.5]* ).

In patients >65 years of age, including those with normal renal function prior to treatment, renal function should be monitored during and following treatment with VANCOCIN to detect potential vancomycin induced nephrotoxicity.<sup>81</sup>

In contrast to these explicit instructions to monitor renal function for vancomycin induced nephrotoxicity in all elderly (“including those with normal renal function prior to treatment”),<sup>82</sup> generic labeling omitting these statements would contain no mention of nephrotoxicity in either the elderly specifically or adults generally.<sup>83</sup> Elderly patients whose physicians relied on the generic labeling would be less likely to receive renal function monitoring despite their greater need for it – clearly a less safe or effective result.

5. Renal Function Monitoring is Critical for All Vancocin Patients

Some might claim that the Vancocin nephrotoxicity data and associated instruction to monitor renal function derive from Vancocin studies in CDAD patients, such that their absence from generic labeling would not render generics less safe or effective if the generic were only labeled for staphylococcal enterocolitis. The instruction for renal function monitoring, however, is “to detect potential vancomycin induced nephrotoxicity”<sup>84</sup> and thus linked to vancomycin exposure, not a particular bacterium. Indeed, as Vancocin's labeling states, vancomycin exposure can occur in “patients with inflammatory disorders of the intestinal mucosa,”<sup>85</sup> which would include *S. aureus* enterocolitis.

Moreover, omission of Vancocin's protected nephrotoxicity labeling on the ground that it is based on studies in *C. difficile* patients and thus irrelevant to a generic that will only be labeled for *S. aureus* would imply the existence of evidence that, to ViroPharma's knowledge, does not exist. Specifically, one would need to show that nephrotoxicity seen in *C. difficile* patients treated with Vancocin 125 mg q.i.d. is not relevant to *S. aureus* enterocolitis patients. In other words, one would need to demonstrate that CDAD and staphylococcal enterocolitis are sufficiently distinct disease states with respect to nephrotoxicity such that nephrotoxicity data generated in one disorder do not inform potential nephrotoxicity issues in the other.

<sup>81</sup> Vancocin® Package Insert, §5.3: Warnings and Precautions, Nephrotoxicity, §6.1: Adverse Reactions: Clinical Trial Experience; §8: Use in Specific Populations (Dec. 2011).

<sup>82</sup> Vancocin® Package Insert, §5.3: Warnings and Precautions, Nephrotoxicity (Dec. 2011).

<sup>83</sup> As explained above, the only non-exclusivity protected mention of nephrotoxicity that would remain after omitting Vancocin's protected labeling concerns infant nephrotoxicity when vancomycin solution was administered intravenously to pregnant mothers for serious staphylococcal infections complicating intravenous drug abuse.

<sup>84</sup> Vancocin® Package Insert, § 5.3: Warnings and Precautions, Nephrotoxicity (Dec. 2011).

<sup>85</sup> Vancocin® Package Insert, § 5.2: Warnings and Precautions, Ototoxicity (Dec. 2011).

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If such data exist, then the relevance of the Vancocin nephrotoxicity labeling derived from studies in CDAD patients to a generic that is only labeled for staphylococcal enterocolitis might be questioned. Absent such data to rule out what medical logic would otherwise consider relevant to *S. aureus* patients, omission of the nephrotoxicity monitoring instruction and Nephrotoxicity section from generic vancomycin capsule labeling would render the generic product less safe or effective.

### C. Generics That Omit Vancocin's Protected Labeling Would Not Have the Required Geriatric Use Subsection

Vancocin treats serious, life-threatening disease that disproportionately affects the elderly. The two studies which supplied the basis for Vancocin's new sNDA included robust data in elderly patients, whereas Vancocin's old labeling had none. As a result, the entire geriatric use subsection of Vancocin's labeling was rewritten based on the new study data. Consequently, generic products that seek FDA approval prior to expiry of Vancocin's 3 year exclusivity would have to remove the geriatric subsection from their labeling.

Generic labeling that does not include a geriatric subsection, however, would violate FDA's labeling regulations. Full prescribing information for prescription drug products "must contain" a subsection on geriatric use. 21 C.F.R. § 201.57(c); (c)(9). "Specific statements on geriatric use of the drug for an indication approved for adults generally ... must be contained in the 'Geriatric use' subsection..." 21 C.F.R. § 201.57(c)(9)(v)(B). Where, as here, evidence indicates that use of Vancocin in the elderly "is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment" then "the 'Geriatric use' subsection must contain a brief description of observed differences or specific monitoring or dosage requirements" as well as appropriate cross-references to other sections of the labeling. 21 C.F.R. § 201.57(c)(9)(v)(B)(3).

Generic products omitting Vancocin's protected labeling would violate these regulations. Although prescription drug labeling "must contain" a geriatric use subsection, generic labeling would not. Absent a geriatric subsection, it would also fail to contain "[s]pecific statements on geriatric use of the drug for an indication approved for adults generally." 21 C.F.R. § 201.57(c)(9)(v)(B). And the new labeling instructions regarding renal function monitoring and premature discontinuation of treatment in the elderly would be gone as well.

In addition to violating FDA's labeling regulations, the omission of all geriatric information from the labeling of generic vancomycin capsules would render the generics less safe or effective than Vancocin. As discussed above, all of the geriatric information in Vancocin's new labeling is protected by 3 year exclusivity, so generic products would have none. Clinicians who treat the elderly in the absence of geriatric use information would do so less safely and effectively than clinicians to whom geriatric use information is available.

Nor are there other, unprotected statements in the labeling which could be considered to adequately replicate Vancocin's new protected geriatric data and instructions, e.g., for

nephrotoxicity monitoring and not to prematurely discontinue treatment.<sup>86</sup> Whether specific to geriatrics or more generally, all of these statements are protected by Vancocin's new 3 year exclusivity.<sup>87</sup> Because heretofore there were no vancomycin capsule clinical safety and efficacy data, and these new statements were explicitly based on those new data, the remaining, unprotected portions of Vancocin's new labeling would not prevent a generic that omits the new labeling from being less safe or effective.

D. Generics That Omit Vancocin's Protected Labeling Would Fail To Instruct Clinicians About the Risks of Premature Discontinuation and Switching to Alternative Treatments

The new investigations submitted in the Vancocin sNDA resulted in the important finding that efficacy in elderly patients may take longer than in non-elderly patients:

Patients >65 years of age may take longer to respond to therapy compared to patient's — 65 years of age ( *see CLINICAL STUDIES, Diarrhea Associated with Clostridium difficile [14.1]* ).<sup>88</sup>

This new finding based on the new clinical safety and efficacy data submitted in the recent Vancocin sNDA led to a new labeling instruction that Vancocin prescribers should:

be aware of the importance of appropriate duration of VANCOCIN treatment in patients >65 years of age and not discontinue or switch to alternative treatment prematurely.<sup>89</sup>

These labeling statements are directly based on the new clinical safety and efficacy studies submitted in the Vancocin sNDA and therefore protected by Vancocin's new 3 year exclusivity. Generic products that omit these statements would be less safe or effective than Vancocin because clinicians relying on the generic labeling would not know of the lag seen in elderly response rates, or the associated instruction to be aware of the risk of premature discontinuation and switching. Such prescribers would thus be more likely to prematurely discontinue or switch treatment of elderly patients, resulting in preventable treatment failures, an obviously less safe and effective result.

<sup>86</sup> By contrast, new geriatric labeling for another drug was “unusual because all the safety and effectiveness issues addressed in the new geriatric use information are of concern within the general adult population and, as a consequence, are adequately addressed elsewhere in the label.” Letter from Steven K. Galson to Edward John Allera et al. Response to Citizen Petition Docket No. 2005P-0383/CP1, at 13 (Dec. 1, 2006) [hereinafter *Oxandrin Letter* ]. Here, as discussed above, not all of the geriatric issues (i.e. premature discontinuation) are even mentioned elsewhere in Vancocin's label and, to the extent they are (e.g., nephrotoxicity), they are protected by 3 year exclusivity. Thus the proper “case-specific analysis” ( *Oxandrin Letter* at 13) demonstrates that in the case of generic vancomycin capsules, omission of Vancocin's geriatric labeling would result in less safe or effective generic products.

<sup>87</sup> Because omission of Vancocin's geriatric labeling would leave generic products bereft of any geriatric section, nephrotoxicity warning, etc., this is not a case where “selective deletions and *de minimis* modifications in the labeling ... can adequately ensure that the necessary safety information is conveyed” ( *Lyrice Letter* at 9), nor would it be accurate to replace the entirety of Vancocin's geriatric labeling with statements that only “[c]ertain geriatric use information is protected by marketing exclusivity” ( *Oxandrin Letter* at 20), when in fact all geriatric use information is protected.

<sup>88</sup> Vancocin® Package Insert, §8.5: Use in Specific Populations, Geriatric Use (Dec. 2011).

<sup>89</sup> Vancocin® Package Insert, §8.5: Use in Specific Populations, Geriatric Use (Dec. 2011).

## E. Generics that Omit Vancocin’s CDAD Indication Would Have No Indication and Therefore Be Unapprovable

FDA’s labeling regulations require that all prescription drug product labeling “must state” an indication. 21 C.F.R. § 201.57(c)(2) (the “indication regulation”). Vancocin labeling has only one indication: the treatment of CDAD.<sup>90</sup> Thus, an ANDA applicant would violate the indication regulation if the labeling for its vancomycin capsule product does not state that it is indicated for CDAD.

Vancocin’s CDAD indication, however, was one of the new changes to the Vancocin labeling approved in the recent sNDA, such that it is protected by Vancocin’s new 3 year exclusivity. Therefore, to comply with the indication regulation and become approvable, generic vancomycin drug products must wait until Vancocin’s 3 year exclusivity expires.

### 1. CDAD is Vancocin’s Only Indication

ANDA applicants may contend that, in addition to *C. difficile* -associated diarrhea, Vancocin labeling contains a second indication: enterocolitis caused by *S. aureus* . The Vancocin labeling, however, would not support such a contention. Vancocin’s labeling states that Vancocin is only “indicated for” the treatment of *C. difficile* -associated diarrhea.

Vancocin’s labeling does not state that Vancocin is “indicated for” *S. aureus* . Rather, it merely advises that Vancocin is “also used for the treatment of” *S. aureus* . Consequently, the labeling language regarding Vancocin usage in the treatment of *S. aureus* does not meet the indication regulation’s requirement that labeling “must state that the drug is indicated for the treatment” of *S. aureus* .

*C. difficile* ’s status as the only Vancocin indication reflects the differing levels of evidence supporting the use of Vancocin in *C. difficile* -associated diarrhea versus *S. aureus* colitis. As explained above, Vancocin’s use in the treatment of *C. difficile* -associated diarrhea is supported by safety and efficacy data from 260 Vancocin-treated patients in two prospective, randomized, double-blind, controlled clinical studies. No such clinical studies support the use of Vancocin in *S. aureus* .

FDA’s regulations further provide that all indications “must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b)...” 21 C.F.R. § 201.57(c)(2)(iv).<sup>91</sup> As discussed above, ViroPharma is unaware of sufficient evidence

<sup>90</sup> Vancocin® Package Insert, §1: Indications and Usage (Dec. 2011) (“Vancocin Capsules are indicated for the treatment of *C. difficile* -associated diarrhea. Vancocin Capsules are also used for the treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains).”).

<sup>91</sup> 21 C.F.R. § 201.57(c)(2)(iv) also states that the requirement of “substantial effectiveness based on adequate and well-controlled studies” may be “waived under § 201.58 or §314.126(c).” 21 C.F.R. 201.58 requires a written request that must be granted in writing by the Director of CDER, whose determination would need to comply with FDA’s regulations, e.g., 21 C.F.R. § 314.127(a)(7). 21 C.F.R. § 314.126(c) also requires the CDER Director’s accord, and is limited to waivers of the criteria for “adequate and well-controlled studies” for a “specific clinical investigation, either prior to the investigation or in the evaluation of a completed study” such that the study can still be relied upon as “substantial evidence of effectiveness, notwithstanding nonconformance with the criteria.” It thus applies to the question of whether a study can be included in RLD labeling – a determination already made by the Office of New Drugs – not whether a study can be removed from generic labeling.

to establish that the use of Vancocin for enterocolitis caused by *S. aureus* meets this standard.<sup>92</sup> This lack of evidence supports the differentiation in Vancocin’s labeling between *C. difficile* -associated diarrhea – the data for which meet the standard required of a labeled indication – and *S. aureus* enterocolitis, which, based on presently available evidence, do not.

## 2. Stand-alone *S. aureus* Labeling Would Be Less Safe and Effective

Generic interests may seek to persuade FDA that even without any evidence of clinical safety and efficacy, generic products would be no “less safe or effective” than Vancocin “for all remaining, non-protected conditions of use.” 21 C.F.R. § 314.127(a)(7). The argument, presumably, would be that a generic product may omit Vancocin’s indication for CDAD and be approved only for use in treating enterocolitis caused by *S. aureus*. That argument would fail.

There is no indication that FDA’s Division of Anti-Infective Products (DAIP) would approve Vancocin with only the *S. aureus* portions of the Vancocin labeling. DAIP approved Vancocin’s new labeling (including the *S. aureus* portions thereof) only in the context of ViroPharma submitting data from 260 Vancocin-treated patients in 2 clinical safety and effectiveness studies. Review and approval of this comprehensive new label for Vancocin did not require assessment of whether the *S. aureus* portions of Vancocin’s label, standing alone and without any of the new changes approved in the sNDA, might independently constitute a safe and effective label in their own right. Indeed, as discussed above, ViroPharma is unaware of adequate and well-controlled studies establishing substantial evidence of effectiveness of vancomycin capsules in treating patients with staphylococcal enterocolitis, 21 C.F.R. § 201.57(c)(2)(iv), and the use of vancomycin capsules for this infection is *de minimis*.

FDA’s labeling regulations also require that the Dosage and Administration section “must state the recommended dose.” 21 C.F.R. § 201.57(c)(3)(i). Vancocin labeling states a recommended dose, but only for CDAD.<sup>93</sup> The absence of a recommended dose for *S. aureus* reflects that while the drug has been used in treating *S. aureus* enterocolitis, the available evidence does not support a labeled *S. aureus* indication.

In sum, at the present time there is little basis to support a stand-alone *S. aureus* label. ViroPharma would not request such a label. And there is little reason to believe that FDA would approve Vancocin with a stand-alone *S. aureus* label, given the current level of evidence. 21 U.S.C. 355 (d); 21 C.F.R. 314.125(b)(2)-(5).<sup>94 95</sup>

<sup>92</sup> This is not to say that there is no evidence of Vancocin efficacy in *S. aureus*, but merely that available evidence does not rise to the level required to be an indication in FDA-approved prescription drug product labeling.

<sup>93</sup> Vancocin® Package Insert, §2.1 (Dec. 2011).

<sup>94</sup> See also, 21 C.F.R. 314.126(e) (“Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.”).

<sup>95</sup> An ANDA applicant might argue that even if DAIP would not approve a *S. aureus* -only Vancocin product, a generic *S. aureus* -only vancomycin capsule would be no “less safe or effective” than a hypothetical *S. aureus* -only Vancocin. It would be absurd, however, to bootstrap the approval of a *S. aureus* -only generic on the ground that it is no “less safe or effective” than a hypothetical drug which itself would not be approvable due to insufficient evidence of safety and effectiveness. Unless and until FDA’s Division of Anti-Infective Drug Products concludes that there is sufficient evidence of safety and efficacy to support approval of a stand-alone, *S. aureus* -only Vancocin capsule, no *S. aureus* -only ANDA should be approved.

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#### F. Generics That Include Vancocin's CDAD Indication Would Not Be Approvable

Generic applicants might also argue that Vancocin's new CDAD indication is not protected by 3 year exclusivity. As an initial matter, Vancocin's CDAD indication is protected by Vancocin's new 3 year exclusivity, as explained above.

However, even assuming *arguendo* that Vancocin's CDAD indication were not protected by Vancocin's new 3 year exclusivity, generic products which include the CDAD indication would nonetheless fail to meet the standards for approval. Even if ANDA labeling could carry Vancocin's new indication and dosing regimen, it could not include the new exclusivity-protected Vancocin conditions of use discussed above. ANDAs would therefore not have a Clinical Studies section, an Adverse Reactions: Clinical Trial Experience section, a Nephrotoxicity section, or a Geriatric Use section. As explained above, omission of any one of these would violate FDA's labeling regulations and render generic products less safe or effective. Thus, even if a generic product could carry Vancocin's CDAD indication, it would not be approvable because it could not include these other important sections of labeling.

#### V. Carved-Out Generic Labels Would Create Prescriber Confusion

Multiple different carved-out labels for oral vancomycin capsules would be confusing. Confused clinicians would put at risk the safe and effective treatment of patients.

Confusion would result from a multiplicity of vancomycin capsule labels. FDA documents indicate that at least 11 generic vancomycin capsule applicants seek approval.<sup>96</sup> In the past FDA has indicated that it evaluates each generic applicant's proposed carved-out label independently while reviewing each ANDA.<sup>97</sup> Thus, it is possible that, in addition to the Vancocin labeling, prescribers could be exposed to 11 additional versions (or more, if more applications have been filed) of oral vancomycin capsule labeling.

Twelve (or more) different oral vancomycin capsule labels would not be a beneficial public health result. Vancocin's new labeling is significantly different from its old labeling, making critical the uniform dissemination of this new information. Prescribers should learn of Vancocin's new FDA approved labeling in its complete form as approved in the recent Vancocin sNDA. Indeed, even when only contemplating a scenario of two (not twelve) different labels, FDA has previously determined that generic labeling that differs from the RLD labeling could nonetheless result in "potentially dangerous prescriber confusion, posing risks to all patients."<sup>98</sup>

Such would be the case here. Prescribers confronted with carved-out generic vancomycin capsule labels versus Vancocin's new labeling would face confusion about whether vancomycin capsules, for example:

- Have been demonstrated to be safe and effective in well-controlled trials, or, if so, for which uses;

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<sup>96</sup> Email from Pamela G. Pisner, FDA to Jane A. Axelrad, FDA, et al., Subject: Vancomycin, Attachment: Vancomycin Bioequivalence Issues 2 (Apr 15, 2009; 4:24 PM). *Attached*.

<sup>97</sup> *See, e.g., Lyrica Letter* at 10 n.13.

<sup>98</sup> *Rapamune Letter* at 3.

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- Should be dosed at 125 mg q.i.d. for 10 days, or 500 mg to 2 g in 3-4 divided doses per day for 7-10 days;
  - Have controlled clinical adverse event data, and if so, at which dose(s);
  - Should always be accompanied by renal function monitoring, need never be accompanied by renal function monitoring (generics omitting Vancocin’s new labeling would not mention renal function monitoring), or should sometimes be accompanied by renal function monitoring, because carved-out generic labeling would state that “monitoring of serum concentrations of vancomycin may be appropriate in some instances, e.g., in patients with renal insufficiency and/or colitis or in those receiving concomitant” aminoglycosides, which some clinicians might interpret to mean renal function monitoring “may be appropriate” in those instances
  - Take longer to work in elderly patients, or that there is no risk of premature discontinuation or switching to another medication in this population

These many triggers of prescriber confusion exist because the recent Vancocin sNDA extensively and fundamentally changed Vancocin’s labeling, such that omitting generics would be replete with missing sections, not a few minor “selective deletions and *de minimis* modifications.”<sup>99</sup> Nor is there any evidence that replacing vast swathes of Vancocin’s new labeling with statements like “[c]ertain geriatric use information is protected by marketing exclusivity”<sup>100</sup> would lessen prescriber confusion. Indeed, unless FDA has data proving otherwise, non-scientific, non-medical phrases like this one, popping up and then disappearing (after expiry of 3 year exclusivity) would seem only to worsen the confusion.

#### VI. The 3 Year Exclusivity Incentive Worked to Modernize Vancocin Labeling

Based on the incentive of 3 year exclusivity, ViroPharma elected to make a substantial investment in updating the Vancocin labeling with data from modern controlled clinical safety and efficacy studies. Whether other antibiotic companies follow suit is up to FDA. If FDA decides Vancocin does not get exclusivity, or that generics can carve-out Vancocin’s new protected labeling, then further investment in modernizing old antibiotic labeling would become highly unlikely. On the other hand, if FDA agrees that there is exclusivity and that it cannot be carved-out, the incentive will remain viable, and lead to further research on old antibiotics.

### ADDITIONAL ACTIONS REQUESTED

Based on the above grounds, ViroPharma amends this petition to request the following additional actions of FDA, to wit, that:

- a. FDA not approve generic (21 U.S.C. § 355(j) or 21 U.S.C. § 355 (b)(2)) applications referencing Vancocin (vancomycin hydrochloride) capsules until at least December 15, 2014;

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<sup>99</sup> *Lyrice Letter* at 9.

<sup>100</sup> *Oxandrin Letter* at 20.

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- b. If FDA determines to approve generic (21 U.S.C. § 355(j) or 21 U.S.C. § 355 (b)(2)) applications referencing Vancocin (vancomycin hydrochloride) capsules prior December 15, 2014, that FDA:
- i. Notify ViroPharma at least 30 days prior to final approval of any such generic applications such that, inter alia, ViroPharma may determine whether to seek judicial relief;
  - ii. Notify each Member of the U.S. Senate Health, Education, Labor and Pensions and U.S. House Energy and Commerce Committees at least 30 days prior to final approval of any such generic applications that FDA has determined that old antibiotics for which new clinical investigations are submitted are not eligible for 3 year exclusivity, despite the 2008 Congressional enactment of this incentive and the need for modern data on old antibiotics.

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## CONCLUSION

Generic vancomycin capsule labeling, without the fundamental and extensive changes approved in the recent Vancocin sNDA, would violate FDA's prescription drug labeling regulations and be less safe or effective than Vancocin. Accordingly, generic vancomycin capsule applications cannot be approved until expiry of Vancocin's 3 year exclusivity.

Sincerely,

A handwritten signature in blue ink, appearing to read "T. Doyle".

Thomas F. Doyle  
Vice President, Strategic Initiatives  
ViroPharma Incorporated

cc: Elizabeth Dickinson, Esq., Office of Chief Counsel  
Jane Axelrad, Esq., Office of Regulatory Policy, CDER