VIROPHARMA INCORPORATED v. HAMBURG et al Doc. 29

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

VIROPHARMA, INCORPORATED,	
Plaintiff,	
v.	**Civil Action No. 10-1529 (ESH)**
MARGARET A. HAMBURG, M.D., in her official capacity as Commissioner, Food and Drug Administration, *et al.*,	
Defendants.	

MEMORANDUM OPINION

Plaintiff ViroPharma Incorporated ("ViroPharma") brings this action against the Food and Drug Administration ("FDA") and the Department of Health and Human Services, seeking review under the Administrative Procedure Act ("APA"), 5 U.S.C. §§ 701-706. Specifically, ViroPharma claims that that FDA failed to conduct notice-and-comment rulemaking prior to what plaintiff claims was a decision by the FDA to change its regulations regarding the permissible methods by which an applicant for an Abbreviated New Drug Application ("ANDA") can demonstrate that the drug is the "bioequivalent" of a previously approved drug. Defendants has moved to dismiss pursuant to Federal Rules of Civil Procedure 12(b)(1) and 12(b)(6) on the grounds that this Court has no subject matter jurisdiction because of lack of standing and ripeness and that plaintiff has failed to state a claim upon which relief can be granted. For the reasons explained herein, the Court will grant defendants' motion on the basis of a lack of standing.

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BACKGROUND

I. STATUTORY AND REGULATORY FRAMEWORK

Under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, a "pioneer" or "innovator" drug may not be marketed until the FDA has approved a new drug application ("NDA") that includes, *inter alia*, reports from clinical studies establishing the safety and effectiveness of the drug. 21 U.S.C. § 355(b)(1). An applicant may obtain FDA approval to market generic copies of an FDA-approved brand-name drug, known as the "reference listed drug" ("RLD"), by submitting an Abbreviated New Drug Application ("ANDA"). 21 U.S.C. § 355(j). In order to rely upon a RLD's record of safety and effectiveness for approval, an ANDA must include information demonstrating that the generic drug is the same as the RLD in a number of specified ways. 21 U.S.C. § 355(j)(2)(A). Of particular relevance here, the ANDA must demonstrate that the generic is the "bioequivalent" of the RLD, and is therefore absorbed into the body at the same rate and to the same extent as the innovator drug. 21 U.S.C. § 355(j)(2)(A)(iv). Where, as here, "a drug . . . is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the [RLD] in safety and therapeutic effect." 21 U.S.C. § 355(j)(8)(C).

Depending on the circumstances and the particular drug in question, the FDA may require an applicant use one or more of a variety of different methodologies in order to demonstrate bioequivalence. In general, however, methodologies for demonstrating bioequivalence may be classified as either *in vivo* (*i.e.*, through human testing) or *in vitro* (*i.e.*, laboratory testing). The requirements for demonstrating bioequivalence are the subject of a number of regulations, the correct interpretation of which is at the crux of the parties' dispute. According to ViroPharma, 21 C.F.R § 320.21(b) sets forth a general requirement that

bioequivalence be demonstrated through *in vivo* testing, unless the drug product meets one of the waiver criteria set forth in 21 C.F.R. § 320.22. (Compl. ¶¶ 35-37.) The FDA, however, argues that there is no such "default requirement for *in vivo* data to establish bioequivalence." (Reply at 15.) Instead, the FDA relies on language in 21 C.F.R. § 320.24, which states that "FDA may require in vivo or in vitro testing, or both, to . . . establish the bioequivalence of specific drug products." FDA therefore asserts that it has discretion to determine, on a case-by-case basis, whether it will require *in vivo* testing, *in vitro* testing, or both in order to establish the bioequivalence of a drug product. According to ViroPharma, however, 21 C.F.R. § 320.24 merely lists the various methods for establishing either *in vivo* or *in vitro* bioequivalence, depending on which of those two types of testing is otherwise required by the regulations. (Compl. ¶ 39.)

II. FACTUAL HISTORY

A. Acarbose

On November 9, 2007, Cobalt Laboratories Inc. and Cobalt Pharmaceuticals (collectively, "Cobalt") submitted a citizen petition and petition for stay of action regarding the bioequivalence requirements for generic versions of the locally acting GI drug Precose (acarbose). (*Id.* ¶ 49 & Ex. 1.) This petition asked FDA to require all ANDAs for generic acarbose to include *in vivo* bioequivalence studies. (*Id.*) FDA responded to Cobalt's petitions on May 7, 2008, denying the request for a stay of action. (*Id.* ¶ 50.) In its to the acarbose petition, FDA asserted that under "§ 320.24 of the regulations, FDA has the discretion to accept in vitro studies for a nonsystemically absorbed drug product such as acarbose when such studies are determined to be a scientifically valid method of determining bioequivalence." (*Id.* ¶ 51 & Ex. 2.) ViroPharma claims that this response "effectively amended [FDA] regulations" by "interpret[ing] the list of bioequivalence methods provided in 21 C.F.R. § 320.24 as a separate

and sufficient regulatory basis for waiving *in vivo* bioequivalence requirements independent of 21 C.F.R. § 320.22." (*Id.* ¶ 52.)

B. Vancomycin

ViroPharma, a small pharmaceutical company headquartered in Exton, Pennsylvania, acquired the exclusive right to the prescription drug Vancocin in the United States from Eli Lilly and Company in 2004. (*Id.* ¶¶ 7, 13.) Vancocin is the trade name for the FDA-approved drug vancomycin hydrochloride capsules ("vancomycin") and is used to treat life-threatening gastrointestinal infections such as *C. difficile* ("CDI"). (*Id.* ¶¶ 14, 15.) Vancocin is one of only two drugs that ViroPharma markets and is the primary source of ViroPharma's revenue. (*Id.* ¶ 20.)

In 1996, FDA recommended that ANDA sponsors submit a clinical *in vivo* study to demonstrate bioequivalence of generic vancomycin. (Mot. at Ex. 5.) FDA revised these bioequivalence recommendations in early 2006 to include data generated by *in vitro* methods for demonstrating bioequivalence. (*Id.*; Compl. ¶ 23.) In March 2006, ViroPharma filed a petition for stay of action challenging FDA's revised recommendation. (Compl. ¶ 59.) The FDA has yet to complete its response to this petition. (Mot. at 12.) In December 2008, FDA revised its draft recommendation for the appropriate bioequivalence methodology for vancomycin, requesting public comment on the most recent version. (*Id.* at Ex. 5.) FDA continues to accept comments from the public on the draft guidance document (*id.*), and has not yet finalized it. (*Id.* at 12).

ViroPharma alleges that the FDA has received at least eleven ANDAs for vancomycin. (Compl. ¶ 72), but FDA has yet to approve any ANDA. (*Id.* ¶ 65.)

C. Procedural History

On September 10, 2010, ViroPharma filed the instant complaint, challenging the FDA's interpretation of 21 C.F.R. § 320.24 in the acarbose petition response. ViroPharma alleges that

the acarbose petition response amounts to an amendment of FDA regulations that should have been subject to notice-and-comment rulemaking. (Compl. ¶¶ 52-55, 78-81.) FDA has moved to dismiss under Rule 12(b)(1) for lack of standing and lack of ripeness, or, in the alternative, under Rule 12(b)(6) for failure to state a claim upon which relief can be granted.

ANALYSIS

I. STANDARD OF REVIEW

A. Motion to Dismiss for Lack of Jurisdiction

On a motion to dismiss pursuant to Rule 12(b)(1), plaintiff bears the burden of establishing by a preponderance of the evidence that the court has subject matter jurisdiction. *See Lujan v. Defenders of Wildlife*, 504 U.S. 555, 561 (1992). The Court must accept all factual allegations in the complaint as true and give plaintiff the benefit of all reasonable inferences from the facts alleged. *See Jerome Stevens Pharms., Inc. v. Food & Drug Admin.*, 402 F.3d 1249, 1253-54 (D.C. Cir. 2005). A court may dismiss for lack of subject matter jurisdiction only if "'it appears beyond doubt that the plaintiff can prove no set of facts in support of his claim which would entitle him to relief.'" *Richardson v. United States*, 193 F.3d 545, 549 (D.C. Cir. 1999) (quoting *Caribbean Broad. Sys., Ltd. v. Cable & Wireless PLC*, 148 F.3d 1080, 1086 (D.C. Cir. 1998)). Moreover, where a court's subject matter jurisdiction is called into question, the court may consider matters outside the pleadings to ensure it has power over the case. *Teva Pharms., USA, Inc. v. U.S. Food & Drug Admin.*, 182 F.3d 1003, 1008 (D.C. Cir. 1999).

B. Standing

Article III of the United States Constitution limits the judicial power to deciding 'Cases and Controversies.'" *In re Navy Chaplaincy*, 534 F.3d 756, 759 (D.C. Cir. 2008) (quoting U.S. Const. art. III, § 2). "[T]he core component of standing is an essential and unchanging part of the case-or-controversy requirement of Article III." *Lujan*, 504 U.S. at 560. In order to satisfy

the "irreducible constitutional minimum of standing," a plaintiff must demonstrate: (1) that it has suffered injury in fact, an actual or imminent invasion of a legally protected, concrete and particularized interest; (2) a causal connection between the alleged injury and the defendant's conduct at issue; and (3) that it is "likely," not "speculative," that the court can redress the injury. *Id*. at 560-61. "Where plaintiffs allege injury resulting from violation of a *procedural* right afforded to them by statute and designed to protect their threatened concrete interest, the courts relax—while not wholly eliminating—the issues of imminence and redressability, but not the issues of injury in fact or causation." *Ctr. for Law & Educ. v. Dep't of Educ.*, 396 F.3d 1152, 1157 (D.C. Cir. 2005) (citing *Fla. Audubon Soc'y v. Bentsen*, 94 F.3d 658, 664-65 (D.C. Cir. 1996) (en banc); *Lujan*, 504 U.S. at 572-73 & nn.8-9).

II. VIROPHARMA LACKS STANDING

ViroPharma alleges two general types of injury that will result or has already resulted from the FDA's 2008 acarbose petition response: future lost profits from generic competition to Vancocin and current harms to ViroPharma's ongoing business operations as a result of the FDA's actions. The Court will address each *seriatim*.

A. Future Lost Profits from Generic Competition

As the D.C. Circuit has repeatedly held, "a procedural-right plaintiff must demonstrate standing by 'show[ing] not only that the defendant's acts omitted some procedural requirement, but also that it is substantially probable that the procedural breach will cause the essential injury to the plaintiff's own interest.'" *Ctr. for Law & Educ.*, 396 F.3d at 1159 (quoting *Fla. Audubon Soc'y*, 94 F.3d at 664-65). The chain of causation between the procedural violation and the concrete interest may not be merely "speculative." *See id.*; *Fla. Audubon Soc'y*, 94 F.3d at 667-68.

In order to demonstrate standing, ViroPharma must therefore demonstrate that it is "substantially probable" that the FDA's actions in issuing the 2008 acarbose petition response will cause injury to plaintiff in the form of future lost profits from generic competition. This has not been done.

ViroPharma alleges that the 2008 acarbose petition response effectively amended the FDA's bioequivalence regulations without notice and comment, which it claims will result in "lost sales as a result of the approval of vancomycin ANDAs" based on the allegedly amended regulations. (Compl. ¶ 76.)

As the FDA points out, however, ViroPharma will not suffer that injury unless, and until, two events occur: (1) the FDA must actually approve an ANDA for vancomycin and (2) such approval must be based upon the same interpretation of Section 320.24 set forth by the FDA in its acarbose petition response. (Mot. at 13.)

Although ViroPharma has alleged that there are currently at least eleven ANDAs for generic vancomycin that have been under review by the FDA for at least two years (*see* Opp. at Ex. 11), this fact does not make it "substantially probable" that the FDA will ultimately approve these ANDAs. The Court cannot assume from the mere fact of FDA acceptance of an ANDA for processing that the FDA will ultimately approve the drug. *See Pfizer v. Shalala*, 182 F.3d 975, 978 (D.C. Cir. 1999) ("The critical fact remains that the FDA may never approve [the ANDA] —whether because it decides in the end that the dosage form of [the generic] is different . . . or for some entirely different reason, such as a lack of bioequivalence.").

Moreover, if and when the FDA ultimately approves an ANDA for vancomycin, it cannot be assumed that it will rely upon the challenged interpretation of Section 320.24 used in the acarbose petition response. If the FDA ultimately concludes that it will require *in vivo* tests for

generic vancomycin, then the agency's interpretation of Section 320.24 will be irrelevant and will in no way cause injury to ViroPharma. Although FDA issued a draft bioequivalence recommendation in 2006 that included *in vitro* studies as a method for demonstrating bioequivalence for vancomycin (Mot. at 11; Compl. ¶ 23),[1] FDA has not yet finalized these recommendations. Indeed, in 2008 FDA requested public comment on a revised version of its Draft Guidance on Vancomycin Hydrochloride (Mot. at Ex. 5), and the 2006 recommendation has since evolved as a result. For instance, a change from the 2006 version, the 2008 draft guidance proposed *in vitro* studies be permitted only if the ANDA product contains the same inactive ingredients in the same quantifies as Vancocin. (*Id.*) Otherwise, *in vivo* studies would be required. (*Id.*) FDA continues to accept comments from the public on this draft guidance. (*Id.* at 3). In light of this current situation, the Court cannot conclude that it is substantially probable that, if and when FDA ultimately approves an ANDA for vancomycin, it will rely upon the challenged interpretation of Section 320.24.[2]

B. Current Harms to ViroPharma's Ongoing Business Operations

In addition to the alleged future lost profits from generic competition to Vancocin, ViroPharma also claims that the FDA's actions have had *present* effects on its ongoing business operations. These, too, are insufficient to confer standing.

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[1] In March 2006, ViroPharma filed a petition for a stay of action challenging these recommendations. (Compl. ¶ 59.) The FDA has not completed its response to this petition. (Mot. at 12.)

[2] Nor can ViroPharma overcome these hurdles by arguing that the FDA's interpretation of 21 C.F.R. § 320.24 has "increased the risk" that the company will be harmed by lost sales of Vancocin. (*See* Opp. at 29, 31, 33.) "Outside of increased exposure to environmental harms, hypothesized 'increased risk' has never been deemed sufficient 'injury.' . . . Indeed, were all purely speculative 'increased risks' deemed injurious, the entire requirement of 'actual or imminent injury' would be rendered moot, because all hypothesized, non-imminent 'injuries' could be dressed up as 'increased risk of future injury.'" *Ctr. for Law & Educ.*, 396 F.3d at 1161.

Through the declaration of one of its Vice Presidents, Thomas F. Doyle, ViroPharma asserts that the FDA's actions have altered its operations in a variety of ways. (Opp. at Ex. 16.) Specifically, plaintiff claims that the FDA's regulatory change generally "impacts ViroPharma's operations, investment decisions, and strategic planning" (*id.* ¶ 9); that as a result of the FDA action, ViroPharma reduced or eliminated various educational, promotional, and marketing activities (*id.* ¶¶ 10-13); that ViroPharma "has eliminated plans to invest in any additional clinical development of Vancocin" (*id.* ¶ 14); that ViroPharma has been "forced" to invest in developing a "distribution channel for an authorized generic version of Vancocin" so that ViroPharma will be better prepared to compete (*id.* ¶ 15); that ViroPharma's "ability to construct strategic plans" has been "impacted" by FDA's actions "as a result of cash flow uncertainties" (*id.* ¶ 16); and that the "uncertainty" associated with FDA's actions has caused ViroPharma's stock price to be lower that it otherwise would be. (*Id.* ¶ 17).

ViroPharma's allegations present a number of problems, each of which would be sufficient to undercut its rationale for standing. ViroPharma complains that its operations have been variously changed or "impacted," that it has cut back on some investments while increasing investments in other areas, and that it suffers from "uncertainties" regarding the future regulatory and competitive environment.[3] These "harms" are highly nebulous in both character and degree, and are a far cry from the type of "concrete and particularized" injury required for Article III standing.

Furthermore, ViroPharma has failed to demonstrate a causal connection between FDA's actions and the changes the company has made to its business practices. While Mr. Doyle

[3] Indeed, plaintiff's frequent references to the "uncertainty" associated with the FDA's actions only highlights the speculative nature of any future injury ViroPharma may suffer due to FDA's actions in issuing the acarbose petition response. *See supra* II.A.

variously claims that the FDA's actions "required" or "forced" ViroPharma to take certain steps (*see id.* ¶¶ 10, 15), plaintiff fails to explain how these changes were in fact required or mandated by the FDA. In reality, nearly all of the "harms" complained of by Mr. Doyle represent actions that ViroPharma *elected* to take in response to its own predictions about what the FDA may do in the future, presumably in order to better position itself should these predictions prove accurate.[4] Perhaps these steps will prove to be wise business decisions. Perhaps they will not. Either way, they are not "harms" that can be said to have been caused by the FDA.[5]

Even if the various modifications ViroPharma has made to its current business practices can be said to rise to the level of injury in fact, this injury is not "fairly traceable" to the 2008 acarbose petition response at issue in this case. *See Lujan*, 504 U.S. at 560 ("[T]here must be a causal connection between the injury and the conduct complained of . . . ."). Doyle attributes the company's alleged injury to the "FDA's regulatory change." (Opp. Ex. 16 ¶¶ 9, 10, 16, 17.) But according to Doyle, the "change" occurred not in 2008, but in 2006 when "the FDA dramatically changed course, and stated that it would consider *in vitro* bioequivalence testing methods for generic [ANDA] versions of Vancocin." (*Id.* ¶ 3; Compl. ¶¶ 23-25.) This action by the FDA did not go unnoticed by ViroPharma, which that same year filed a petition for stay of action

[4] These steps also appear to include diversifying the company's revenue stream to become less reliant upon sales of Vancocin, which now accounts for 60% of the company's total revenues, compared with nearly 100% a few years ago. (*See* Compl. ¶ 7.)

[5] ViroPharma's reliance on *Clinton v. City of New York*, 524 U.S. 417 (1998) is misplaced. In *Clinton*, the City of New York "suffered an immediate, concrete injury the moment that the President used the Line Item Veto . . . and deprived [it] of the benefits of the [vetoed] law." *Id.* at 430. The fact that the City had the right to try to secure a waiver of the tax liability it owed did not, in the Supreme Court's view, extinguish its injury. *Id. Clinton* does not, however, stand for the proposition that any potential future harm, no matter how speculative, can be transformed into a legally cognizable injury in fact.

regarding the new draft bioequivalence standards. (Compl. ¶ 59.) The FDA actions challenged in this case, however, did not occur until two years later.

Because ViroPharma has not demonstrated that it is "substantially probable" that the 2008 acarbose petition response will result in future lost profits to the company, nor that it is currently suffering from a concrete, particularized harm that is traceable to the acarbose petition response, it has failed to satisfy the "irreducible constitutional minimum of standing." *Lujan*, 504 U.S. at 560.[6]

CONCLUSION

For the foregoing reasons, the Court grants defendants' motion to dismiss. A separate order accompanies this Memorandum Opinion.

/s/
ELLEN SEGAL HUVELLE
United States District Judge

Date: April 15, 2011

[6] Although the Court need not resolve defendants' ripeness challenge, it is mindful that, as is often the case, standing and ripeness are closely related in this case, and "indeed [are] not always clearly separable" from each other. *Wyo. Outdoor Council v. U.S. Forest Serv.*, 165 F.3d 43, 48 (D.C. Cir. 1999). In particular, ViroPharma's ability to make the necessary showing of hardship sufficient to overcome the FDA's interest in postponing review until such time that it actually approves an ANDA turns on similar considerations to those that the Court has addressed in the context of standing.