UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

ViroPharma, Inc.,

Plaintiff,

v.

Margaret A. Hamburg, M.D., in her official capacity as Commissioner, Food and Drug Administration, *et al.*,

Defendants,

and

Akorn, Inc., *et al.*,

Intervenor-Defendants.

Civil Action No. 12-0584 (ESH)

MEMORANDUM OPINION

ViroPharma, Inc. manufactures the antibiotic Vancocin®. On April 13, 2012, ViroPharma sued Margaret Hamburg, in her official capacity as the Commissioner of the Food and Drug Administration; Kathleen Sebelius, in her official capacity as the Secretary of the Department of Health and Human Services; and the agencies themselves (collectively, the "FDA") to challenge the FDA's approval, on April 9, 2012, of three Abbreviated New Drug Applications ("ANDAs") permitting the marketing of generic versions of Vancocin (vancomycin hydrochloride capsules or "vancomycin"). (*See* Complaint (Apr. 13, 2012) [ECF No. 1] ("Compl.").) ViroPharma alleges that the FDA approved the three ANDAs (1) in violation of ViroPharma's statutory right under the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. §§ 301 *et seq.*, to a three-year period of exclusivity for Vancocin, extending through December 15, 2014; and (2) based solely on *in vitro* (laboratory) bioequivalence testing in

violation of the FDA's own regulations requiring *in vivo* (human) bioequivalence testing. (*Id.* ¶ 2.) The Court will refer to these as ViroPharma's "statutory exclusivity claim" (*see id.* ¶¶ 75–78 (Count II)) and its "bioequivalence claim." (*See id.* ¶¶ 69–74 (Count I).) The three generic manufacturers whose vancomycin ANDAs were approved – Akorn, Inc., Alvogen, Inc., and Watson Laboratories, Inc. – have also joined the suit as intervenor-defendants.

On April 23, 2012, this Court denied ViroPharma's motion for a preliminary injunction to require the FDA to withdraw its approval of the three vancomycin ANDAs and to refuse to approve any additional vancomycin ANDAs until ViroPharma's claims were adjudicated on the merits. *See ViroPharma Inc. v. Hamburg*, No. 12-584, 2012 WL 1388183 (D.D.C. Apr. 23, 2012) ("Memorandum Opinion"). Now seeking adjudication on the merits, ViroPharma has filed a motion for summary judgment (*see* Plaintiff's Motion for Summary Judgment (July 20, 2012) [ECF No. 51] ("Pl. Mot.")), urging the Court to reconsider its arguments "with the benefit of the additional elaboration herein and additional time to consider the law and arguments." (*Id.* at 10.) Defendants have also filed a motion to dismiss, or, in the alternative, for summary judgment (*see* Federal Defendants' Motion to Dismiss or, in the Alternative, for Summary Judgment (Sept. 4, 2012) [ECF No. 53] ("Def. Mot.")), and intervenor-defendants have likewise filed a motion to dismiss, or, in the alternative, for summary judgment. (*See* Intervenor-Defendants' Motion to Dismiss, or, in the Alternative, for Summary Judgment (Sept. 4, 2012) [ECF No. 56] ("Inter.-Def. Mot.").)

ViroPharma is correct that a court's determinations regarding a motion for preliminary relief are not considered to be the law of the case. (*See* Pl. Mot. at 9 (quoting *Belbacha v. Bush*, 520 F.3d 452, 458 (D.C. Cir. 2008) and citing *Kuzinich v. Cnty. of Santa Clara*, 689 F.2d 1345, 1350-51 (9th Cir. 1982) and *Nat'l Football League Players Ass'n v. Pro-Football, Inc.*, 857 F.

Supp. 71, 79 (D.D.C. 1994).)) However, nothing in the parties' submissions convinces the Court to reach a different conclusion today. ViroPharma all but admits that it has presented no substantially new arguments, but rather it relies on "additional elaboration" (Pl. Mot. at 10), none of which persuades the Court to reverse itself. Moreover, no new facts have been presented that would dictate a different result. Although the parties have submitted additional excerpts from the administrative record, which the Court has reviewed, these submissions do not alter the Court's judgment. To the extent that any portion of the supplemented record affects the Court's opinion, it serves only to bolster it. (*See, e.g.*, Memo from Lorenz re: Consult Response on ViroPharma December 22, 2011 Submission (Apr. 9, 2012), Part H to Joint Appendix, FDA004629-4637 (outlining reasons that data from Genzyme trial was not "essential to approval" of Vancocin sNDA and subsequent labeling changes)). Therefore, the Court incorporates by reference the conclusions that it reached in its prior Memorandum Opinion, and will limit its discussion to the few additional points that are arguably being raised for the first time.

BACKGROUND

The Court assumes familiarity with the relevant statutory and procedural background, which was described in great detail in the Court's Memorandum Opinion. In the briefest terms, ViroPharma states a statutory exclusivity claim based on QI Program Supplemental Funding Act of 2008, Pub. L. No. 110-379, 122 Stat. 4075 (the "QI Act"). That Act amended the FFDCA to render "Old Antibiotics," including Vancocin, eligible for three-year market exclusivity for changes approved on the basis of "new clinical investigations (other than bioavailability studies) . . . conducted or sponsored by the person submitting the [sNDA]." 21 U.S.C. § 355(j)(5)(F)(iv). ViroPharma made certain changes to the labeling of Vancocin, and on this basis, it sought three-

year exclusivity. The FDA denied ViroPharma's request in accordance with its interpretation of 21 U.S.C. § 355(v)(3)(B), which provides that exclusivity is not available for "any condition of use for which the [Old Antibiotic] . . . was approved before the date of the enactment [of the QI Act]." In the FDA's view, "the labeling changes related to and refined the already-approved indication for treatment of [*Clostridium difficile*], and included a dosing regimen that was encompassed within, and at most refined, the prior regimen." (Def. Mot. at 9-10.) In short, the new labeling pertained only to previously-approved conditions of use and thus, under § 355(v)(3)(B), was excluded from exclusivity. ViroPharma has challenged the FDA's interpretation and application of § 355(v)(3)(B) and the administrative actions taken based thereon – specifically, the denial of exclusivity to ViroPharma, and the approval of ANDAs for three generic versions of Vancocin.

ViroPharma also states a bioequivalence claim, arguing that the FDA violated its own regulations when it approved generic copies of Vancocin based on *in vitro* rather than *in vivo* testing. ViroPharma alleges that the FDA's regulations establish a default requirement that *in vivo* testing must be submitted to demonstrate that a generic drug is "bioequivalent" to the original, pioneer drug. (*See* Pl. Mot. at 21-22.) The FDA counters that there is no such default rule; on the contrary, the agency retains the discretion to determine the appropriate method for demonstrating the bioequivalence of a given drug on a case-by-case basis. (*See* Def. Mot. at 34-35.) In this instance, the FDA concluded that *in vitro* dissolution tests were "the most accurate, sensitive, and reproducible approach for demonstrating bioequivalence" for vancomycin. (*Id*. at 33.)

ANALYSIS

I. LEGAL STANDARDS

A. Motion for Summary Judgment

Normally, a motion for summary judgment under Rule 56 shall be granted if "the pleadings, depositions, answers to interrogatories, . . . admissions on file, . . . [and] affidavits . . . show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247 (1986) (quoting Fed. R. Civ. P. 56(c)). "In a case involving review of a final agency action under the [APA], however, the standard set forth in Rule 56(c) does not apply because of the limited role of a court in reviewing the administrative record." *Sierra Club v. Mainella*, 459 F. Supp. 2d 76, 89 (D.D.C. 2006) (citation omitted). Under the APA, it is the role of the agency to resolve factual issues to arrive at a decision that is supported by the administrative record, whereas "the function of the district court is to determine whether or not as a matter of law the evidence in the administrative record permitted the agency to make the decision it did." *Id.* at 90 (quoting *Occidental Eng'g Co. v. INS*, 753 F.2d 766, 769-70 (9th Cir. 1985)).

B. Standard of Review

The Court begins "with the first step of the two-part framework announced in *Chevron* . . . and asks[s] whether Congress has 'directly addressed the precise question at issue.'" *Mayo Found. for Med. Educ. & Research v. United States*, 131 S. Ct. 704, 711 (2011) (quoting *Chevron, U.S.A., Inc. v. Natural Res. Def. Council*, 467 U.S. 837, 842-843 (1984)). If the statutory language in 21 U.S.C. § 355(v)(3)(B) is unambiguous and "the intent of Congress is clear, that is the end of the matter; for the [C]ourt, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Chevron*, 467 U.S. at 842–43. However, "if the

statute is silent or ambiguous with respect to the specific issue," the Court will proceed to step two of the *Chevron* analysis and ask whether the FDA's interpretation is "permissible." *Id.* at 843. At this step, the interpretation is "given controlling weight unless" it is "manifestly contrary to the statute." *Id.* at 844. As the D.C. Circuit recently reaffirmed, "[t]he *Chevron* step two question . . . is not whether the [plaintiff's] proposed alternative is an acceptable policy option but whether the [agency action] reflects a reasonable interpretation of [the statute]. *Coalition for Common Sense in Gov't Procurement v. United States*, No. 11-535, slip op. at 12 (D.C. Cir. Jan. 4, 2013).

II. VIROPHARMA'S STATUTORY EXCLUSIVITY CLAIM

This Court extensively analyzed ViroPharma's statutory exclusivity claim in its prior Memorandum Opinion, concluding that the claim would likely fail on the merits. In its summary judgment motion, ViroPharma has added a single alternative justification in addition to rehashing the same arguments that the Court has already rejected – ViroPharma suggests that "[i]f the labeling changes approved in the Vancocin sNDA constituted previously approved conditions of use, then the structure of innovator drug regulation under the FDCA would be seriously compromised." (Pl. Mot. at 20.) ViroPharma claims that if the FDA's logic is applied, as ViroPharma interprets it, manufacturers could make labeling changes without prior FDA approval because the changes would be considered "previously approved." (*Id.*) And although the statute requires that generic drug labels reflect the same "previously approved" "conditions of use" as the innovator drug label, ViroPharma asserts that the FDA's logic would also lead to the unacceptable conclusion that "generic vancomycin manufacturers could have – before the Vancocin sNDA was approved – adopted the labeling changes included therein *on their own accord*." (Pl. Mot. at 20-21 (emphasis in original).)

ViroPharma seriously misconstrues the FDA's position. The FDA does not claim that *the labeling changes* were "previously approved." Rather, "*the conditions of use* for the drug – how, to whom, and for what purpose the drug is administered – were previously approved." (Def. Mot. at 27 (emphasis added).) The FDA has been very clear, from its response to ViroPharma's Citizen Petition through its briefing of the present motions, that it considered the new Vancocin labeling to have "merely refined and added new details *to describe the previously approved conditions of use*." (*Id*. (emphasis added).) The FDA has used the same definition of "condition of use" in applying subsection (v)(3)(B) that it has used in applying other subsections of the statute, such as subsection (j)(2)(A)(i), which requires ANDAs to have the same conditions of use as the innovator. (*See id*.)

As the Court explained at length in its prior Memorandum Opinion, the agency acted within its discretion to determine that "the revision of the Vancocin label to incorporate clinical data that supports and refines labeling regarding already approved conditions of use, does not constitute approval for a condition of use that has not been 'approved before the enactment' within the meaning of section 505(v)(3)(B)." (CP Resp. at 71; *see also* Memorandum Opinion at 30.) The Court reaffirms this conclusion here, especially given the "high level of deference," *Serono Labs. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998) (internal quotation marks and citation omitted), accorded to the agency where the agency's decision "involve[s] a subject matter [that] is technical, complex, and dynamic," *Nat'l Cable & Telecomms. Ass'n v. Brand X Internet Servs.*, 545 U.S. 967, 1002–03 (2005) (internal quotation marks and citation omitted; some alterations in the original), and "rests on the 'agency's evaluations of scientific data within its area of expertise,'" *Serono Labs.*, 158 F.3d at 1320 (quoting *A.L. Pharma, Inc. v. Shalala*, 62

F.3d 1484, 1490 (D.C. Cir. 1995); citing *Schering Corp. v. FDA*, 51 F.3d 390, 399–400 (3rd Cir. 1995)).

Notably, ViroPharma's argument that its labeling changes reflect a new dosing regimen and thus a new "condition of use" conflicts with its own prior treatment of its sNDA. ViroPharma never previously suggested that the sNDA presented a new indication, dosing regimen, or route of administration. (*See* Inter.-Def. Mot. at 12.) Significantly, if ViroPharma had considered its sNDA as presenting a new condition of use, it "would have been required to conduct an assessment under the Pediatric Research Equity Act, P.L. 108-155 ("PREA")." *Id*. "PREA requires that for certain applications, including sNDAs, for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration, the applicant must conduct pediatric studies unless a waiver or deferral has been obtained." (*Id*. at 12-13 (citing 21 U.S.C. § 355C(a).) ViroPharma did not submit any PREA assessments and did not seek a waiver or deferral of such requirements. (*Id*. at 13 (citing CP Resp. at 72.)) Furthermore, FDA's approval letter to ViroPharma explicitly stated that none of the PREA criteria applied and ViroPharma never objected to that conclusion. (*Id*. at 13 (citing Approval Letter for Supplement 28 with Approved Labeling (Dec. 14, 2011), Part P of Joint Appendix, at FDA005129).)

The FDA made this very point in its opposition to ViroPharma's preliminary injunction motion (*see* Federal Defendants' Memorandum in Opposition to Plaintiff's Motion for Temporary Restraining Order and/or Preliminary Injunction (April 17, 20120) [ECF No. 22], at 27-28) and in its briefing of the instant motion. (*See* Fed. Mot. at 29-30). Intervenor-defendants have also cited this omission by ViroPharma. (*See* Inter.-Def. Mot. at 12-13). ViroPharma's silence in response is deafening. ViroPharma's failure to conduct pediatric studies certainly further bolsters the Court's conclusion that the new labeling did not constitute or reflect new

conditions of use, nor did ViroPharma consider it as such until it was expedient to do so in the course of this litigation.

The Court also notes that the additional portions of the administrative record that have now been submitted reveal that the Genzyme studies upon which ViroPharma based its exclusivity claim were not essential to the approval of changes in the label. (*See* Inter.-Def. Mot. at 20.) For example, one internal FDA memorandum concluded,

> This dosing regimen is neither a new dose (*i.e.* outside of the range of the currently approved dose) nor a regimen for a new condition. The "125 mg administered 4 times daily" dose of vancomycin has been adopted as *the "standard dose" since the 1980's* . . . Although the Genzyme study uses the lower dose of 125 mg four times daily . . . it does not compare different dosing regiments of vancomycin . . . . The Genzyme studies do *support the previous findings* that the lower dose is an effective regimen, *but the Division approved this change in the DOSAGE AND ADMINISTRATION section of the prescribing information based upon the current clinical practice and guidelines* in order to clarify the language in the dosing administration . . . The new information provided by this study, for the purposes of this label, are limited to the content of its results, which were applied to sections 6 ADVERSE REACTIONS (including common adverse event profile), 8.5 Geriatric Use and 14 CLINICAL STUDIES (including clinical success rates).

(Memo from OAP/DAIP re: Sponsor's Request for Three Year Extension of Exclusivity (Dec. 12, 2011), Part H of Joint Appendix, at FDA004623 (emphasis added).) This information further affirms the Court's conclusion.[1]

[1]It is noteworthy that another court in this jurisdiction recently reached the same conclusions that this Court does regarding the meaning of the 3-year exclusivity provision:

> FDA regulations make clear that 3-year exclusivity is not triggered merely by labeling changes related to the safety or risks posed by the drug for indications already approved; such changes, if known, would have been incorporated into the original labeling at the time of the approval of the original NDA. Nor is a 3-year period of exclusivity triggered by the simple submission of new clinical investigations or on the applicant's "say-so."

AstraZeneca Pharms. LP v. FDA, 872 F. Supp. 2d 60, 66 (D.D.C. 2012).

III. VIROPHARMA'S BIOEQUIVALENCE CLAIM

As with its statutory exclusivity claim, ViroPharma fails to present any new arguments or facts to support its bioequivalence claim. It has merely added two additional examples to support its previously articulated argument, neither of which compels a different result.

First, ViroPharma asserts that the FDA has removed some of the grounds for waiver that were listed in § 320.22, and "in doing so reiterated its view that the grounds enumerated there were exclusive, and do not permit the FDA to excuse *in vivo* testing in favor of *in vitro* absent an applicable ground for waiver." (Pl. Mot. at 26.) ViroPharma claims that "in notice-and-comment rulemaking to implement Hatch-Waxman, FDA expressly relinquished [the] discretion" to permit waiver of *in vivo* testing when the generic drug "'contains the same active drug ingredient . . . and is in the same strength and dosage form . . . and *both drug products meet an appropriate in vitro test that has been approved by the [FDA]*.'" (Pl. Mot. at 26-27 (quoting 54 Fed. Reg. 1624, 1649 (Jan. 7, 1977)) (plaintiff's emphasis).) However, the FDA convincingly contests this characterization of its actions, explaining that it sought to remove the blanket waiver because there was "'no evidence to show that *in vitro* data alone *are regularly sufficient* to assure bioequivalence.'" (Def. Mot. at 38 (quoting 54 Fed. Reg. 28,872, 28,912, (July 10, 1989)) (defendants' emphasis).) The FDA maintains that its "elimination of a *blanket waiver* did not 'expressly relinquish' the agency's statutory discretion to determine for itself the appropriate bioequivalence method on a case-by-case basis. (*Id*. (quoting Pl. Mot. at 27) (defendants' emphasis).)

ViroPharma also suggests that the FDA recognized §320.22 as the sole authority for waiver of the *in vivo* requirement when it removed another ground for waiver formerly found at § 320.22(b)(3). The FDA "explained that an automatic waiver for all drugs covered by that

provision was unwarranted – but that removing the automatic waiver did not mean that a waiver could *never* be granted[,]" but rather, it would be granted on a case-by-case basis "'*provided the product meets the [waiver] criteria in 320.22.*'" (Pl. Mot. at 27 (quoting 57 Fed. Reg. 17,950, 17,975 (Apr. 28, 1992)) (plaintiff's emphasis).) Again, ViroPharma reads this history too expansively, for the agency was speaking only about "applicants' ability to *request* waivers under section 320.22, but [did] not 'expressly relinquish' FDA's statutory discretion to make independent determinations of the appropriate bioequivalence method, pursuant to subsection 320.24(a)." (Def. Mot. at 38 (defendants' emphasis).)

Finally, ViroPharma asserts that the FDA again affirmed that the §320.22 criteria must be met in order to permit *in vitro* bioequivalence when it corrected a typographical error. The FDA explained at that time: "Section 320.21(f) inaccurately includes a reference to criteria set forth in § 320.24 as containing information under which FDA could waive the requirement for submission of evidence demonstrating *in vivo* bioavailability or bioequivalence." 63 Fed. Reg. 64,222, 64,223 (Nov. 19, 1998). Again, however, ViroPharma makes too much of this fact; the FDA did not claim to "waive" an *in vivo* bioequivalence requirement pursuant to 320.24(a) in this instance. Rather, the FDA was "exercising its authority under subsection 320.24(a) to determine that in vitro dissolution studies are the 'most accurate, sensitive, and reproducible approach' to determine vancomycin bioequivalence." (Def. Mot. at 39.) For the reasons set forth in its Memorandum Opinion, the Court is satisfied that the FDA has not abused its authority in reaching this determination.

Given the absence of changed facts or new legal arguments or authority, the Court's judgment remains the same: the FDA acted well within its discretion in denying three-year exclusivity to ViroPharma and in approving the ANDAs of intervenor-defendants.

CONCLUSION

For the foregoing reasons, the Court denies plaintiff ViroPharma's Motion for Summary Judgment and grants defendant FDA's Cross-Motion for Summary Judgment as well as intervenor-defendants' Cross-Motion for Summary Judgment. A separate Order accompanies this Memorandum Opinion.

/s/
ELLEN SEGAL HUVELLE
United States District Judge

DATE: January 9, 2013