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.*,

Defendants-intervenors.

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, April 13, 2012 [Dkt. 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).)

Before the Court is 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 are adjudicated on the merits. (*See* Motion for a Temporary Restraining Order and/or Preliminary Injunction, April 13, 2012 [Dkt. No. 4] ("Pl.'s Mot.").[1]) The FDA has opposed ViroPharma's motion (*see* Federal Defendants' Memorandum in Opposition to Plaintiff's Motion for Temporary Restraining Order and/or Preliminary Injunction, April 17, 2012 [Dkt. No. 22] ("FDA Opp'n")), as have defendants-intervenors, the three generic manufacturers whose vancomycin ANDAs have been approved. (*See* Intervenor-Defendant Akorn's Memorandum in Opposition to ViroPharma Incorporated's Motion for a Temporary Restraining Order, April 17, 2012 [Dkt. No. 23] ("Akorn Opp'n"); Alvogen, Inc.'s Memorandum in Opposition to Plaintiff ViroPharma Inc.'s Motion for Temporary Restraining Order and/or Preliminary Injunction, April 17, 2012 [Dkt. No. 24] ("Alvogen Opp'n"); Opposition of Defendant-Intervenor Watson Laboratories, Inc. to Plaintiff's Motion for Temporary Restraining Order and/or Preliminary Injunction and Expedited Hearing, April 17, 2012 [Dkt. No. 25] ("Watson Opp'n").)

Following a hearing held on April 19, 2012, and having considered all of the parties' arguments and pleadings, including the reply filed by plaintiff after the hearing (*see* Reply, April

[1] With the parties' consent, the Court has collapsed ViroPharma's requests for a temporary restraining order and a preliminary injunction.

20, 2012 [Dkt. No. 32] ("Pl.'s Reply")), the Court concludes that ViroPharma has not demonstrated that it is entitled to a preliminary injunction. Therefore, its motion will be denied.

BACKGROUND

Prior opinions of this Court and others describe the background relevant to ViroPharma's statutory exclusivity and bioequivalence claims.

I. STATUTORY AND REGULATORY FRAMEWORK

A. ViroPharma's Statutory Exclusivity Claim

> Prior to 1997 and the passage of the [Food and Drug Modernization Act of 1997 ("FDAMA"), Pub. L. No. 105–115, 111 Stat. 2296], "antibiotic" drugs were approved under Section 507 of the FFDCA, 21 U.S.C. § 357 ("Section 507"), and non-antibiotic drugs were approved under Section 505, 21 U.S.C. § 355 ("Section 505"). This difference had a long history, dating back to the development of penicillin, the first drug to have the capacity to kill microbes, *i.e.*, be "anti-biotic." Because penicillin was manufactured in batches through fermentation, its strength and efficacy could vary depending on the rigor of that process. Congress required that FDA test all batches of penicillin to ensure that appropriate doses were administered to the military during World War II. Initially, Section 507 applied only to penicillin or any derivative of penicillin; other named antibiotic drugs were added to the statute as they were developed. When the FFDCA was amended in 1962, a more generalized definition was added so that the law would not need amending with each new discovery of an antibiotic drug. [*See* Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780.]
>
> Two key consequences arose from these different treatments. Applicants for generic versions of antibiotic drugs were only requested to show conformance with statutorily-mandated, published standards of identity, strength, quality, and purity for the antibiotic substance, as reflected in antibiotic "monographs" published by FDA. Pharmaceutical companies did not have to submit the safety and efficacy data that was required for pioneer and generic non-antibiotic drugs. Therefore, generic antibiotics were developed and marketed fairly readily. *See Glaxo, Inc. v. Heckler*, 623 F. Supp. 69, 72 (E.D.N.C. 1985); Abbreviated New Drug Applications, Proposed Rule, 54 Fed. Reg. 28,872, 28,878 (July 10, 1989). However, antibiotic drugs did not receive the patent listing, patent certification, and marketing exclusivity benefits available to pioneer and non-antibiotic drugs after enactment of the Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman"), Pub. L. No. 98–417, 98 Stat. 1585 (1984). . . .
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> The significance of the Hatch-Waxman Amendments to FFDCA cannot be understated. Prior to 1984, all applicants seeking to market pioneer drugs or generic non-antibiotic drugs had to file [a new drug application ("NDA")]

> containing, *inter alia*, extensive scientific data demonstrating the safety and effectiveness of the drug. *See* 21 U.S.C. § 355(a)–(b); 21 C.F.R. § 314.50. As a result, few generic non-antibiotic drugs were approved by [the] FDA. *See Glaxo*, 623 F. Supp. at 72. Hatch–Waxman created an abbreviated approval process for generic non-antibiotic drugs, while retaining incentives for pioneer drugs, such as marketing exclusivity and patent protections. *See* 21 U.S.C. § 355(jj). The abbreviated new drug application ("ANDA") process shortens the time and effort needed for approval of a generic drug by allowing the applicant to merely demonstrate its product's bioequivalence to the NDA drug, without reproducing the entirety of the NDA's extensive scientific research. *See Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990) (describing the ANDA process).
>
> Because Congress still wanted to provide incentives for new drug development, alongside the ANDA process that eased the marketing of generic drugs, Hatch-Waxman entitles an NDA applicant to a period of market exclusivity (3 or 5 years, depending on the degree of innovation reflected in the NDA) which bars FDA approval of a generic ANDA for the NDA product. *See* 21 U.S.C. § 355(c)(3)(D)(ii)–(iv), (j)(5)(D)(ii)–(iv).

Allergan, Inc. v. Crawford, 398 F. Supp. 2d 13, 16–17 (D.D.C. 2005) (footnotes omitted, citation formats altered).

Thus, pursuant to Hatch-Waxman's provisions, "pioneer drug companies are entitled to certain periods of marketing exclusivity during which they are protected from generic competition." *AstraZeneca Pharm. LP v. FDA*, --- F. Supp. 2d ----, ----, 2012 WL 983481, at *2 (D.D.C. 2012). "Included among these various exclusivity periods is what is sometimes referred to as a 'new patient population' or 'new indication' exclusivity because it frequently arises when a pioneer drug company conducts post-approval clinical studies, submits a supplemental application to the FDA [(an "sNDA")], and secures the FDA's approval to market an approved drug to a new population or for a new indication." *Id.* Specifically, if an sNDA is approved and it

> contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the [sNDA] and conducted or sponsored by the person submitting the [sNDA], the [FDA] may not make the approval of an [ANDA] submitted . . . for a change approved in the supplement effective before the expiration of three years from the date of the approval of the [sNDA].

21 U.S.C. § 355(j)(5)(F)(iv).

Although referred to "new indication exclusivity," this provision applies beyond situations where an existing drug is approved for the treatment of a disease for which it had not been approved before. "The FDA has interpreted [§ 355(j)(5)(F)(iv)] as establishing a relationship between the information obtained from the clinical investigation, the change approved through the pioneer drug company's [sNDA], and the scope of the information relied upon by a generic competitor in a specific ANDA." *AstraZeneca*, 2012 WL 983481, at *3. Therefore, labeling changes approved in an sNDA can qualify for exclusivity under § 355(j)(5)(F)(iv) as well. As relevant here, if an sNDA that prescribes labeling changes is approved on the basis of "new clinical investigations (other than bioavailability studies) . . . conducted or sponsored by the person submitting the [sNDA]," then an ANDA that includes the labeling changes may only be approved three years thereafter. 21 U.S.C. § 355(j)(5)(F)(iv). And because a generic drug product may not be approved unless its label is (with certain exceptions not relevant here) the "same as" the brand-name drug's label, *id.* § 355(j)(2)(A)(v); 21 C.F.R. § 2314.94(a)(8)(iv), if an approved sNDA prescribing labeling changes qualifies under 21 U.S.C. § 355(j)(5)(F)(iv), then the three years of labeling exclusivity the statute provides can in practice amount to an exclusive right to market the drug for that time period.

As described above, however, when Hatch-Waxman was enacted, its exclusivity provisions did not apply to antibiotics such as Vancocin. In 1997, with the enactment of the FDAMA, Congress extended Hatch-Waxman to antibiotics by repealing

> Section 507 of the FFDCA and requir[ing] that all applications for antibiotic drugs be submitted under Section 505. FDAMA § 125(d)(1) (Transition). In subsection (d)(1), the Transition provided that applications for antibiotic drugs approved under Section 507 before FDAMA would be considered approved under

> Section 505. *Id.* However, subsection (d)(2) added the provision that when "the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application" received by FDA before the enactment of FDAMA, it is exempt from Hatch-Waxman benefits. FDAMA § 125(d)(2); Proposed Rule: Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs, 65 Fed. Reg. 3,623, 3,624–25 (Jan. 24, 2000); Section 507 Repeal Guidance at 2. Specifically, § 125(d)(2) exempts from Hatch–Waxman:
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> > any application for marketing in which the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application for marketing received by the Secretary of Health and Human Services under section 507 of such Act (21 U.S.C. § 357 [Section 507]) before the date of enactment of this Act.
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> Pub. L. No. 105–115, 111 Stat. 2327 (1997), § 125(d)(2) (*reprinted in* 21 U.S.C.A. § 355 Historical and Statutory Notes, "Transition"). Antibiotic drugs that were the subject of pre-FDAMA applications are known as "[O]ld [A]ntibiotics" and will be so referenced here.

Allergan, 398 F. Supp. 2d at 17–18. Thus, with the enactment of the FDAMA in 1997, Congress eliminated the separate approval pathway for antibiotics and made antibiotics approved *after* the statute's effective date, *but not Old Antibiotics*, eligible for exclusivity provided the other statutory criteria were met. As discussed below, ViroPharma's Vancocin is an Old Antibiotic.

Congress closed this gap when it enacted the QI Program Supplemental Funding Act of 2008, Pub. L. No. 110-379, 122 Stat. 4075 (the "QI Act"). Section 4 of the QI Act, entitled "Incentives for the Development of, and Access to, Certain Antibiotics," amended the FFDCA to make Old Antibiotics eligible for exclusivity. *Id.* § 4. Thus, the FFDCA now provides:

> Notwithstanding any provision of the [FDAMA] or any other provision of law, a sponsor of [an Old Antibiotic] shall be eligible for, with respect to the drug, the 3-year exclusivity period referred to under clauses (iii) and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable.

21 U.S.C. § 355(v)(1)(A). However, Section 4 of the QI Act also provides that the 3-year

exclusivity period provided in 21 U.S.C. § 355(j)(5)(F)(iv) 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]." *Id.* § 355(v)(3)(B). The FDA's interpretation of this exemption is the focus of ViroPharma's statutory exclusivity claim.

B. ViroPharma's Bioequivalence Claim

Under the FFDCA, in order for a generic applicant to rely on the record of safety and effectiveness demonstrated by a pioneer drug, known as the "reference listed drug" ("RLD") for purposes of the process by which a generic copy gains 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. [*Id.*] § 355(j)(2)(A)(iv).[2] Where . . . "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." [*Id.*] § 355(j)(8)(C).
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> Depending on the circumstances and the particular drug in question, the FDA may require an applicant [to] 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).

ViroPharma, Inc. v. Hamburg, 777 F. Supp. 2d 140, 143 (D.D.C. 2011) ("*ViroPharma I*") (some

[2] FDA regulations define bioequivalence as "the absence of a significant difference [as between the generic drug and the RLD] in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action." 21 C.F.R. § 320.1(e). The rate of absorption itself is referred to as "bioavailability." *Id.* § 320.1(a) ("Bioavailability means the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of action."). In approving an NDA, the FDA requires applicants to submit data on *bioavailability*. *Id.* § 320.21(a). In approving an ANDA, as discussed below, the FDA requires data on *bioequivalence* to show that the proposed generic has the same bioavailability as the RLD. *Id.* § 320.21(b).

alterations in the original; citations and some internal quotation marks omitted),[3] *aff'd*, No. 11-5143, 2012 WL 1138803 (D.C. Cir. Mar. 21, 2012); *see* 21 C.F.R. Part 320 (FDA regulations regarding bioequivalence). The FDA's interpretation of various regulatory provisions in 21 C.F.R. Part 320 is the focus of ViroPharma's bioequivalence claim.

II. FACTUAL AND PROCEDURAL BACKGROUND

A. ViroPharma and Vancocin

ViroPharma, founded in September 2004, is a small pharmaceutical company headquartered in Exton, Pennsylvania. (Compl. ¶ 6; Pl.'s Mot., Ex. A ("Rowland Decl."[4]) ¶ 4.) In addition to Vancocin, ViroPharma currently sells three other drugs and biologic products: Cinryze™, Buccolam®, and Diamorphine. (Pl.'s Mot. at 2; Rowland Decl. ¶ 7.) Prior to the FDA's approval of generic vancomycin ANDAs, Vancocin represented "roughly half" of ViroPharma's revenue. (Compl. ¶ 18; *see* Rowland Decl. ¶ 8 ("In 2011, Vancocin sales were $389 million and accounted for 53% of ViroPharma's total revenue.").)

Vancocin was developed by Eli Lilly and Company and approved by the FDA in April 1986 for the treatment of, *inter alia*, "a dangerous gastrointestinal infection" called *Clostridium difficile* associated diarrhea (or "CDAD").[5] *ViroPharma Inc. v. Dep't of Health & Human Servs.*, --- F. Supp. 2d ----, ----, 2012 WL 892926, at *1 (D.D.C. 2012) ("*ViroPharma II*").[6] (*See*

[3] In *ViroPharma I*, this Court concluded that ViroPharma lacked standing to sue on its bioequivalence claims where the FDA had not yet granted any vancomycin ANDAs. 777 F. Supp. 2d at 148.

[4] Charles Rowland is ViroPharma's Chief Financial Officer. (Rowland Decl. ¶ 1.)

[5] Because Vancocin was first approved by the FDA prior to the enactment of the FDAMA, it qualifies as an Old Antibiotic. *See Allergan*, 398 F. Supp. 2d at 17–18.

[6] In *ViroPharma II*, Judge Friedman addressed cross-motions for summary judgment in a FOIA

Rowland Decl. ¶¶ 16–19, 22; Compl., Ex. A ("CP Response")[7] at 8.) Vancocin, delivered orally in capsule form, releases the antibiotic vancomycin into the gastrointestinal tract where the drug acts to attack *C. difficile* bacteria. (Rowland Decl. ¶ 20.) Accordingly, Vancocin is a "locally acting" drug; it acts in the GI tract but is not systemically absorbed into the bloodstream or the rest of the body. (*Id.*; *see* CP Response at 3 ("Vancomycin acts locally in the GI tract . . . and is poorly absorbed after oral administration, meaning it does not enter the body systemically.").)

In November 2004, ViroPharma "exclusively licensed from Eli Lilly the right to manufacture, market, and sell Vancocin in the United States and its territories." (Rowland Decl. ¶ 22.) However, Vancocin's last core patent expired in 1996. (*Id.* ¶ 23.) Therefore, "absent statutory exclusivity, the market for Vancocin is open to generic substitutes upon FDA approval." (*Id.*)

B. ViroPharma's Efforts To Forestall the Approval of a Generic Vancomycin

ViroPharma presented its statutory exclusivity and bioequivalence claims to the FDA in a series of filings commencing in 2006. As the basis for its statutory exclusivity claim, ViroPharma cited the fact that on December 14, 2011, the FDA approved an sNDA for Vancocin that, according to plaintiff, "fundamentally changed the labeling" for the drug by adding "new conditions of use relating to Clinical Studies, Adverse Reactions: Clinical Trials, Nephrotoxicity,

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action brought by ViroPharma related to the FDA's deliberations and decisions regarding Vancocin and potential generic vancomycin ANDAs. 2012 WL 892926, at *1–2.

[7] As discussed further below, CP Response consists of a single-spaced, eighty-five page letter from the FDA to ViroPharma denying the "citizen petition" through which ViroPharma raised, *inter alia*, its statutory exclusivity and bioequivalence claims before the agency. (*See infra* n.11 (describing the "citizen petition" process).) The Court references the letter ruling's comprehensive treatment of the history of this dispute for purposes of providing relevant background information.

and Geriatric Use, by modifying Vancocin's indication, and by specifying a recommended dosing regimen." (*Id.* ¶ 24.) These changes "were based on new clinical safety and efficacy data to which ViroPharma has exclusive rights."[8] (*Id.*) Accordingly, ViroPharma argued that Vancocin is entitled to a three-year period of exclusivity to run through December 15, 2014. *See* 21 U.S.C. § 355(j)(5)(F)(iv).

ViroPharma's bioequivalence claim relies on a more complicated regulatory backdrop. Because Vancocin is the only RLD for vancomycin, any ANDA for generic vancomycin must establish bioequivalence to Vancocin to gain approval from the FDA. (CP Response at 8.) "Prior to 2006 the FDA recommended using *in vivo* studies . . . to establish the bioequivalence of generic versions of vancomycin." *ViroPharma II*, 2012 WL 892926, at *1. (See CP Response at 9 ("FDA's initial recommendation for sponsors to establish bioequivalence to [Vancocin] was to conduct *in vivo* studies with clinical endpoints.").) However, generic manufacturers told the FDA that it was "nearly impossible to do" an *in vivo* bioequivalence study of a proposed generic for Vancocin. (Pl.'s Mot., Ex. A ("McCalips Decl."), Ex. 5 at 1.[9]) As of 2006 there had been no ANDAs submitted for the drug, and therefore no generic products competed with it. (*Id.*)

[8] ViroPharma's data was based on two clinical safety and efficacy studies for an unsuccessful drug, tolevamer. (McCalips Decl., Ex. 2 at 4.) ViroPharma had purchased the rights to those studies from their sponsor, Genzyme Corporation. (*Id.*) In those studies, Vancocin was administered to the control group, in accordance with its labeled use in populations for which Vancocin had previously been approved. (*Id.* at 4–5.)

[9] Indeed, in considering Eli Lilly's NDA for Vancocin in the 1980s, the "FDA concluded that it could not assess systemic bioavailability of [the drug] from the *in vivo* bioavailability data Lilly had submitted because of low absorption of the capsule product." (CP Response at 8; *see supra* n.2 (discussing bioavailability).) The FDA nonetheless approved the NDA by waiving the *in vivo* bioavailability data requirement pursuant to a regulatory provision that is not relevant to the present dispute. (CP Response at 8.) Still, it is worth emphasizing that the FDA approved the Vancocin NDA based largely on the same kind of dissolution data which ViroPharma now argues is insufficient for the approval of an ANDA. (*See id.* at 8 & n.8.)

In February of that year, the FDA "changed its bioequivalence recommendation for vancomycin" and began to permit generic applicants "to establish bioequivalence with certain *in vitro* dissolution studies in lieu of *in vivo* data." (CP Response at 9.) The FDA maintains that its revised recommendation was based on 1) guidance it had issued in August 2000 which provided for the waiver of *in vivo* data requirements for RLDs which were rapidly dissolving, highly soluble, and highly permeable (the "BCS Guidance"); 2) draft guidance it issued shortly thereafter noting "that bioequivalence for orally administered drugs intended for local action in the GI tract" could be demonstrated by *in vitro* studies in certain circumstances; 3) an ANDA for vancomycin submitted in late 2004 which "purported to show" that Vancocin was "'rapidly dissolving' under the BCS Guidance definition thereby justifying waiver of the *in vivo* clinical data requirement in place at that time;" and 4) independent FDA analysis confirming that vancomycin is highly soluble.[10] (CP Response at 9–11.) The revised recommendation provided "that '[v]ancomycin is a highly soluble drug and [Vancocin] is rapidly dissolving. Waivers of *in vivo* bioequivalence testing can be requested in [ANDAs], provided that the test product is rapidly dissolving at the conditions specified in the [BCS Guidance].'" (*Id.* at 12 (some alterations in the original) (quoting a letter from the FDA to an interested party).) The "FDA did not publicly announce the change in policy, but provided information to companies that submitted inquiries regarding the bioequivalence standards for vancomycin." *ViroPharma II*, 2012 WL 892926, at *1. (*See* Pl.'s Mot. at 7; CP Response at 9, 11.) When one company publicized the new standards, the value of ViroPharma's stock dropped by "roughly 40%." *ViroPharma II*, 2012 WL 892926, at *1. (*See* Compl. ¶ 41.)

[10] The FDA "did not independently assess the ANDA applicant's dissolution data." (CP Response at 11.)

On March 17, 2006, ViroPharma filed a citizen petition[11] to stay the approval of any vancomycin ANDA under the FDA's new bioequivalence testing method. (*See* McCalips Decl. ¶ 2; *id.*, Ex. 1 (ViroPharma's Petition for Stay of Action, Docket No. FDA-2006-P-007 (as amended, "Citizen Petition")).) Shortly thereafter, ViroPharma supplemented its petition to include data purporting to show that Vancocin is *not* rapidly dissolving.[12] (CP Response at 13.) In response to this supplement, the FDA commissioned a study which ultimately confirmed "that Vancocin is not 'rapidly dissolving' as defined in the BCS Guidance." (*Id.*)

Nonetheless, on December 16, 2008, and while ViroPharma's Citizen Petition remained pending, the FDA issued a "draft guidance for industry entitled 'Bioequivalence Recommendation for Vancomycin HCl,'" Notice, 73 Fed. Reg. 76,362, 76,362 (Dec. 16, 2008), that allowed generic applicants to demonstrate bioequivalence through *in vitro* testing if their proposed vancomycin capsules contained inactive ingredients which were qualitatively and quantitatively the same as Vancocin. *See ViroPharma II*, 2012 WL 892926, at *1. ViroPharma alleges that "[n]either the notice of the Draft Guidance published in the Federal Register, nor the Draft Guidance itself, identified the regulatory authority for the recommendation." (Pl.'s Mot. at 8; *see* Compl. ¶ 50.)

"[T]wo key factors" led the FDA to the conclusion "that notwithstanding that

[11] When the FDA is considering an ANDA, those with rights to or scientific knowledge of the innovator drug may provide technical information relating to the generic drug's bioequivalence by filing a "citizen petition" with the FDA. *See AstraZeneca Pharm.*, 2012 WL 983481, at *3; *Biovail Corp. v. FDA*, 448 F. Supp. 2d 154, 157 n.2 (D.D.C. 2006); 21 C.F.R. §§ 10.25(a), 10.30(e).

[12] After ViroPharma's sNDA was approved on December 14, 2011, ViroPharma filed another supplement to its Citizen Petition requesting three years of exclusivity pursuant to 21 U.S.C. § 355(j)(5)(F)(iv). (*See* McCalips Decl., Ex. 2.) All told, the FDA maintains that "ViroPharma has . . . supplemented and/or amended its petition twenty times." (FDA Opp'n at 9 (emphasis deleted).)

vancomycin capsules are not 'rapidly dissolving' under the BCS Guidance, *in vitro* dissolution studies still are an appropriate method of demonstrating bioequivalence for vancomycin capsules":

> First, vancomycin acts primarily in the colon, and GI transit times for drugs to reach the colon average 3 to 4 hours. Dissolution even at 60 minutes, which all but one Vancocin lot demonstrated in [a 2008 study conducted by the FDA], ensures that even in patients with faster transit times than healthy subjects, vancomycin will be completely dissolved when it reaches the colon. Second, . . . similar dissolution profiles across the pH ranges recommended in the bioequivalence recommendation ensure that generic and reference products will have equivalent release even in patients with extremely short GI transit times or in conditions that would not permit either the [RLD] or the generic product to completely dissolve.

(CP Response at 14.) However, in noticing the 2008 Draft Guidance in the Federal Register, the FDA stressed that it represented only the agency's "current thinking on this topic" and stated that "an alternate approach" to bioequivalence may be used if the approach satisfied "the requirements of the applicable statutes and regulations." 73 Fed. Reg. at 76,363.

According to the FDA, it then "received and carefully considered comments" on the Draft Guidance "from a variety of parties," including ViroPharma, other innovator drug manufacturers, generic drug manufacturers, doctors, patients, patient advocacy groups, and concerned citizens. (CP Response at 16.[13]) In 2009, FDA convened its Advisory Committee for Pharmaceutical Science to consider the Draft Guidance. (*Id.* at 17.) The FDA and industry representatives, including representatives of ViroPharma, presented materials at the meeting, and members of the public also had an opportunity to comment. (*Id.* at 18.) After "an extensive discussion of the scientific bases for the bioequivalence recommendation" in the Draft Guidance,

[13] *See* Docket Folder Summary, Draft Guidance for Industry on Bioequivalence Recommendation for Vancomycin HCl, http://www.regulations.gov/#!docketDetail;D=FDA-2008-D-0626 (last visited April 23, 2012).

the Committee "voted unanimously in favor of endorsing" it. (*Id.*)

C. The FDA's Response to ViroPharma's Citizen Petition

On April 9, 2012, the FDA denied ViroPharma's Citizen Petition in a comprehensive letter ruling, concluding that Vancocin was not entitled to statutory exclusivity (*see id.* at 66–73; *infra* Section II.C.1) and that ViroPharma's bioequivalence claims failed. (*See* CP Response at 52–60; *infra* Section II.C.2.)

1. ViroPharma's Statutory Exclusivity Claim

In denying ViroPharma's Citizen Petition, the FDA determined that Vancocin was not entitled to statutory exclusivity under 21 U.S.C. § 355(j)(5)(F)(iv) "due to the limitation on such exclusivity for certain antibiotic products set forth in" 21 U.S.C. § 355(v)(3)(B). (CP Response at 67.) The FDA reasoned that the QI Act created "a *limited* opportunity for an application containing an Old Antibiotic to obtain Hatch-Waxman exclusivity, if that application (or supplemental application) was submitted after" the Act's enactment in 2008. (CP Response at 68–69 (emphasis added).) As described above, § 355(v)(3)(B) provides that exclusivity "is not available for 'any condition of use for which the [Old Antibiotic] . . . was approved before'" the QI Act's enactment. (*Id.* at 69 (quoting 21 U.S.C. § 355(v)(3)(B)).)

Noting that "[t]he QI Act does not expressly define what constitutes a 'condition of use . . . approved before the date of enactment,'" the FDA first concluded that Congress must have intended for the limitation to have some meaning; it "must exclude from exclusivity some applications and supplements containing new clinical studies that otherwise would qualify a non-Old Antibiotic product for 3-year Hatch-Waxman exclusivity," for, "[t]o conclude otherwise would render [it] meaningless" by "exclud[ing] from" exclusivity "only those studies that already do not qualify for" it. (*Id.*) "To give content to this limitation," the FDA concluded that

it "must find that there is a higher hurdle for exclusivity for an Old Antibiotic than there is for another kind of product seeking 3-year exclusivity." (*Id.*)

Turning to the QI Act's legislative history, the FDA determined that the Act was passed "to encourage development of *truly novel* antibiotics and *novel uses* of Old Antibiotics." (*Id.* (emphasis added); *see id.* at 69–70 & nn.333–36 (surveying the legislative history).) Accordingly, the FDA announced that it would interpret § 355(v)(3)(B) "to permit 3-year Hatch-Waxman exclusivity for Old Antibiotics only for *a significant new use* for an Old Antibiotic (such as a new indication for a previously approved antibiotic . . .), not for refinements in labeling related to previously approved uses for Old Antibiotics." (*Id.* at 70 (emphasis added).) The FDA justified its interpretation as "consistent with the balance sought by Congress in the QI Act to reward and provide incentives for companies to develop innovative new uses of Old Antibiotics while also facilitating antibiotic access generally through generic approvals and limiting the time period in which the innovator product is the only product on the market." (*Id.*)

Applying its interpretation, the FDA then determined that Vancocin was not eligible for Hatch-Waxman exclusivity because the December 2011 approval of ViroPharma's sNDA did not constitute approval of a significant new use for the drug. (*Id.* at 70–73.) With respect to the three changes to the Vancocin label on which ViroPharma based its claim of exclusivity, the FDA concluded that granting such exclusivity would violate § 355(v)(3)(B). The FDA determined that the inclusion of (1) more specific dosing information that was within the range specified on the prior label and was consistent with the well-established standard dosage, (2) new instructions on monitoring patients' renal function, and (3) new instructions for the continuation of treatment in older patents served only "to incorporate clinical data that supports and refines labeling regarding already approved conditions of use" and to bring the labeling into compliance

with the "Physician Labeling Rule" (or "PLR"). (*Id.* at 66, 71.) The labeling changes did not effect a "significant new use" for Vancocin because they only "refine[d] the currently approved indication for treatment of CDAD in already identified patient populations." (*Id.* at 71–72.) In support of its analysis, the FDA cited the fact that had ViroPharma "intended to seek approval for a new indication or a new dosing regimen," its sNDA would have had to comply with certain other statutory requirements, which it did not. (*Id.* at 72 & n.344.) Thus, the FDA concluded that the sNDA did not constitute approval for a new "condition of use" as that term is used in § 355(v)(3)(B). (*Id.* at 71.)

The agency stated that it encouraged pioneer manufacturers' efforts "to modify labeling to provide doctors and patients with current information based on clinical data" and "to bring their labels into compliance with the PLR." (*Id.* at 73.) However, it concluded that "[r]evising the labeling and providing clinical data that supports or, at most, refines information about already approved conditions of use . . . does not give rise to an approval for a condition of use that has not been previously approved and therefore merits the limited 3-year exclusivity available for an Old Antibiotic product." (*Id.*)

2. ViroPharma's Bioequivalence Claim

The FDA also rejected ViroPharma's bioequivalence claim. (See CP Response at 52–56, 59.) ViroPharma had argued that 21 C.F.R § 320.21(b) establishes a default requirement that bioequivalence be demonstrated through *in vivo* testing,[14] subject to the waiver criteria set forth

[14] 21 C.F.R. § 320.21(b) provides that "[a]ny person submitting an abbreviated new drug application to FDA shall include in the application either: (1) Evidence demonstrating that the drug product that is the subject of the abbreviated new drug application is bioequivalent to the [RLD]" or "(2) Information to show that the drug product is bioequivalent to the reference listed drug which would permit FDA to waive the submission of evidence demonstrating *in vivo* bioequivalence as provided in paragraph (f) of this section." Subsection (f) is described below.

in 21 C.F.R. § 320.22, which permits *in vitro* testing in limited circumstances.[15] On the basis of a lengthy analysis of the relevant regulations, which assessed their text, structure, and history, the FDA concluded that there is no such default requirement. For example, the agency cited 21 C.F.R. § 320.24(a), which provides that the agency "may require *in vivo* or *in vitro* testing, or both, to . . . establish the bioequivalence of specific drug products." 21 C.F.R. § 320.24(a).[16] Overruling ViroPharma's objection that § 320.24 merely lists the various approaches for establishing either *in vivo* or *in vitro* bioequivalence, depending on which of those two types of testing is otherwise required by the regulations, the FDA asserted in its response to ViroPharma's Citizen Petition that § 320.24 provides the agency with discretion to determine, on a case-by-case basis, whether it will require *in vivo* testing, *in vitro* testing, or both. (CP Response at 52–54.) Exercising that discretion, and having gone to great lengths to buttress the scientific propriety and necessity of its approach, the FDA "determined . . .that the most

[15] 21 C.F.R. § 320.21(f), referenced in § 320.21(b)(2) as instructing an applicant as to the information "which would permit FDA to waive the submission of evidence demonstrating *in vivo* bioequivalence," cross-references § 320.22. Subsections (b), (c), (d), and (e) of § 320.22, in turn, enumerate the relevant criteria and circumstances.

[16] 21 C.F.R. § 320.24 is entitled "Types of evidence to measure bioavailability or establish bioequivalence." Section 320.24(a) begins by stating that "bioequivalence may be demonstrated by several *in vivo* and *in vitro* methods," and goes on to provide that "[t]he selection of the method used to meet an *in vivo* or *in vitro* testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product." Section 320.24(a) concludes by specifying that generic "[a]pplicants shall conduct . . . bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in" section 320.24(b). Section 320.24(b), in turn, lists "*in vivo* and *in vitro* approaches, in descending order of accuracy, sensitivity, and reprudicity," which are "acceptable for determining the . . . bioequivalence of a drug product." Subsections (1)(i), (2), and (3) describe specific *in vivo* testing approaches; subsections (1)(ii) and (5) describe specific *in vitro* testing approaches; subsection (4) refers to "[w]ell-controlled clinical trials"; and subsection (6) allows "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence." 21 C.F.R. 320.24(b).

accurate, sensitive, and reproducible approach available for demonstrating vancomycin capsule bioequivalence is one using *in vitro* dissolution data, and not clinical study data, which is the least sensitive for this product." (*Id.* at 53; *see id.* at 19–51 (providing the scientific rationale).)

In the alternative, the FDA found that even if it lacked this discretion, it had "determined that [it] would waive [any *in vivo* data] requirement for generic vancomycin applicants that meet the criteria for *in vitro* data set forth" in 21 C.F.R. § 320.22(e). (CP Response at 59.) That provision allows the FDA to waive an *in vivo* bioequivalence testing requirement "for good cause . . . if waiver is compatible with the protection of the public health." 21 C.F.R. § 320.22(e). The FDA concluded "that such a waiver would be" appropriate "for generic vancomycin capsules for several reasons," especially in light of its prior conclusion that *in vivo* bioequivalence testing was scientifically unsound in this application. (CP Response at 59.[17])

On the same day that it issued its response to ViroPharma's Citizen Petition, the FDA approved ANDAs for generic vancomycin submitted by Akorn, Alvogen, and Watson Laboratories. (*Id.* at 2 n.6.) ViroPharma brought this action four days later, on April 13, 2012.

[17] Specifically, the FDA stated that:

> [V]ancomycin is one of only two FDA-approved treatments for the fast-moving, life-threatening colitis associated with CDAD. . . . [I]ncreased incidence of CDAD infections as well as more severe instances of the disease have been extensively reported in the medical literature and general media. Medical literature also indicates that in light of the high demand and high cost of Vancocin . . ., doctors and hospitals have begun administering vancomycin parenteral solution[, an alternative formulation of the antibiotic that is injectable,] to patients orally to treat CDAD. This formulation has never been approved for oral use or for use in this fashion, and thus raises potential public health concerns including a risk of dosage errors. The availability of safe and effective generic vancomycin capsules would mitigate these concerns consistent with the fundamental purposes of Hatch-Waxman: to make available to consumers safe and effective generic drug products.

(CP Response at 59–60. *But see infra* n.26.)

ViroPharma claims that the FDA's rejection of its statutory exclusivity claim violated the FFDCA, and that the agency's rejection of its bioequivalence claim violated the agency's own regulations.

ANALYSIS

The Supreme Court has described the relief sought by ViroPharma as "an extraordinary and drastic remedy." *Munaf v. Geren*, 553 U.S. 674, 689–90 (2008) (internal quotation marks and citation omitted). To obtain a preliminary injunction, a plaintiff "must establish that he is likely to succeed on the merits, that he is likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in his favor, and that an injunction is in the public interest." *Winter v. Natural Resources Defense Council, Inc.*, 555 U.S. 7, 20 (2008) (citing, *inter alia*, *Munaf*, 553 U.S. at 689–90). The movant "bears the burden of persuasion and must demonstrate, 'by a clear showing,' that the requested relief is warranted." *McGinn, Smith & Co., Inc. v. Fin. Indus. Regulatory Auth.*, 786 F. Supp. 2d 139, 144 (D.D.C. 2011) (quoting *Chaplaincy of Full Gospel Churches v. England*, 454 F.3d 290, 297 (D.C. Cir. 2007)).[18]

While the four factors *Winter* recites "have typically been evaluated on a sliding scale," *Davis v. Pension Benefit Guaranty Corp.*, 571 F.3d 1288, 1291 (D.C. Cir. 2009) (internal quotation marks and citation omitted), "'[i]t is particularly important for [the movant] to demonstrate a substantial likelihood of success on the merits.'" *McGinn*, 786 F. Supp. 2d at 144 (quoting *Barton v. Dist. of Columbia*, 131 F. Supp. 2d 236, 242 (D.D.C. 2001)); *see Sherley v.*

[18] Where a plaintiff seeks a mandatory injunction, *i.e.*, one that would alter, rather than preserve, the status quo, some courts have applied an even more exacting standard. *See Allina Health Servs. v. Sebelius*, 756 F. Supp. 2d 61, 69–70 & n.5 (D.D.C. 2010) (collecting cases). However, "the D.C. Circuit has yet to address this question," *id.* at 70, and the Court does not need to here because ViroPharma's claims fail under either standard.

Sebelius, 644 F.3d 388, 393 (D.C. Cir. 2011) ("[W]e read *Winter* at least to suggest if not to hold 'that a likelihood of success is an independent, free-standing requirement for a preliminary injunction.'" (quoting *Davis*, 571 F.3d at 1296 (Kavanaugh, J., concurring))). Moreover, the movant must demonstrate an actual "likelihood" of success, not merely the existence of "questions so serious, substantial, difficult and doubtful, as to make them fair ground for litigation." *Munaf*, 553 U.S. at 690 (internal quotation marks and citation omitted).

III. LIKELIHOOD OF SUCCESS ON THE MERITS

Because the FDA's denial of ViroPharma's Citizen Petition is subject to review under the Administrative Procedure Act, 5 U.S.C. §§ 701 *et seq*., ViroPharma will only succeed on the merits if it demonstrates that the FDA's decision was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." *Id.* § 706(2)(A).[19] This standard of review is narrow and highly deferential; it presumes agency action to be valid, and it prohibits a court from substituting its judgment for that of the agency. *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971); *Int'l Fabricare Inst. v. EPA*, 972 F.2d 384, 389 (D.C. Cir. 1992). It bears emphasis that "[i]n an area as complex as" the regulatory "system" for pharmaceuticals, "the agency Congress vests with administrative responsibility must be able to

[19] ViroPharma's complaint states two counts, both of which center on the FDA's denial of ViroPharma's Citizen Petition and its approval of generic vancomycin ANDAs. Count I, entitled "Agency Action Not in Accordance with Regulations," alleges that the FDA violated its governing regulations and states ViroPharma's bioequivalence claim. (*See* Compl. ¶¶ 69–74). Count II, entitled "Agency Action Not in Accordance with Statute, alleges that the FDA violated the FFDCA and states ViroPharma's statutory exclusivity claim. (*See id.* ¶¶ 75–78.) Neither count challenges the substance of the FDA's scientific analysis. Accordingly, ViroPharma's claims relate only to whether the FDA's actions were "in accordance with law." 5 U.S.C. § 706(2)(A). Therefore, as counsel for all parties agreed at oral argument, this Court may assess them without recourse to the administrative record. *See Am. Bankers Ass'n v. Nat'l Credit Union Admin.*, 271 F.3d 262, 266–67 (D.C. Cir. 2001); *Hosp. Partners, L.P. v. Sebelius*, 794 F. Supp. 2d 162, 171 (D.D.C. 2011).

exercise its authority to meet changing conditions and new problems." *Bob Jones Univ. v. United States*, 461 U.S. 574, 596 (1983); *see Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1280 (D.C. Cir. 2004) ("There is no denying the complexity of the statutory regime under which the FDA operates . . . .").

A. ViroPharma's Statutory Exclusivity Claim

ViroPharma's statutory exclusivity claim, which alleges that the FDA's letter ruling denying ViroPharma's Citizen Petition and its approval of vancomycin ANDAs are inconsistent with the FFDCA, presents an issue of first impression. To address it, 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 Resources Defense Council*, 467 U.S. 837, 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 the second step 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.

Despite these bedrock principles, ViroPharma states, without elaboration, that the FDA's interpretation of 21 U.S.C. § 355(v)(3)(b) is not entitled to *Chevron* deference because the agency's letter ruling denying its Citizen Petition is an "informal agency pronouncement . . . that lacks the force of law." (Pl.'s Mot. at 19 n.9 (citing *United States v. Mead Corp.* 553, U.S. 219,

229 (2001).) This contention is meritless. First, ViroPharma does not, and cannot, challenge the FDA's authority to issue letter rulings and approve ANDAs. Second, agency interpretations reached through means less formal than notice and comment rulemaking are not automatically deprived of the judicial deference that they are otherwise due. *Barnhart v. Walton*, 535 U.S. 212, 221 (2002). Rather, "whether a court should give such deference depends in significant part upon the interpretive method used and the nature of the question at issue." *Id.* at 222 (citing *Mead*, 533 U.S. at 229–31). In *Barnhart*, the Court concluded that "the interstitial nature of the legal question, the related expertise of the [a]gency, the importance of the question to administration of the statute, the complexity of that administration, and the careful consideration the [a]gency has given the question over a long period of time all indicate that *Chevron* provides the appropriate legal lens through which to view the legality of the [a]gency interpretation" it was reviewing. *Id.* Pursuant to *Barnhart*, the D.C. Circuit has consistently accorded *Chevron* deference to the FDA's letter rulings, including its responses to citizen petitions. *See Mylan Labs.*, 389 F.3d at 1280 (collecting cases); *accord Apotex, Inc. v. FDA*, No. 06-5060, 226 Fed. App'x 4, 5 (D.C. Cir. Feb. 23, 2007); *Teva Pharm. Indus. Ltd. v. Crawford*, 410 F.3d 51, 53 (D.C. Cir. 2005). *Chevron* applies here.[20]

Finally, ViroPharma is wrong to suggest that *Chevron* deference should not apply because the FDA issued its interpretation "after the commencement of litigation with ViroPharma." (Pl.'s Mot. at 19 n.9.) Neither Vancocin's eligibility for 3-year statutory exclusivity in general nor the FDA's specific interpretation of 21 U.S.C. § 355(v)(3)(b) were at issue in the prior litigation. *See ViroPharma I*, 777 F. Supp. 2d 140. Moreover, the Circuit has

[20] Regardless, as did the Circuit in *Mylan Laboratories*, the Court concludes that "[e]ven were the FDA's decision subject only to *Skidmore* deference, the result would likely be the same." 389 F.3d at 1280 n.6.

applied *Chevron* to the FDA's response to a citizen petition even though the FDA acted after the plaintiff "had already moved for injunctive relief in the district court." *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1325 (D.C. Cir. 1998). In *Serono*, the Circuit characterized the FDA's letter ruling as "represent[ing] the considered views of the agency decisionmaker . . ., announced at the usual point in the agency's decision-making process (the end), rather than the views of litigation counsel trying to come up with an explanation after the fact." *Id.* In such circumstances, the Circuit held, "'[t]here is simply no reason to suspect that the interpretation does not reflect the agency's fair and considered judgment on the matter in question.'" *Id.* (quoting *Auer v. Robbins*, 519 U.S. 452, 462 (1997)).

Therefore, the Court proceeds to *Chevron*'s step one and applies "the traditional tools of statutory construction in order to discern whether Congress has spoken directly to the question at issue." *Eagle Broad. Grp., Ltd. v. FCC*, 563 F.3d 543, 552 (D.C. Cir. 2009). The Court finds it likely that the statute is ambiguous. The FFDCA does not address what constitutes a "condition of use . . . approved before" the date of the QI Act's enactment. 21 U.S.C. § 355(v)(3)(B). Starting with the plain meaning of the text and looking to the language itself, *Blackman v. Dist. of Columbia*, 456 F.3d 167, 176 (D.C. Cir. 2006), "condition of use" is not defined in the FFDCA. And while the mere "absence of a statutory definition does not render a [phrase] ambiguous," *Natural Resources Defense Council v. EPA*, 489 F.3d 1364, 1373 (D.C. Cir. 2007), nothing about "the specific context in which [the phrase] is used" or "the broader context of the statute as a whole" is likely to compel the conclusion that the phrase has a definite meaning. *Blackman*, 456 F.3d at 176 (internal quotation marks omitted). ViroPharma's strongest argument is that "conditions of use" is used throughout the FFDCA and in the FDA's regulations to unambiguously include a variety of aspects of a drug and its administration that go beyond the

"significant new uses" contemplated by the FDA's interpretation of § 355(v)(3)(B). (*See* Pl.'s Mot. at 15, 20–23 (citing 21 U.S.C. §§ 321(p), 355(d)(1),(5), 355(j)(2)(A)(i)).) Yet, that fact is of little moment where the term is far from unambiguous no matter the application.[21] Neither its repetition in the FFDCA nor, as counsel for ViroPharma pressed at oral argument, its common usage in industry transforms it into a clear term.

More importantly, although it is true that "[w]hen Congress uses the same [phrase] in different parts of a statute, it usually means the same thing," the Circuit has instructed that "statutory interpretation is not just about logic" and a statute's terms "should be read in context, the statute's place in the overall statutory scheme should be considered, and the problem Congress sought to solve should be taken into account." *PDK Labs. Inc. v. DEA*, 362 F.3d 786, 796 (D.C. Cir. 2004) (internal quotation marks and citations committed). With respect to this final admonition, the FDA has demonstrated that when § 355(v)(3)(B) was promulgated as part of the QI Act, Congress sought to address a problem much more specific than that motivating the FFDCA as a whole. This alone is enough to differentiate "conditions of use" as employed in § 355(v)(3)(B) from the employment of that same term in unrelated statutory provisions. *Cf. Abbott Labs. v. Young*, 920 F.2d 984, 987 (D.C. Cir. 1990) ("it is not impermissible under *Chevron* for an agency to interpret an imprecise term differently in two separate sections of a statute which have different purposes"). Moreover, "[i]t was only years" after the enactment of the QI ACT in 2008 "that the" specific issue addressed by the agency in 2012—whether a drug manufacturer is entitled to renewed exclusivity where it makes changes to the drug's label that

[21] ViroPharma's appeal to the *FDA's* definition of "condition of use" in a regulation not related to the issues before this Court (*see* Pl.'s Mot. at 20 (citing 21 C.F.R. § 314.53(d)(2)(B)) undercuts its argument. If the statute is as unambiguous as ViroPharma contends, then reference to an unrelated regulatory definition would be unnecessary.

the agency deems minor—arose. *PDK Labs.*, 362 F.3d at 796. "This is at least some indication that Congress, in [§ 355(v)(3)(B)], did 'not directly address[] the precise question at issue' in this case." *Id*. (quoting *Chevron*, 467 U.S. at 843).[22]

Furthermore, ViroPharma provides scant support for its contention that the "ordinary and natural meaning [of 'conditions of use'] plainly encompasses *any* qualifications concerning the proper usage of the drug for its intended purpose, most obviously in the form of instructions or recommendations to the users of the drug." (Pl.'s Mot. at 14 (emphasis added).) Where courts address a complex statutory regime, laden with scientific language and other terms of art, dictionary definitions do not suffice to show an unambiguous meaning. *See, e.g.*, *Emerson v. Steffen*, 959 F.2d 119, 121 (8th Cir. 1992) (holding that a provision of Title XIX of the Social Security Act remained ambiguous even though a key phrase was defined by Webster's Third New International Dictionary because, "[w]hile we do not dispute the correctness of this definition, we do not believe that our agreement with the dictionary necessitates agreement with the plaintiffs").[23] And the fact "[t]hat a statute is susceptible of one construction does not render its meaning plain if it is also susceptible of another, plausible construction," as the Court concludes § 355(v)(3)(B) is. *PDK Labs.*, 362 F.3d at 796.

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[22] Tellingly, ViroPharma has not cited any agency or court decisions conferring Hatch-Waxman exclusivity in response to changes of the type that were made to Vancocin's labeling after the company's sNDA was approved in December 2011.

[23] *Cf. A.T. Massey Coal Co. v. Holland*, 472 F.3d 148, 160 (4th Cir. 2006) (concluding that, although a certain term had "several meanings, as demonstrated by . . . dictionary definitions," the provision at issue was not ambiguous because "statutory context and historical context . . . both reveal[ed] a uniform and precise meaning of the term"); *New Castle Cnty. v. Hartford Accident & Indem. Co.*, 933 F.2d 1162, 1193–94 (3d Cir. 1991) ("Although dictionaries are helpful insofar as they set forth the ordinary, usual meaning of words, they are imperfect yardsticks of ambiguity" because they "define words in the abstract, whereas" courts "must ascertain whether [a specific term] is ambiguous in the context of a" statute.).

Nor would an examination of the QI Act's purpose and legislative history undercut the FDA's interpretation. *See Nat'l Cable & Telecomms. Ass'n v. FCC*, 567 F.3d 659, 663 (D.C. Cir. 2009) (instructing courts to use "all 'traditional tools of statutory interpretation,' including 'text, structure, purpose, and legislative history,' to ascertain Congress' intent at *Chevron* step one" (quoting *Pharm. Research & Mfrs. of Am. v. Thompson*, 251 F.3d 219, 224 (D.C. Cir. 2001))); *PDK Labs.*, 362 F.2d at 798 n.4. To the contrary, as the Court's *Chevron* step-two analysis demonstrates, the FDA's interpretation is reasonable in large part because it furthers Congress's express purpose.

Having concluded that § 355(v)(3)(B) is ambiguous, the Court will move to *Chevron*'s second step and defer to the agency's reasonable interpretation of the provision as set forth in its response to ViroPharma's Citizen Petition. While ViroPharma may argue with that interpretation on policy grounds and present alternative readings of the provision's purpose and legislative history, such claims fail in the face of the agency's carefully considered decision. *See Serono Labs.*, 158 F.3d at 1321 (under *Chevron* step two, "courts are bound to uphold an agency interpretation as long as it is reasonable—regardless whether there may be other reasonable, or even more reasonable, views"); *Bush-Quayle '92 Primary Cmty., Inc. v. FEC*, 104 F.3d 448, 453 (D.C. Cir. 1997) ("When confronted with alternative sensible readings of an ambiguous statute the court is directed by *Chevron* to adopt the one the agency presents." (citing *Chevron*, 467 U.S. at 844)).

First, the legislative history supports the FDA's conclusion that Congress's purpose in the QI Act was to "balance the need to encourage development of new antibiotic drugs to combat the growing number of disease-resistant bacterial infections and the desire to ensure access to previously approved antibiotics through approval of generic versions of such antibiotics." (CP

Response at 69.) *See, e.g.*, 154 Cong. Rec. S9638, 9638 (daily ed. Sept. 26, 2008) (statement of Sen. Burr) ("Section 4 of [the bill which eventually became the QI Act], entitled 'Incentives for the Development of and Access to Certain Antibiotics,' is an important step forward to help spur research on new antibiotics and provide incentives for the creation of additional generic antibiotics."); 153 Cong. Rec. S5759, 5823 (daily ed. May 9, 2007) (statement of Sen. Kennedy) (in discussing what is now codified at § 355(v)(3)(B) when it was originally proposed in 2007, noting that the subsection "includes limits that would prevent pharmaceutical manufacturers from abusing the process to extend the life of old active ingredient drugs"); 153 Cong. Rec. S5630, 5630 (daily ed. May 7, 2007) (statement of Sen. Kennedy) ("The amendment strikes the right balance between innovation and access . . . ."). The FDA's interpretation of § 355(v)(3)(B) also furthers Congress's more general purpose of "'increas[ing] competition in the drug industry by facilitating the approval of generic copies of drugs.'" *Serono Labs.*, 158 F.3d at 1319 (D.C. (quoting *Mead Johnson Pharm. Grp. v. Bowen*, 838 F.2d 1332, 1333 (D.C. Cir. 1988)).

Second, especially in light of this legislative history, the FDA was within its discretion to apply a limiting principle so that Hatch-Waxman's exclusivity provisions do not apply to *all* approved changes that are "new" (in that they derive from new clinical investigations). As the FDA explained (*see* CP Response at 69), the general exclusivity period provided in § 355(j)(5)(F)(iv), which was made applicable to Old Antibiotics by § 355(v)(1)(A), is itself limited to that which is "new" about the given drug. Thus, for § 355(v)(3)(B) to be something more than mere surplusage, it must impose a further limitation on the availability of three-year exclusivity. *See, e.g., TRW Inc. v. Andrews*, 534 U.S. 19, 31 (2001) ("It is a cardinal principle of statutory construction that a statute ought . . . to be so construed that . . . no clause, sentence, or word shall be superfluous, void, or insignificant." (internal quotation marks and citations

omitted)).

Third, once the FDA reasonably determined that § 355(v)(3)(B) must impose a limitation, it was well-within the agency's authority to set the bounds of that limitation. "Such interpretive line drawing lies at the heart of *Chevron* deference." *Dickow v. United States*, 654 F.3d 144, 151 (1st Cir. 2011). Here, because the line the FDA drew was eminently "reasonable, *Chevron* requires" the Court to accept it. *Nat'l Cable & Telecomms. Ass'n v. Brand X Internet Servs.*, 545 U.S. 967, 981 (2005). The FDA, "[u]pon review[ing] the statute and the available legislative history," stated that it

> interprets [§] 355(v)(3)(B) to permit 3-year Hatch-Waxman exclusivity for Old Antibiotics only for a significant new use for an Old Antibiotic (such as a new indication for a previously approved antibiotic, or a new approval for a submitted but never previously approved antibiotic), not for refinements in labeling related to previously approved uses for Old Antibiotics.

(CP Response at 70.) ViroPharma has not demonstrated that this interpretation of "conditions of use," 21 U.S.C. § 355(v)(3)(B), is anything other than "'a reasonable policy choice for the [FDA] to [have made].'" *Nat'l Cable*, 545 U.S. at 986 (quoting *Chevron*, 467 U.S. at 845).

ViroPharma protests that the agency has gone too far, that the statute contemplates some limitation on exclusivity but not one with this much bite. In particular, ViroPharma argues at length that the FDA's letter ruling shows that the agency will only allow exclusivity where an sNDA specifies a new indication for an Old Antibiotic. (*See* Pl.'s Mot. at 19–24; Pl.'s Reply at 1–2.) But the Court "need not decide whether a construction [of § 355(v)(3)(B)] that resulted in these consequences would be unreasonable because [it does] not believe that these results follow from the construction the [FDA] adopted." *Nat'l Cable*, 545 U.S. at 997. The FDA cited a "new indication" only as an *example* of a "significant new use," as evidenced by the fact that "new indication" is contained in a parenthetical and introduced by the words "such as." (CP Response

at 70.) The crux of the agency's interpretation is "significant new use," and by its terms it clearly includes more than just new indications.

The FDA's application of its interpretation to Vancocin underscores this point. In concluding that "the revision of the Vancocin label . . . does not constitute approval for a condition of use that has not been 'approved before the date of [the QI Act's] enactment' within the meaning of [§ 355(v)(3)(B)]," the FDA determined that the new label (1) did "not constitute a significant expansion in the conditions of use of the product" to new "patient populations;" (2) did not "support[] a changed indication;" and (3) did not prescribe "a new dosing regimen." (*Id.* at 71–72.) Only the second factor relates to new indications, whereas the first and third factors confirm that "significant new use" is broader. The FDA's construction "does not leave all" changes in a drug's labeling "exempt from" Hatch-Waxman exclusivity. *Nat'l Cable*, 545 U.S. at 997. As such, it is nowhere near as "radical" as ViroPharma suggests in its motion. (Pl.'s Mot. at 21.[24])

Finally, given this Court's conclusion that the FDA's interpretation of § 355(v)(3)(B) is permissible under *Chevron*, it follows that ViroPharma's protests regarding the purported significance of Vancocin's new label are unavailing. ViroPharma has failed to demonstrate that Watson Laboratories is incorrect when it argues that "[u]nder the sNDA language, patients [are]

[24] ViroPharma concedes as much in its reply brief. There, ViroPharma acknowledges that the FDA, in opposing its motion before this Court, "offers a *perfectly acceptable* definition of 'conditions of use'—they 'encompass how, to whom, and for which purposes a drug product is used,'" but argues that the agency, in denying its Citizen Petition, did not use this definition. (Pl.'s Reply at 1–2 (emphasis added) (quoting FDA Opp'n at 21; citing *SEC v. Chenery Corp.*, 318 U.S. 80, 93–94 (1943)).) As the foregoing discussion makes clear, the FDA indeed defined and applied "conditions of use" in terms of how a drug is used (the third factor above), to whom it is prescribed (the first factor), and for what purposes (the second factor). Furthermore, this shows that ViroPharma may not rely on *Chenery*, as in upholding the FDA's interpretation, the Court has considered only the very "grounds upon which the agency acted." 318 U.S. at 94.

being given the same drug, in the same dosage, and in the same method of administration as had been given before the label was changed." (Watson Opp'n at 7.) Because the agency was within its discretion to interpret § 355(v)(3)(B) as denying exclusivity where a pioneer manufacturer puts forward only "refinements in labeling related to previously approved uses for Old Antibiotics" (CP Response at 70), then it was certainly entitled to conclude, on the basis of its expertise, that the changes to the Vancocin labeling do nothing more than "support[] and refine[]" materials "regarding already approved conditions of use." (*Id.* at 71.) The FDA's decision "involve[s] a subject matter [that] is technical, complex, and dynamic," *Nat'l Cable*, 545 U.S. at 1002–03 (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 (3d Cir. 1995)). Accordingly, it "is entitled to a high level of deference from" reviewing courts, *id.* (internal quotation marks and citation omitted), and applying this standard, the Court concludes that ViroPharma is not likely to succeed on the merits of its statutory exclusivity claim.

B. ViroPharma's Bioequivalence Claim

The "FDA's 'judgment[] as to what is required to ascertain the safety and efficacy of drugs,'" including its decisions regarding bioequivalence, also "'fall[s] squarely within the ambit of the FDA's expertise and merit[s] deference from'" reviewing courts. *A.L. Pharma*, 62 F.3d at 1490 (quoting *Schering Corp.*, 51 F.3d at 399); *see Graceway Pharm., Inc. v. Sebelius*, 783 F. Supp. 2d 104, 111 (D.D.C. 2011) (applying a "'high degree of deference . . . to the FDA's determinations regarding which methodologies it determines are needed to test the bioequivalency of a given generic'" (quoting *Astellas Pharma U.S., Inc. v. FDA*, 642 F. Supp. 2d

10, 19 (D.D.C. 2009)). Moreover, it is undisputed that the FDA has broad statutory authority to establish bioequivalence standards, including permitting *in vitro* testing. 21 U.S.C. § 355(j)(8)(C). (*See* Pl.'s Mot. at 33.) Nor does ViroPharma challenge the FDA's scientific conclusion that *in vitro* testing is appropriate in these circumstances or request that the Court ignore the well-established principles of deference described above.

Rather, ViroPharma argues that the FDA violated its *regulations* in approving vancomycin ANDAs without *in vivo* bioequivalence testing. This Court described the dispute in *ViroPharma I*:

> 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. . . . The FDA, however, argues that there is no such default requirement for *in vivo* data to establish bioequivalence. . . . Instead, the FDA relies on language in 21 C.F.R. § 320.24[(a)], which states that "FDA may require *in vivo* or *in vitro* testing, or both, to . . . establish the bioequivalence of specific drug products." [The] 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.

777 F. Supp. 2d at 143.

As described above (*see supra* Section II.C.2), in denying ViroPharma's Citizen Petition, the FDA rejected each of plaintiff's arguments. (*See* CP Response at 52–56.) The agency set forth its interpretation of its regulations and justified that interpretation with reference to the regulatory text, structure, and history. The FDA carefully explained why the regulations contain no default requirement for *in vivo* bioequivalence data, and therefore why no waiver was required for the vancomycin ANDAs. (*Id.*) The agency then stated that, in the alternative, even if such a waiver were required, it would issue it to generic vancomycin applicants "for good

cause" and in order to "protect[] . . . the public health." 21 C.F.R. § 320.22(e).[25] (*See* CP Response at 59–60.) The FDA expressly found that the waiver was appropriate because, among other factors, "vancomycin is one of only two FDA-approved treatments for the fast-moving, life-threatening colitis associated with CDAD," such that "[t]he availability of safe and effective generic vancomycin capsules would" protect the public health and further "the fundamental purposes of Hatch-Waxman." (*Id.*[26])

An agency's interpretation of its own regulations is "controlling" unless it is "plainly erroneous or inconsistent with the regulation." *Auer*, 519 U.S. at 461 (internal quotation marks

[25] ViroPharma tries to narrow the applicability of 21 C.F.R. § 320.22(e) by relying on an explanatory statement accompanying the provision's promulgation in the *Federal Register*. *See* Final Rule, 42 Fed. Reg. 1,624, 1,642 (Jan. 7, 1977). But contrary to ViroPharma's arguments, its "alternative reading" of the regulation is not "compelled" by any "indication[] of the [Commissioner's] intent at the time of the regulation's promulgation." *Gardebring v. Jenkins*, 485 U.S. 415, 430 (1988). Rather, the explanatory statement confirms the FDA's position that it will not insist on, or even permit, *in vivo* bioequivalence data where such data does not demonstrate a drug's safety and effectiveness, but where it is otherwise known that the drug is suitable and needed. *See* 42 Fed. Reg. at 1,642 (section 320.22(e) allows the "FDA to permit the continued marketing of medically important drug products while adequate methodology is being developed or bioavailability studies are being conducted"). Second, and more importantly, the statement predates the Hatch-Waxman generic drug approval amendment and the attendant regulations that allow FDA to determine which bioequivalence testing is appropriate in a particular situation. *See* Final Rule, 57 Fed. Reg. 17,950, 17,951 (April 28, 1992) (implementing Hatch-Waxman and leaving in place the broad language in 21 C.F.R. § 320.22(e)).

[26] In its response to ViroPharma's Citizen Petition, the FDA also stated that a waiver under 21 C.F.R. § 320.22(e) would protect the public health because the "high demand and high cost" of Vancocin had caused doctors to resort to administering injectable vancomycin orally, despite the fact that the injectable "formulation has never been approved for oral use." (CP Response at 59.) At oral argument, counsel for ViroPharma argued that the FDA has, in fact, approved injectable vancomycin for oral use. The FDA subsequently admitted error. (*See* Pl.'s Reply at 5 ("As the Government has now conceded, that reasoning . . . is 'incorrect,' as 'the FDA-approved labeling for the parenteral (*i.e.*, injectable) dosage form of vancomycin HCl provides for oral administration of the drug.'" (quoting an April 19, 2012 email from the FDA's counsel)). Accordingly, in rejecting ViroPharma's bioequivalence claim, the Court does not rely on the FDA's erroneous second argument for waiver under 21 C.F.R. § 320.22(e).

and citation omitted). Especially given the scientific expertise driving the FDA's well-reasoned decision in this matter, *see Serono Labs.*, 158 F.3d at 1320, the Court concludes that ViroPharma is unlikely to prevail on the merits of its bioequivalence claim. The FFDCA and a number of the FDA's own regulations grant the agency wide discretion in "determin[ing] whether bioequivalence has been established." *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 217 (D.D.C. 1996).[27] Furthermore, in addition to the provision on which the agency specifically relied, 21 C.F.R. § 320.22(e), "waivers" of any *in vivo* bioequivalence requirement for ANDAs may be permitted pursuant to, *inter alia*, §§ 320.21(b)(2), 320.21(f), 320.22, and 320.24(b)(6). Where the regulations allow so many "waivers," the "default" position that ViroPharma argues is difficult to discern.[28] In light of the deference owed, the Court has no basis for overruling the

[27] At oral argument, counsel for ViroPharma acknowledged that Judge Urbina's decision in *Bristol-Myers* supports the FDA's position but argued that it was wrongly decided. Counsel, however, could not cite any authority in support of ViroPharma's reading of the regulations.

[28] ViroPharma is of course correct that an agency's interpretation of its own regulations is owed no deference if that interpretation is inconsistent with the agency's "intent at the time of the regulation's promulgation," *Gardebring*, 485 U.S. at 430, and that "the preamble to a regulation is evidence of an agency's contemporaneous understanding of its proposed rules." *Wyoming Outdoor Council v. U.S. Forest Serv.*, 165 F.3d 43, 53 (D.C. Cir. 1997). (*See* Pl.'s Reply at 5.) However, the FDA's lengthy preamble to the rules at issue here contains statements that support both parties' positions. ViroPharma points to the agency's statement that, "[i]n general, the submission of *in vivo* data is required." 57 Fed. Reg. at 17,976. The FDA, on the other hand, relies on its statement that

> Bioequivalence can be established by pharmacodynamic measurement as well as by *in vitro* techniques and bioequivalence studies with clinical endpoints. The preferred method for establishment of bioequivalence . . . is determined on a case-by-case basis, depending on the drug under study.

57 Fed. Reg. at 17,972. In the end, these dueling passages do little to illuminate the Secretary's intent, and only underscore the fact that the regulations allow the FDA significant leeway to make decisions about bioequivalence based on its particular expertise.

FDA's interpretation of 21 C.F.R. Part 320. Whether it is the "most natural" interpretation is immaterial. *Pauley v. BethEnergy Mines, Inc.*, 501 U.S. 680, 702 (1991); *see Young v. Cmty. Nutrition Inst.*, 476 U.S. 974, 980 (1986). Because it is not clearly erroneous, the Court must defer to it.

IV. IRREPARABLE HARM

ViroPharma's showing of irreparable injury is especially unpersuasive. "The irreparable injury requirement erects a very high bar for a movant." *Coal. for Common Sense in Gov't Procurement v. United States*, 576 F. Supp. 2d 162, 168 (D.D.C. 2008).[29] The injury must "be both certain and great; it must be actual and not theoretical." *Wis. Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985) (per curiam). Of relevance here, economic loss qualifies only if it "threatens the very existence of the movant's business," *id.*,[30] or where the movant, in addition to making a very strong showing of likely success on the merits, "has little hope of obtaining 'adequate compensatory or other corrective relief at a later date' if the injunction does not issue." *O'Donnell Constr. Co. v. Dist. of Columbia*, 963 F.2d 420, 428 (D.C. Cir. 1992) (quoting *Va. Petroleum Jobbers Ass'n v. Fed. Power Comm'n*, 259 F.2d 921, 925 (D.C. Cir. 1958)); *cf. Chaplaincy*, 454 F.3d at 297 (to be irreparable, an injury "must be beyond remediation," and

[29] Albeit in a concurring opinion, two Circuit judges have stated that, notwithstanding courts' traditional sliding scale analysis of the preliminary injunction factors, the Supreme Court in *Winter* "ruled that the movant *always* must show a likelihood of irreparable harm." *Davis*, 571 F.3d at 1296 (emphasis added) (Kavanaugh, J., concurring) (citing *Winter*, 555 U.S. at 21–22); *accord Am. Trucking Ass'ns v. City of Los Angeles*, 559 F.3d 1046, 1052 (9th Cir. 2009). At minimum, a party seeking a preliminary injunction must "demonstrate at least 'some injury'" to succeed on its motion "since '[t]he basis of injunctive relief in the federal courts has always been irreparable harm.'" *CityFed Fin. Corp. v. Office of Thrift Supervision*, 58 F.3d 738, 747 (D.C. Cir. 1995) (some internal quotation marks omitted) (quoting *Sampson v. Murray*, 415 U.S. 61, 88 (1974)).

[30] *See Astellas Pharma*, 642 F. Supp. 2d at 22 ("[I]t is well-settled that economic loss alone will rarely constitute irreparable harm." (citing *Wis. Gas Co.*, 758 F.2d at 674)).

"'[t]he possibility that adequate compensatory . . . relief will be available at a later date, in the ordinary course of litigation weighs heavily against a claim of irreparable harm'" (quoting *Wis. Gas Co.*, 758 F.2d at 674)); *accord Nat'l Med. Care, Inc. v. Shalala*, No. 95-860, 1995 WL 465650, at *3 (D.D.C. June 6, 1995) (concluding that, where plaintiffs had demonstrated an "overwhelming likelihood that" they would prevail on the merits, they had also demonstrated irreparable injury despite alleging threatened economic harms because upon prevailing they would not be able to "bring an action to recover" their damages). Where a plaintiff cannot recover money damages from the government owing to sovereign immunity, for example, some courts have held that "any loss of income suffered by a plaintiff is irreparable *per se*." *Feinerman v. Bernardi*, 558 F. Supp. 2d 36, 51 (D.D.C. 2008) (citing *United States v. New York*, 708 F.2d 92, 93–94 (2d Cir. 1983)); *accord Woerner v. U.S. Small Bus. Admin.*, 739 F. Supp. 641, 650 (D.D.C. 1990) (finding economic loss constituted irreparable harm "because the government is immune from damage suits").

Yet, irreparability aside, it remains incumbent on plaintiffs to demonstrate, first, that they are threatened with serious *injury*. *See, e.g.*, *N. Air Cargo v. USPS*, 756 F. Supp. 2d 116, 125 n.6 (D.D.C. 2010) ("While the Court agrees that irrecoverable financial loss may constitute irreparable injury in some cases, this Court is of the opinion that a party asserting such a loss is not relieved of its obligation to demonstrate that its harm is 'great.'" (quoting *Wis. Gas Co.*, 758 F.2d at 674)); *Gulf Oil Corp. v. Dep't of Energy*, 514 F. Supp. 1019, 1026 (D.D.C. 1981) (to qualify, injury must be "more than simply irretrievable; it must also be serious in terms of its effect on the plaintiff").

ViroPharma has not made the requisite showing here. It alleges that "if injunctive relief is not granted," its "revenue from Vancocin will likely be significantly and rapidly eroded, as its

share of the market for vancomycin capsules is taken over by generic competition." (Pl.'s Mot. at 41 (citing Rowland Decl. ¶¶ 26–32); *see* Rowland Decl. ¶ 26 ("If FDA approval to market generic copies of Vancocin is not immediately enjoined and, as a result, if the generic companies continue marketing generic copies of Vancocin, ViroPharma will suffer immediate and irreparable injury from a substantial decrease in ViroPharma's sales of Vancocin.").) Courts have consistently held, however, that such vague allegations do not satisfy the high irreparable injury standard. *See Astellas Pharma*, 642 F. Supp. 2d at 21–23 (concluding that plaintiff pioneer drug company had not established irreparable injury where sales of the RLD constituted "approximately half of its total U.S. revenue for [a given] fiscal year" (collecting cases)).[31] ViroPharma cannot escape the fact that "'[t]he mere existence of competition is not irreparable harm, in the absence of substantiation of severe economic impact.'" *Bristol-Myers Squibb Co.*, 923 F. Supp. at 221 (quoting *Wash. Metro. Area Tran. Comm'n v. Holiday Tours, Inc.*, 559 F.2d 841, 843 n.3 (D.C. Cir. 1977)).

[31] Cases holding that "'[w]here a plaintiff cannot recover damages from an agency because the agency has sovereign immunity, '*any* loss of income suffered by [the] plaintiff is irreparable *per se*'" are thus inapplicable here, where ViroPharma's allegations of injury are too vague to be credited. *Smoking Everywhere, Inc. v. FDA*, 680 F. Supp. 2d 62, 77 n.9 (D.D.C. 2010) (emphasis added) (quoting *Feinerman*, 558 F. Supp. 2d at 51). *Smoking Everywhere* is also distinguishable on its facts, as there the court's irreparable injury determination was based in large part on the fact "that the potential economic loss and loss of good will are substantial, especially for a fledgling company like [plaintiff, founded just one year prior,] that has only one product line." *Id.* at 76. ViroPharma, by contrast, was founded in 1994 and has at least four product lines at present and is currently developing three more. (Rowland Decl. ¶¶ 4, 7, 10.) Finally, if *Feinerman* would hold that ViroPharma has shown irreparable injury because it has put forward some allegation of threatened harm, however vague, 558 F. Supp. 2d at 51,this Court is persuaded by Judge Sullivan that "prospective injunctive relief would often cease to be an 'extraordinary remedy' in cases involving government defendants." *N. Air Cargo*, 756 F. Supp. 2d at n.6 (quoting *Winter*, 555 U.S. at 22); *see also Gulf Oil Corp.*, 514 F. Supp. at 1025–26 (surveying the case law and concluding that, although "there is some appeal to the proposition that any damage, however slight, which cannot be made whole at a later time, should justify injunctive relief," the better rule is to require plaintiffs to demonstrate a "serious" injury because "some concept of magnitude . . . is implicit" in the standards governing preliminary injunctions).

ViroPharma also claims that it will suffer reputational injury if the approved vancomycin generics prove "unsafe or ineffective." (Pl.'s Mot. at 42.) This allegation is too speculative. *See Astellas Pharma*, 642 F. Supp. 2d at 23 (finding no irreparable harm where "plaintiff's concerns about the potential loss of goodwill and reputation are founded entirely on its belief that the approved generic [drug] may be more harmful than [its own brand-name drug], a belief that . . . lacks evidentiary support and is entirely speculative"); *Bristol-Myers Squibb Co.*, 923 F. Supp. at 221 (holding that the plaintiff failed to establish irreparable harm because "there is nothing before the court which would lead it to conclude that [the competing drug] will cause any harmful health effects"). Because ViroPharma has not alleged that there are in fact any quality or safety issues associated with generic vancomycin products, its fear of reputational injury can be dismissed out of hand. Moreover, the suggestion that patients and physicians would mistake generic vancomycin and any associated negative occurrences for Vancocin ignores that fact that "[i]f some confusion were to occur, [ViroPharma] has the tools that any manufacturer would have at its disposal to establish its product uniquely in the minds of customers and their doctors." *Somerset Pharm., Inc. v. Shalala*, 973 F. Supp. 443, 455 (D. Del. 1997).

Most importantly, as to both its alleged economic and reputational harms, ViroPharma's claims are belied by its own statements. The day after the vancomycin ANDAs were approved, ViroPharma announced to investors that three other drugs, not Vancocin, were the company's "growth drivers." (*See* FDA Opp'n, Ex. A at 9 (transcript of April 10, 2012 call with ViroPharma Chairman, President, and CEO Vin Milano, other ViroPharma officials, and investor representatives); *see id.* at 13 (stating that Cinryze in particular is "the anchor and remains the anchor with or without Vancocin in the mix"); *see also* Rowland Decl. ¶ 31 (reporting that 2011 sales of Cinryze amounted to "approximately $251 million and . . . 46% of

ViroPharma's revenue).)

The company also announced that it would "be launching [its] own authorized generic" of Vancocin "soon." (FDA Opp'n, Ex. A at 6.[32]) Indeed, ViroPharma's CEO stated that the company had been "prepar[ing] an authorized generic for years" and that "the work [is] in place and essentially on the shelf waiting for the need to deploy it" and, in response to a question, clarified that "[t]here is no need to file an[] ANDA for an authorized generic." (*Id.* at 7.) He further stated that the company's officials had "spent [their] entire lives assuming Vancocin was going to go away" and had "been building the company expecting it someday to go away." (*Id.* at 8.[33]) In fact, not a day later—and two days before filing the present lawsuit—ViroPharma launched an authorized generic version of Vancocin to be sold by Prasco Laboratories. (*See* Watson Opp'n at 10; *id.*, Ex. 3 (April 11, 2012 press release from Prasco announcing that it "will exclusively sell and distribute the authorized generic version of Vancocin . . . as part of an agreement with ViroPharma" (capitalization altered)); *see also* Alvogen Opp'n, Hill Decl. ¶¶ 26–29 (as of April 14, 2012, ViroPharma's authorized generic for Vancocin had established itself as a dominant player in the newly formed vancomycin generic market).)

Perhaps most damning to ViroPharma's position is its CEO's rosy description, at the end

[32] An "authorized generic" is a generic drug that is marketed by the NDA-holder—in this case, ViroPharma—as opposed to a generic marketed by the ANDA-holder, such as defendants-intervenors. *See* 21 C.F.R. § 314.3(b).

[33] *See Altana Pharma AG v. Teva Pharm. USA, Inc.*, 532 F. Supp. 2d 666, 682 (D.N.J. 2007) (concluding that there was no showing of irreparable injury where, "[a]lthough [the RLD] ma[de] up a large portion of [plaintiff's] sales, [plaintiff] ha[d] known for over three years . . . that" its period of exclusivity would be ending; stating that "[i]t is difficult to accept that [plaintiff] does not have a business plan in place to deal with the introduction of a generic version of [the RLD], whether that includes [plaintiff's] marketing of its own authorized generic version of [the RLD] or some other business strategy"); *id.* at 682 n.26 (relying in part on the plaintiff company's executive's statements to investors in order to discern the plaintiff's plans).

of the April 10 call, of the company's immediate future:

> [W]e have a very strong balance sheet. We have cash flow from the Cinryze business. We have a credit facility that allows us a low cost of capital . . . to pursue the acquisition of things that we believe fit the strategic intent of the company. And we still have Vancocin cash flow[;] it doesn't go to zero.

(*Id.* at 13.[34])

ViroPharma has failed to demonstrate irreparable injury.

V. BALANCE OF EQUITIES

In considering whether the balance of equities favors granting a preliminary injunction, courts consider whether an injunction would "'substantially injure other interested parties.'" *McGinn*, 786 F. Supp. 2d at 144 (quoting *Chaplaincy*, 454 F.3d at 297); *see Winter*, 555 U.S. at 24 (courts 'must balance the competing claims of injury and must consider the effect on each party of the granting or withholding of the requested relief.'" (quoting *Amoco Prod. Co. v. Village of Gambell*, 480 U.S. 531, 542 (1987)). Here, defendants-intervenors have all demonstrated that they would suffer serious harm were the Court to grant the injunction that ViroPharma requests.

First, the FFDCA entitles generic drug companies to FDA approval of their ANDAs when all requisite conditions have been met, *see* 21 U.S.C. § 355(j)(4), and this Court has held that ViroPharma is unlikely to prevail on its claim that the generic vancomycin ANDAs were

[34] While the CEO addressed ViroPharma's future in terms of its entire drug portfolio, the company's CFO, in the declaration that purports to substantiate plaintiff's claim to irreparable injury, carefully limited his statements to the market for Vancocin. (*See, e.g.*, Rowland Decl. ¶ 29 ("*Without the revenue from Vancocin sales*, ViroPharma will have a restricted ability to raise capital . . . ." (emphasis added)); *id.* ¶ 32 ("While ViroPharma may market an authorized generic form of Vancocin, in a fully genericized market ViroPharma believes that *sales of Vancocin* may amount to less than $20 million." (emphasis added)).) Moreover, the CFO's figures do not account for any expected revenues from the authorized generic that ViroPharma has already begun to sell.

somehow insufficient. (*See supra* Section III.) Second, all three defendants-intervenors would lose the substantial benefits of their early entry into this market, and furthermore would suffer significant costs, if the Court were to order the FDA to withdraw approval of their vancomycin products. (*See* Akorn Opp'n, Bonaccorsi Decl. ¶¶ 16–17; Alvogen Opp'n, Hill Decl. ¶¶ 29, 32, 25, 37; Watson Opp'n, Boyer Decl. ¶ 8.) It is perhaps for this reason that the parties have only been able to find one instance, among all the decisions in this circuit addressing a pioneer drug manufacturer's challenge to the FDA's approval of an ANDA, where a court ordered the agency to withdraw its approval after the generic had hit the market. *See Serono Labs., Inc. v. Shalala*, 974 F. Supp. 29, 37 (D.D.C. 1997). There, the Circuit immediately stayed the issuance of the preliminary injunction pending its resolution of defendants' appeal, and ultimately reversed. *Serono Labs.*, 158 F.3d at 1316, 1327. To the best of the parties' and the Court's knowledge, the extraordinary relief that ViroPharma seeks is unprecedented in this jurisdiction.[35]

Finally, the "effect of an injunction on [defendants-intervenors] would be dramatically greater than the harm to [ViroPharma]." *Bristol-Myers Squibb Co.*, 923 F. Supp. at 221. Regardless of whether this Court grants plaintiff the relief it requests, ViroPharma will be able to continue selling both Vancocin and its authorized generic version. The same cannot be said for defendants-intervenors, all of whom expect to earn substantial revenues from vancomycin. (*See*

[35] Following oral argument, counsel for ViroPharma supplied two citations to cases from other circuits where courts issued preliminary injunctions against already introduced generic drugs. (*See* April 20, 2012 email from ViroPharma's counsel (citing *Sanofi-Synthelabo v. Apotex, Inc.*, 488 F. Supp. 2d 317 (S.D.N.Y.), *aff'd*, 470 F.3d 1368 (Fed. Cir. 2006); *Sciele Pharma Inc. v. Lupin Ltd.*, No. 09-cv-037, 2011 WL 6097741 (D. Del. Dec. 6, 2011)).) As counsel acknowledged, however, "these are patent cases" (*id.*), where a party that "clearly establishes likelihood of success on the merits 'receives the benefit of a presumption on the [irreparable harm]' factor," and therefore an advantage on the balance of equities factor as well. *Sanofi-Synthelabo*, 488 F. Supp. 2d at 342 (quoting *Reebok Int'l Ltd. v. J. Baker, Inc.*, 32 F.3d 1552, 1556 (Fed. Cir. 1994)). Accordingly, these cases provide little guidance to this Court.

Akorn Opp'n, Bonaccorsi Decl. ¶¶ 7, 19; Alvogen Opp'n, Hill Decl. ¶ 24, 30–34; Watson Opp'n, Boyer Decl. ¶ 7.)

VI. THE PUBLIC INTEREST

In exercising their "'sound discretion'" when deciding a motion for a preliminary injunction, courts are instructed to "'pay particular regard for the public consequences in employing the extraordinary remedy of injunction.'" *Winter*, 555 U.S. at 24 (quoting *Weinberger v. Romero-Barcelo*, 456 U.S. 305, 312 (1982)). Here, as in *Serono Laboratories*, the public interest factor "is inextricably linked with the merits of the case." 158 F.3d at 1326. ViroPharma may be correct that "the public always has an interest in agency compliance with the law." (Pl.'s Mot. at 44.) However, because this Court has held that ViroPharma "is not likely to establish that" the FDA erred in denying its Citizen Petition and approving ANDAs for generic vancomycin, "public interest considerations weigh against an injunction." *Serono*, 158 F.3d at 1326. As discussed above, Hatch-Waxman and the QI Act aim to increase competition in the drug industry and "'to make available more low cost generic drugs." *Id.* (quoting H.R. Rep. No. 98-857, pt. 1, at 14 (1984)). "Congress' purpose is directly implicated here," *id.*, as generic vancomycin sells for considerably less than Vancocin. (*See* Watson Opp'n, Boyer Decl. ¶ 9 (providing, under seal, proprietary, comparative pricing data for Watson's vancomycin generic); Rowland Decl. ¶ 27 ("generics typically cost 50–70% less than the grand-name drug"); *see also* Akorn Opp'n, Bonaccorsi Decl. ¶ 26 ("Publicly available documents reveal that ViroPharma has increased the price of Vancocin seven times since January 2009 to the present, from approximately $442 to $1284 per 20-unit box for 250 mg Vancocin . . . .").[36]) The public "has a

[36] The FDA's own guidance confirms the effect of the introduction of generic drugs on market prices. While the first generic competitor on the market prices its product only slightly lower

well-recognized interest in receiving generic competition to brand-name drugs as soon as possible . . . and a delay in the marketing of [the generic] drug could easily be against the public interest in reduced prices." *Biovail Corp. v. FDA*, 519 F. Supp. 2d 39, 50 (D.D.C. 007) (some alterations in the original; internal quotation marks and citation omitted). Therefore, it is "not in the public interest for the Court to grant a preliminary injunction preventing these generic drugs from being sold on the market." *Hill Dermaceuticals, Inc. v. FDA*, --- F. Supp. 2d ----, ----, 2011 WL 6005195, at *10 (D.D.C. 2011).

CONCLUSION

For these reasons, it is clear that ViroPharma is not entitled to a preliminary injunction. ViroPharma has not demonstrated that it is likely to succeed on the merits of its claims; it has not shown irreparable injury; and the balance of the equities and the public interest both tilt against injunctive relief. The Court will deny ViroPharma's motion. A separate Order accompanies this Memorandum Opinion.

/s/
ELLEN SEGAL HUVELLE
United States District Judge

Date: April 23, 2012

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than that of the pioneer manufacturer, "the appearance of a second generic manufacturer reduces the average generic price to nearly half the brand name price," and if "a large number of generic drug manufacturers" enter the market, "the average generic drug price falls to 20% of the branded drug price and lower." FDA, Generic Competition and Drug Prices, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm (last visited April 23, 2012).