UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

COBALT LABORATORIES, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 08-798
	)	
FOOD AND DRUG ADMINISTRATION, *et al*.,	)	
	)	
	)	
Defendants.	)	
	)	

DEFENDANTS' MEMORANDUM IN OPPOSITION TO PLAINTIFF'S MOTION FOR A TEMPORARY RESTRAINING ORDER

INTRODUCTION

Plaintiff, Cobalt Laboratories, Inc. ("Cobalt"), a generic drug manufacturer, filed this motion against the U.S. Food and Drug Administration ("FDA")[1] challenging FDA's implementation of certain of the drug approval provisions of the Federal Food, Drug, and Cosmetic Act ("FCDA") with respect to Cobalt's generic version of Precose (a drug that helps lower blood glucose in certain diabetes patients) because that means that Cobalt has forfeited 180 days of exclusivity to market its product free from competition by other generic versions of Precose. FDA's implementation, however, is consistent with the plain language of the statute, and Cobalt's arguments that this Court should consider policy concerns to reach a different conclusion than that dictated by the plain language of the statute should be rejected.

In addition, Cobalt is not, nor does Cobalt claim it is, being barred entirely from the marketplace. Rather, Cobalt's only claimed injury is the loss of 180 days of exclusivity (i.e., a

[1] Michael O. Leavitt, Secretary, U.S. Department of Health and Human Services ("HHS"),and Andrew C. von Eschenbach, Commissioner, FDA, are also named defendants.

temporary monopoly in the generic market), which constitutes merely an economic loss that is far from the irreparable harm necessary to justify a temporary restraining order. Nor has Cobalt shown that the $9 million dollar loss it speculates will occur if Bayer does not launch its own generic version of acarbose, threatens the existence of its business. Indeed, Cobalt's President studiously avoids putting its projected financial loss in the context of total corporate sales. For all of these reasons, Cobalt's motion for a temporary restraining order ("Pl. TRO Mem.") should be denied.

BACKGROUND

I. Statutory And Regulatory Framework

A. NDAs

Under the FDCA, pharmaceutical companies seeking to market "pioneer" or "innovator" drugs must first obtain FDA approval by filing a new drug application ("NDA") containing extensive scientific data demonstrating the safety and effectiveness of the drug. 21 U.S.C. §§ 355(a), (b). An NDA applicant must also submit information on any patent that claims the drug, or a method of using the drug, and for which a claim of patent infringement could reasonably be asserted against an unauthorized party. 21 U.S.C. §§ 355(b)(1), (c)(2). FDA must publish the patent information it receives, and does so both in print and electronically, in the Orange Book. Id.; see also 21 C.F.R. § 314.53(e).

B. ANDAs

The Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Amendments"), codified at 21 U.S.C. § 355 and 35 U.S.C. §§ 156, 271, and 282, permits manufacturers to submit abbreviated new drug applications ("ANDAs") requesting

approval of generic versions of approved drug products. 21 U.S.C. § 355(j). The Hatch-Waxman Amendments were intended to balance encouraging innovation in the development of new drugs with accelerating the availability to consumers of lower cost alternatives to innovator drugs. See H.R. Rep. No. 98-857 (Part I), 98th Cong., 2d Sess. at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647-48; see also, e.g., Tri-Bio Labs., Inc. v. United States, 836 F.2d 135, 139 (3d Cir. 1987).

ANDA applicants need not submit clinical data to demonstrate the safety and efficacy of the generic product, as in an NDA. See 21 U.S.C. § 355(j). Rather, an ANDA relies on FDA's previous findings that the product approved under the NDA is safe and effective, and the FDCA sets forth in detail the information an ANDA must contain. See 21 U.S.C. § 355(j)(2)(A). Among other items, an ANDA must include information showing that the generic drug product is bioequivalent to the pioneer drug product. 21 U.S.C. §§ 355(j)(2)(A)(iv), (j)(4)(F); 21 C.F.R. §§ 314.127(a)(6)(i), 314.94(a)(7). A drug is considered to be bioequivalent if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug . . .," 21 U.S.C. § 355(j)(8)(B)(i), and FDA has significant discretion in determining appropriate methodologies to demonstrate bioequivalence. See 21 U.S.C. § 355(j)(8)(C); see also 21 C.F.R. § 320.21(b)(2); 21 C.F.R. §§ 320.24(a), (b).

1. Patent protections and 180-day exclusivity

The timing for approval of ANDAs depends, in part, on statutory patent protections afforded to the innovator drug. Among other things, an ANDA must contain one of four specified certifications for each patent that "claims the listed drug" or claims "a use for such

listed drug for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(vii).[2]

This certification must state one of the following:

> (I) that the required patent information relating to such patent has not been filed;
> (II) that such patent has expired;
> (III) that such patent will expire on a particular date; or
> (IV) that such patent is invalid or will not be infringed by the drug for which approval is being sought.

21 U.S.C. § 355(j)(2)(A)(vii). If an applicant wishes to challenge the validity of a patent, or to claim that the patent would not be infringed by the product covered by the ANDA, the applicant must submit a certification pursuant to paragraph IV of this provision. See 21 U.S.C. § 355(j)(2)(A)(vii)(IV).[3] The applicant must also provide notice of its so-called "paragraph IV certification" to the NDA holder and the patent owner explaining the factual and legal basis for the applicant's opinion that the patent is invalid or not infringed. 21 U.S.C. § 355(j)(2)(B).

The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of infringement. 35 U.S.C. § 271(e)(2)(A). This enables the NDA holder and patent owner to sue the ANDA applicant. If such a suit is brought within 45 days of the date notice of the certification was received by the patent owner or NDA holder, FDA must stay approval of the ANDA for 30 months from that date (commonly referred to as the "30-

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[2] FDA has defined the "listed drug" to mean the approved new "drug product." 21 C.F.R. § 314.3(b).

[3] If a certification is made under paragraph I or II indicating that patent information pertaining to the drug or its use has not been filed with FDA or that the patent has expired, the ANDA may be approved immediately. 21 U.S.C. § 355(j)(5)(B)(i). A paragraph III certification indicates that the ANDA applicant does not intend to market the drug until after the applicable patent has expired, and approval of the ANDA may be made effective on the expiration date. 21 U.S.C. § 355(j)(5)(B)(ii).

month stay"), unless a final court decision is reached earlier in the patent case or the court orders a longer or shorter period. 21 U.S.C. § 355(j)(5)(B)(iii). If no action is brought within the requisite 45-day period, FDA may approve an ANDA with a paragraph IV certification effective immediately, provided that other conditions for approval have been met. 21 U.S.C. § 355(j)(5)(B)(iii); 21 C.F.R. § 314.107(f)(2).

In certain circumstances, the statute provides an incentive and reward to generic drug manufacturers that expose themselves to the risk of patent litigation. It does so by granting a 180-day period of marketing exclusivity (*vis-à-vis* other ANDA applicants) to the manufacturer who is first to file an ANDA containing a paragraph IV certification to a listed patent, provided certain conditions are met. 21 U.S.C. § 355(j)(5)(B)(iv); see Teva Pharm. Indus. v. Crawford, 410 F.3d 51, 52 (D.C. Cir. 2005); Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1064 (D.C. Cir. 1998); Mylan Pharm., Inc. v. Henney, 94 F. Supp. 2d 36, 40 (D.D.C. 2000), vacated as moot sub nom. Pharmachemie B.V. v. Barr Labs., Inc., 276 F.3d 627 (D.C. Cir. 2002). The statutory provision governing 180-day exclusivity provides:

> If the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection [containing] such a certification, the application shall be made effective not earlier than one hundred and eighty days after-
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> > (I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or
> >
> > (II) the date of a decision of a court in an action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed,
>
> whichever is earlier.

21 U.S.C. § 355(j)(5)(B)(iv).[4] Thus, under the statute, an ANDA applicant with a patent certification that is "previous" to all others for that patent may become eligible for a 180-day exclusivity period. During that period, it can market its product and approvals of other ANDAs for the same product are held in abeyance. This 180-day exclusivity is triggered by the earlier of (i) the ANDA applicant's first commercial marketing of the drug (the "commercial marketing trigger"), or (ii) a decision of a court finding the patent at issue invalid or not infringed (the "court decision trigger"). Id.

2. Forfeiture Provisions

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (the "MMA")[5] recently amended the FDCA, in part, by adding provisions that describe sets of conditions under which an ANDA applicant previously eligible for 180-day exclusivity could lose that eligibility. See 21 U.S.C. § 355(j)(5)(D). The Act provides that a 180-day exclusivity period described in 21 U.S.C. § 355(j)(5)(B)(iv) "shall be forfeited by a first applicant if a forfeiture event occurs with respect to that first applicant." 21 U.S.C. § (j)(5)(D)(ii). The forfeiture events are the failure to market; the withdrawal of an application; an amendment of a certification; the failure to obtain tentative approval; and an agreement with another applicant, the listed drug application holder, or a patent owner. 21 U.S.C. § 355(j)(5)(D)(i).

The failure to market forfeiture provisions, which are the provisions relevant to this case,

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[4] Courts have observed that the word "continuing" as it appears in the statute reflects a typographical error and should probably be read as "containing." See Purepac Pharm. Co. v. Friedman, 162 F.3d 1201, 1203 n.3 (D.C. Cir. 1998); Mova, 140 F.3d at 1064 n.3; see also 21 C.F.R. §§ 314.107(c)(1) & (2).

[5] Public Law 108-173, Stat. 2066 (Dec. 8, 2003).

state that a first applicant will forfeit exclusivity if it fails to market its drug by a certain date:

> (I) FAILURE TO MARKET. – The first applicant fails to market the drug by the later of –
>
> (aa) the earlier of the date that is –
> (AA) 75 days after the date on which the approval of the application of the first applicant is made effective under subparagraph (B)(iii); or
> (BB) 30 months after the date of submission of the application of the first applicant; or
>
> (bb) with respect to the first applicant or any other applicant (which other applicant has received tentative approval), the date that is 75 days after the date as of which, as to each of the patents with respect to which the first applicant submitted and lawfully maintained a certification qualifying the first applicant for the 180-day exclusivity period under subparagraph (B)(iv), at least 1 of the following has occurred:
> (AA) In an infringement action brought against that applicant with respect to the patent or in a declaratory judgment action brought by that applicant with respect to the patent, a court enters a final decision from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the patent is invalid or not infringed.
> (BB) In an infringement action or a declaratory judgment action described in subitem (AA), a court signs a settlement order or consent decree that enters a final judgment that includes a finding that the patent is invalid or not infringed.
> (CC) The patent information submitted under subsection (b) or (c) is withdrawn by the holder of the application approved under subsection (b).

21 U.S.C. § 355(j)(5)(D)(i)(I).

Application of these forfeiture provisions requires a series of analyses based on the timing of specific events. The statute directs that a forfeiture event occurs when the first applicant fails to market the drug by the later of two dates. One of these dates is calculated under section (aa) by determining the earlier of a date that is either 75 days after the first applicant's ANDA is approved (subsection (AA)) or 30 months after the date of submission of the first applicant's

ANDA (subsection (BB)). The second date is calculated under section (bb) by determining the date that is 75 days after the occurrence of at least one of three enumerated events. These events include, very generally, when a court enters a final decision that the patent is invalid or not infringed (subsection (AA)), a court signs a settlement order or consent decree entering final judgment that includes a finding that the patent is invalid or not infringed (subsection (BB)), or the patent information for the listed drug is withdrawn by the NDA holder (subsection (CC)).

II. Procedural History

A. Acarbose NDA and ANDAs

Bayer's NDA for Precose (acarbose) 25-mg and 50-mg tablets was approved on September 6, 1995; the 100-mg strength was approved on May 29, 1997. Precose helps to lower blood glucose in patients with type 2 diabetes mellitus. Bayer submitted U.S. Patent Number 4,904,769 ("the '769 patent") to FDA for listing in the Orange Book for all strengths of Precose tablets. By letter dated April 16, 2007, Bayer requested that the '769 patent be delisted from the Orange Book, and on September 25, 2007, FDA published the delisting in the Orange Book.[6]

FDA accepted Cobalt's acarbose ANDA for filing on March 22, 2005.[7] Cobalt's ANDA

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[6] In its April 16, 2007, letter, Bayer informed FDA that the assignee of interest for the '769 patent, Bayer Healthcare AG, had filed a statutory disclaimer under 35 U.S.C. § 253, disclaiming all issued claims to the '769 patent, and that the filed disclaimer had been published by the U.S. Patent and Trademark Office on February 27, 2007. Bayer therefore requested that the '769 patent be delisted from the Orange Book.

[7] Cobalt's ANDA was initially stamped as received by the FDA document room on January 14, 2005. After reviewing the application to determine whether it was sufficiently complete to permit a substantive review, as described in 21 C.F.R. § 314.101(b), FDA refused to receive Cobalt's ANDA for reasons enumerated in a March 9, 2005, letter to Cobalt. On March 22, 2005, FDA concluded that Cobalt's response to the March 9 letter rendered the ANDA acceptable for filing.

contained a paragraph IV certification to the '769 patent, and was the first ANDA referencing Precose to contain a paragraph IV certification. Over the course of its consideration of Cobalt's ANDA, FDA sent Cobalt a number of letters describing scientific deficiencies in the application, and Cobalt responded to these deficiencies. The final step in the application review involved inspection of the Australian facility used by Cobalt to conduct the bioequivalence studies, which facility had never been previously inspected by FDA and which, under FDA's routine practice, FDA did not plan to inspect until it had determined that the studies conducted at the facility were otherwise acceptable to support approval of the ANDA. On December 11, 2007, after conducting an off-site data audit, FDA determined that the facility used by Cobalt was acceptable. FDA approved Cobalt's ANDA on May 7, 2008.

FDA accepted Roxane Laboratories Inc.'s ("Roxane") ANDA for acarbose tablets for filing on August 31, 2006. Roxane's ANDA also contained a paragraph IV certification to the '769 patent. Roxane's ANDA was also approved on May 7, 2008.

B. Exclusivity Forfeiture Docket

FDA established a public docket to give acarbose ANDA applicants and other interested parties an opportunity to provide FDA with comments regarding application of the new MMA forfeiture provisions to Cobalt's eligibility for exclusivity. See Sept. 26, 2007, Letter from Robert L. West to ANDA applicants (attached to Ex. D to Rakoczy Decl. with Pl. TRO Mem.). On October 24, 2007, Cobalt filed a petition for an emergency stay of action, pursuant to 21 C.F.R. § 10.35(e), requesting that FDA stay approval of any subsequent ANDAs for acarbose until Cobalt's 180-day exclusivity period expires. See Oct. 24, 2007, Letter from William A. Rakoczy to Division of Dockets Management (attached hereto as Ex. A).

FDA responded to Cobalt's inquiries regarding its eligibility for 180-day exclusivity by letter dated May 7, 2008.[8] See May 7, 2008, Letter from Gary J. Buehler to William A. Rakoczy ("FDA Forfeiture Resp.," attached hereto as Ex. B, and attached as Ex. D to Rakoczy Decl. with Pl. TRO Mem.). FDA explained that Cobalt had initially been eligible for exclusivity because it filed the first ANDA with a paragraph IV certification, but that Cobalt forfeited its eligibility under 21 U.S.C. § 355(j)(5)(D)(i)(I). Id. at 5. FDA elaborated that application of the forfeiture provisions requires a series of analyses based on the timing of specific events:

> The statute directs that a forfeiture event occurs when the first applicant fails to market the drug by the later of two dates. One of these dates is calculated under item (aa) [21 U.S.C. § 355(j)(5)(D)(i)(I)(aa)] by determining the earlier of a date that is either 75 days after the first applicant's ANDA is approved (subitem (AA)) or 30 months after the date of submission of the first applicant's ANDA (subitem (BB)). Cobalt's ANDA is being approved on May 7, 2008; the 75 day period would expire on July 21, 2008. Cobalt submitted a substantially complete ANDA containing a paragraph IV certification on March 22, 2005; 30 months from that was September 22, 2007. September 22, 2007 is earlier than July 21, 2008. Therefore, September 22, 2007, controls for the analysis of item (aa).
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> The statute directs that we look to the later of the dates under items(aa) and (bb) of [21 U.S.C. § 355(j)(5)(D)(i)(I)]. Item (bb) states that the occurrence of at least one of the enumerated events as to a first applicant or any other applicant will begin a 75-day period leading to possible forfeiture of exclusivity. These events include, very generally, when a court enters a final decision that the patent is invalid or not infringed, a court signs a settlement order or consent decree entering final judgment that includes a finding that the patent is invalid or not infringed, or the patent information for the listed drug is withdrawn by the NDA holder. . . . In this case, the relevant event under [21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)] is that the NDA holder for Precose requested on April 16, 2007, that the '769 patent be delisted from the Orange Book. This triggered the start of the 75-day period under [21 U.S.C.

[8] On the same day, FDA also denied Cobalt's petition for a stay, for the reasons provided in FDA's forfeiture response letter.

> § 355(j)(5)(D)(i)(I)(bb)(CC)], which begins when the patent information submitted to the agency is withdrawn by the holder of the NDA. . . . In this case, the date that is 75 days after the NDA holder withdrew the information on the '796 patent, i.e., April 16, 2007, was June 30, 2007.
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> Forfeiture under [21 U.S.C. § 355(j)(5)(D)(i)(I)] occurs if a first applicant fails to market by the later of the dates under item (aa) or (bb). The September 22, 2007, date under section 355(j)(5)(D)(i)(I)(aa) is the later date, therefore it is the date that controls. Cobalt forfeited its 180-day exclusivity on September 22, 2007, because it did not begin to market its acarbose product by that date.

Id. at 6-8.[9]

In its response letter, FDA rejected comments suggesting that the forfeiture event described in 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(CC) applies only if a patent is withdrawn as a result of a counterclaim by the ANDA applicant in patent infringement litigation (as contemplated by 21 U.S.C. § 355(j)(5)(C)(ii)), concluding that the text of the applicable provision indicates without qualification that 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb) is applicable to all types patent withdrawals. FDA Forfeiture Resp. at 8.

FDA also determined that Cobalt did not forfeit its exclusivity under the failure to obtain tentative approval provision, which provides that an ANDA applicant forfeits exclusivity if it fails to obtain tentative approval with 30 months of filing its ANDA, unless that failure is "caused by a change in or a review of the requirements for approval of the application imposed

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[9] FDA also noted that "[e]ven if FDA were to calculate the forfeiture event under [21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)] from the date the delisting of the '796 patent information was published (which we do not believe is supported by the statutory language), Cobalt would still forfeit exclusivity. If the agency were to use the September 25, 2007, publication date as the date the patent was withdrawn, the date that is 75 days later is December 9, 2007. This date under item (bb) is later than the September 22, 2007 date under item (aa); therefore the later date as between items (aa) and (bb) would be December 9, 2007. Cobalt did not market its acarbose product by December 9, 2007, so even under this analysis, it has forfeited 180-day exclusivity." FDA Forfeiture Resp. at 8, n.14.

after the date on which the application is filed." 21 U.S.C. § 355(j)(5)(D)(i)(IV). In this case, FDA changed the requirements for Cobalt's in vivo bioequivalence study and thus, FDA concluded that Cobalt did not forfeit its exclusivity pursuant to 21 U.S.C. § 355(j)(5)(D)(i)(IV). FDA Forfeiture Resp. at 11.

C. Bioequivalence Citizen Petition and Petition for Stay

On November 9, 2007, Cobalt filed another petition for an emergency stay, as well as a citizen petition, both requesting that FDA refrain from approving any ANDA for acarbose unless and until the ANDA applicant conducts in vivo bioequivalence tests and studies. See Nov. 9, 2007 Letter from William A. Rakoczy to Division of Dockets Management, at 2 (attached as Ex. C); Nov. 9, 2007 Letter from William A. Rakoczy to Division of Dockets Management. Cobalt also requested that FDA refuse to grant any ANDA applicant an in vivo bioequivalence waiver. See id.

Under the Food and Drug Administration Amendments Act of 2007 ("FDAAA")[10], FDA must "take final agency action on a petition not later than 180 days after the date on which the petition is submitted." 21 U.S.C. § 355(q)(1)(F). In accordance with this requirement, FDA responded to Cobalt's citizen petition by letter dated May 7, 2008 – 180 days after Cobalt submitted the petition.[11] See May 7, 2008, Letter from Janet Woodcock to William A. Rakoczy

[10] Public Law 110-85, 121 Stat. 823 (Sept. 27, 2007).

[11] Cobalt's repeated assertions that FDA "ambushed" it with administrative rulings without any prior notice are ridiculous. It was Cobalt's own citizen petition that triggered the 180-day FDAAA clock, and Cobalt was well aware that its ANDA was approvable but for FDA's resolution of the issues raised in Cobalt's petition concerning bioequivalence studies; FDA's January 15, 2008, letter told Cobalt such explicitly. See Jan. 15, 2008, Letter from Gary J. Buehler to Strategic Bioscience Corp. (Cobalt's U.S. agent) (attached hereto as Ex. D). Thus, it requires no great imagination to foresee that once FDA resolved the bioequivalence issues,

(attached as Ex. E). FDA explained that under 21 U.S.C. § 355(j)(8)(C) and 21 C.F.R. § 320.24, FDA has the discretion to accept in vitro studies for a non-systemically absorbed drug product such as acarbose when FDA finds that such studies are a scientifically valid method of determining bioequivalence. See id. at 6. FDA concluded, "[i]n the case of a generic acarbose that has the same quality and quantity of active and inactive ingredients as Precose, we recommend in vitro, rather than in vivo, testing for establishing bioequivalence." Id.

Cobalt filed its complaint and motion for a temporary restraining order on May 8, 2008, challenging only FDA's legal interpretation of the forfeiture provisions and not FDA's scientific determination on the appropriateness of in vitro bioequivalence data.

ARGUMENT

I. Legal Standard

In order to obtain a temporary restraining order, like a preliminary injunction, a party must demonstrate that: (1) it has a substantial likelihood of success on the merits; (2) it will suffer irreparable injury in the absence of preliminary relief; (3) other interested parties will not be substantially injured if the requested relief is granted; and (4) granting such relief would serve the public interest. See Katz v. Georgetown Univ., 246 F.3d 685, 687-88 (D.C. Cir. 2001); see also Biovail Corp. v. FDA, 448 F. Supp. 2d 154, 160 (D.D.C. 2006). The likelihood of success requirement is the most important of these factors. Id. Furthermore, the extraordinary relief Cobalt seeks is demonstrably not to preserve the status quo, but to obtain far-reaching mandatory relief by requiring FDA to revoke an already-issued ANDA approval. Such an action would also require that Roxane, who, according to Cobalt, has already launched its product, see Pl. TRO

FDA would approve Cobalt's ANDA, and of course resolve any questions of exclusivity.

Mem. at 31, halt marketing, thereby further upsetting the status quo. This extraordinary request for relief presents an additional and very high hurdle for Cobalt. A court's power to issue such an order "should be sparingly exercised." Mylan Pharm., Inc. v. Shalala, 81 F. Supp.2d 30, 36 (D.D.C. 2000) ("Mylan (terazosin)"); see also Dorfmann v. Boozer, 414 F.2d 1168, 1173 (D.C. Cir. 1969); see generally Mazurek v. Armstrong, 520 U.S. 968, 972 (1997); Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212, 215 (D.D.C. 1996).

II. Cobalt Is Not Entitled To A Temporary Restraining Order

As shown below, Cobalt has failed to satisfy any of the four elements – a substantial likelihood of success on the merits, irreparable injury, a showing that other interested parties will not be substantially injured by the requested relief, and a showing that granting relief would serve the public interest – needed to obtain a temporary restraining order. FDA appropriately denied Cobalt's citizen petitions and approved Roxane's ANDA. All of Cobalt's purported injuries are "merely economic" and clearly not irreparable; whatever injury Cobalt were to avoid by obtaining a TRO would be visited upon Roxane; and granting the requested relief would harm the public by unnecessarily delaying it access to cheaper acarbose by 180 days. All of Cobalt's arguments to the contrary simply lack merit.

A. Cobalt Is Not Likely to Succeed On The Merits Because FDA Followed the Law and Properly Determined That Cobalt Forfeited Its Exclusivity

FDA's administrative decisions are subject to review by the Court under the Administrative Procedure Act ("APA"), and may be disturbed only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). This standard is highly deferential to the agency. Citizens to Preserve Overton Park, Inc. v. Volpe,

401 U.S. 402, 416 (1971). "There is a presumption in favor of the validity of the administrative action." Bristol-Myers, 923 F. Supp. at 216. Under this "arbitrary and capricious" standard, agency action must be upheld if the action is rational, based upon relevant factors, and within the agency's authority. Motor Vehicle Mfrs. Ass'n of the United States, Inc., v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 42-42 (1983); see also Overton Park, 401 U.S. at 416; AT&T Corp. v. FCC, 349 F.3d 692, 698 (D.C. Cir. 2003). Further, "under this narrow scope of review, 'the court is not empowered to substitute its judgment for that of the agency.'" Bristol-Myers, 923 F. Supp. at 216 (quoting Overton Park, 401 U.S. at 416); see also Motor Vehicle Mfrs. Ass'n, 463 U.S. at 43 ("the scope of review under the 'arbitrary and capricious' standard is narrow and a court is not to substitute its judgment for that of the agency."). In applying the arbitrary and capricious standard, the court reviews the administrative record assembled by the agency and does not undertake its own fact finding. See, e.g., Camp v. Pitts, 411 U.S. 138, 142 (1973).

When the Court is reviewing an agency's construction of statutory provisions, it is governed by the two-step analysis of Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837 (1984). First, the Court must inquire "whether Congress has directly spoken to the precise question at issue;" if Congress's intent is clear, the Court "must give effect to [such] unambiguously expressed intent." Id. at 842-43. Formulated another way, the Court must initially decide "whether the statute unambiguously forbids the Agency's interpretation." Barnhart v. Walton, 535 U.S. 212, 218 (2002) (emphasis added). Chevron deference is appropriate when "the interstitial nature of the legal question, the related expertise of the Agency, the importance of the question to administration of the statute, the complexity of that administration, and the careful consideration the Agency 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 Agency interpretation here at issue." Barnhart, 535 U.S. at 222. This Circuit has held that deference is particularly appropriate in the drug approval context because of "the complexity of the statutory regime" and "FDA's expertise." Mylan v. Thompson, 389 F.3d 1272, 1280 (D.C. Cir. 2004).

Accordingly, the D.C. Circuit has repeatedly given Chevron deference to FDA's interpretation of the FDCA's generic drug provisions, as well as the agency's own implementing regulations. See, e.g., Novartis Pharmaceuticals Corp. v. Leavitt, 435 F.3d 344, 349 (D.C. Cir. 2006) ("We have held on a number of occasions that FDA interpretations of the FDCA receive deference, as do its interpretations of its own regulations unless plainly erroneous or inconsistent with the regulations."); Mylan v. Thompson, 389 F.3d at 1281; Purepac Pharm. Co. v. Thompson, 354 F.3d 877, 883 (D.C. Cir. 2004); Serono Labs., Inc. v. Shalala, 158 F.3d 1313, 1319, 1320 (D.C. Cir. 1998) (citing Auer v. Robbins, 519 U.S. 452, 461 (1997)).

Because FDA has not yet promulgated regulations implementing the new exclusivity forfeiture provisions, FDA must regulate directly from the FDCA to determine whether ANDA applicants are entitled to exclusivity. See FDA Forfeiture Resp. at 4. As explained above, supra at 9-11, and in FDA's response letter, FDA walked through the applicable statutory provisions and concluded that Cobalt forfeited its exclusivity because it failed to begin marketing its product within 75 days of the NDA holder, here Bayer, withdrawing information on the '769 patent. See 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(CC).

It is well settled canon that "[t]he preeminent canon of statutory interpretation requires us to 'presume that [the] legislature says in a statute what it means and means in a statute what it

says there.'" BedRoc Ltd., LLC v. United States, 541 U.S. 176, 183 (2004) (citations omitted); see also Connecticut Nat'l Bank v. Germain, 503 U.S. 249, 253-54 (1992) (same); Qi-Zhuo v. Meissner, 70 F.3d 136, 140 (D.C. Cir. 1995). "Extremely strong, this presumption is rebuttable only in the 'rare cases [in which] the literal application of a statute will produce a result demonstrably at odds with the intention of its drafters.'" Nat'l Public Radio, Inc. v. FCC, 254 F.3d 226, 230 (D.C. Cir. 2001) (quoting United States v. Ron Pair Enterp., Inc., 489 U.S. 235, 242 (1989)). While Cobalt argues vigorously that policy considerations should be incorporated into, and trump, the plain language of the forfeiture provision of the statute, see Pl. TRO Mem. at 16-17, elsewhere in the same memorandum it argues with equal vigor, and correctly, that the "plain language" of the statute controls and that neither "the FDA or [a] Court [have] license to read into the present, clear language of [the Hatch-Waxman provisions] a requirement ... that is simply not there." Id. at 25. As Cobalt makes clear in this argument, such policy interpretations are for Congress to address. Id. Here, as this court has explained, "because the statute is clear, and the FDA's application of the statute is consistent with the plain meaning of the statute, it's decision cannot be considered arbitrary, capricious, or contrary to law." Teva Pharms. v. FDA, 355 F. Supp. 2d 111, 118 (D.D.C. 2004).

FDA concluded that Cobalt had not forfeited its exclusivity under the failure to obtain tentative approval provision because, unlike in the failure to market provision, there is an exception in the failure to obtain tentative approval provision that essentially stops the clock. That provision provides that a forfeiture event occurs when "[t]he first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of

the application imposed after the date on which the application is filed." 21 U.S.C. § 355(j)(5)(D)(i)(IV) (emphasis added). In this case, Cobalt itself submitted the citizen petition that caused FDA to delay approving any acarbose ANDAs so FDA could consider the appropriate methodology for establishing bioequivalence for acarbose products. FDA concluded that Cobalt's failure to obtain tentative approval within 30 months was caused, in part, by a change in bioequivalence requirements.[12]

FDA did conclude, however, that Cobalt forfeited its exclusivity under the failure to market provisions because there is no exception for delays leading to forfeiture under those forfeiture provisions, regardless of who "caused" the delay. Cobalt nonetheless argues that because FDA concluded that the delay in obtaining tentative approval did not cause Cobalt to forfeit its exclusivity under one provision while the delay in obtaining final approval did cause Cobalt to forfeit its exclusivity under a different provision, FDA's decision is "arbitrary, capricious, and unlawful." Pl. TRO Mem. at 21. Cobalt is mistaken. There is no language in the statute that marries the forfeiture provisions in the manner argued by Cobalt. FDA was simply abiding by the plain language of the statute – a delay that does not result in forfeiture under 21

[12] As noted in FDA's forfeiture response letter, this forfeiture provision does not "permit either FDA or an ANDA applicant to comb through the ANDA review records and decide whether, had the review been conducted differently, the application could have received an approval or tentative approval before the forfeiture occurred. The review order for the very large number of ANDAs, amendments, and supplements is established through internal policies and established practice. In 2007, for example, with a total staff of approximately 210, FDA's Office of Generic Drugs (OGD) issued approval, tentative approval, not approvable, or refuse to receive letters on 1,893 ANDAs, in addition to approving or not approving 3,429 chemistry supplements. OGD does not give preferential treatment to ANDAs that are eligible for 180-day exclusivity and are, therefore, subject to the potential forfeiture of that exclusivity. To do so would draw scarce resources away from the review of other applications that may, for example, have been submitted earlier and have been waiting longer in the review queue. FDA Forfeiture Resp. at 11, n.18.

U.S.C. § 355(j)(5)(D)(i)(IV) may very well result in forfeiture under 21 U.S.C. § 355(j)(5)(D)(i)(I). Despite Cobalt's numerous arguments to the contrary, because the plain language of statute controls here, Cobalt must overcome a very high burden to show to that a different reading is appropriate. See, e.g., Nat'l Public Radio, Inc. v. FCC, 254 F.3d 226, 230 (D.C. Cir. 2001) (plaintiff's "burden in rebutting the presumption created by clear language is onerous").

Cobalt also takes issue with FDA's determination of the date on which Bayer withdrew the information on the '769 patent. Pl. TRO Mem. at 24-26. The specific statutory provision reads: "The patent information submitted under subsection (b) or (c) is withdrawn by the holder of the application approved under subsection (b) [i.e., Bayer, the NDA holder]." 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(CC). By letter dated April 16, 2007, Bayer requested that FDA delist the '769 patent from the Orange Book, which is the only way an NDA holder can "withdraw" patent information. It would be impossible for Bayer to actually remove the patent from the Orange Book – as Cobalt well knows – because the Orange Book is a listing that FDA is statutorily required to maintain. Cobalt contends that there is a "significant and material distinction" between a patent that is "withdrawn by the holder of the application" and a "mere 'request for patent listing' such as Bayer made" in this case. Pl. TRO Mem. at 24. However, Cobalt does not – because it cannot – explain how these two things differ or offer any authority for its argument. Thus, FDA's conclusion that a request to withdraw the patent constitutes a withdrawal of the patent information by the NDA holder within the meaning of the FDCA, 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(CC), is the only logical reading of that provision.

Cobalt notes that as of the date it filed its TRO, the '769 remained listed in the Orange

Book. See Pl. TRO Mem. at 14. As FDA explained, however,

> The publication of the request for patent delisting in the Orange Book was accompanied by an annotation reading "Patent number 4904769 listed on all products of NDA 20482 Precose (Acarbose) was requested to be delisted by the sponsor on 4/16/2007. This patent has remained listed because, under section 505(j)(5)(D)(i) of the Act, a first applicant may retain eligibility for 180-day exclusivity based on a paragraph IV certification to this patent for a certain period." Because immediate removal of patent information from the Orange Book upon withdrawal of the patent information by the NDA holder could result in ANDA applicants withdrawing corresponding patent certifications prematurely and thus undermining a first applicant's exclusivity, FDA will leave information related to withdrawn patents in the Orange Book until it has determined that any related 180-day exclusivity has expired. In this case, the patent information was retained in the Orange Book until the agency could resolve these complex issues and respond to Cobalt's questions regarding its eligibility for 180-day exclusivity.

FDA Forfeiture Resp. at 7, n.13. Because FDA left the '769 patent in the Orange Book to assure that Cobalt did not prematurely lose its eligibility for exclusivity, Cobalt's attempt to characterize FDA's actions as a mistake are disingenuous at best.

Cobalt does not, and indeed cannot, cite any support for its argument that 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(CC) requires that the patent no longer appear in the Orange Book listings. None of the cases that Cobalt claims support its argument that FDA's reading impermissibly leads to a system that can easily be manipulated by an NDA holder discuss the MMA forfeiture provisions, and thus Cobalt's reliance on those cases is misplaced. See Pl. TRO Mem. at 23-29. Congress did in fact trigger one piece of one of the forfeiture provisions on actions taken by a NDA holder, to the benefit of the consuming public (who do not have to wait for the lower drug prices brought by generic competition while one generic company enjoys 180 days of exclusivity based on a patent that the patent owner itself has renounced). Moreover, as

explained in FDA's response letter, even if the forfeiture calculations are done using the date FDA published the delisting, September 25, 2007, as the date the patent information was withdrawn by the NDA holder, Cobalt would still have forfeited its exclusivity by failing to being marketing its product by December 9, 2007. See FDA Forfeiture Resp. at 8, n.14.

FDA acknowledges that its need to inspect the Australian facility where Cobalt's bioequivalency studies were conducted lead to a delay in approving Cobalt's ANDA. That delay was not, as Cobalt contends, two years or longer, but rather was just over two months. FDA's ordinary practice is not to inspect a facility until it has determined that the studies conducted at that facility are otherwise acceptable to support approval of an ANDA. See FDA Forfeiture Resp. at 3. More importantly, however, the statute does not take into consideration the reason for the delay in calculating the date which triggers the running of the forfeiture period. Thus, both FDA and this Court are compelled to apply the forfeiture provisions by simply calculating the timing of specific events enumerated in the statute.

Cobalt asserts that under 21 U.S.C. § 355(j)(3)(F), "FDA should not have withheld Cobalt's approval based upon this inspection [of the Australian facility]." Pl. TRO Mem. at 22. The provision cited by Cobalt, however, provides that an approval should not be delayed "because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug." 21 U.S.C. § 355(j)(3)(F) (emphasis added). Here, the facility Cobalt used to conduct its bioequivalency studies had never been previously inspected by FDA, and thus an inspection was necessary to assure the safety and effectiveness of Cobalt's acarbose product. See FDA Forfeiture Resp. at 3, n.5.

In sum, the plain language of the statute provides that Cobalt has forfeited its 180 days of marketing exclusivity by failing to begin marketing within 75 days of the date on which the innovator, Bayer, withdrew the '769 patent.

B. Cobalt Will Not Suffer Irreparable Harm Without Injunctive Relief

Courts insist that only irreparable harm justifies the issuance of a preliminary injunction. "The *sine qua non* of granting any preliminary injunctive relief is a clear and convincing showing of irreparable injury to the plaintiff." Experience Works, Inc. v. Chao, 267 F. Supp. 2d 93, 96 (D.D.C. 2003). Because Cobalt is not likely to succeed on the merits, Cobalt "would have to make a very substantial showing of severe irreparable injury" to prevail on its motion. Nat'l Pharm. Alliance v. Henney, 47 F. Supp. 2d 37, 41 (D.D.C. 1999); see also Apotex, Inc. v. FDA, 2006 U.S. Dist. LEXIS 20894, *54 (D.D.C. Apr. 19, 2006). "Irreparabilty of injury is a very high standard." Bristol-Myers, 923 F. Supp at 220. The injury alleged must be certain, great, actual, and imminent, Wisconsin Gas Co. v. FERC, 758 F.2d 669, 674 (D.C. Cir. 1985), and it must be "more than simply irretrievable; it must also be serious in terms of its effect on the plaintiff." Mylan (terazosin), 81 F. Supp. 2d at 42 (quoting Gulf Oil Corp. v. Dep't. of Energy, 514 F. Supp. 1019, 1026 (D.D.C. 1981)).

It is well settled that mere economic loss in and of itself does not constitute irreparable harm. Wisconsin Gas, 758 F.2d at 674; Apotex, 2006 U.S. Dist. LEXIS 20894, *53; Mylan (terazosin), 81 F. Supp. 2d at 42; Bristol-Myers, 923 F. Supp. at 220. "Mere injuries, however substantial, in terms of money, time and energy necessarily expended" are inadequate. Wisconsin Gas, 758 F.2d at 674 (quoting Virginia Petroleum Jobbers Ass'n v. FPC, 259 F.2d 921, 925 (D.C. Cir. 1958)); see also Sandoz, Inc. v. FDA, 439 F. Supp. 2d 26, 32 (D.D.C. 2006)

(holding that Sandoz failed to carry its burden of demonstrating irreparable harm because the claimed injury was "merely economic") (internal quotations omitted); Apotex, 2006 U.S. Dist. LEXIS 20894, *54-*57 (same). Even irrecoverable economic loss does not rise to the level of irreparable harm unless the financial injury is "serious in terms of its effect on the plaintiff." Gulf Oil, 514 F. Supp. at 1026; see also Apotex, 2006 U.S. Dist. LEXIS 20894, *54; Experience Works, Inc., 267 F. Supp. 2d at 96 ($21.1 million reduction in funding is serious financial blow, but one frequently faced by other similar entities, and not an economic loss that threatens survival of the business); Sociedad Anonima Viña Santa Rita v. Dep't of Treasury, 193 F. Supp. 2d 6, 14 (D.D.C. 2001) ("financial harm alone cannot constitute irreparable injury unless it threatens the very existence of the movant's business"); Mylan (terazosin), 81 F. Supp. 2d at 42-43.

Notwithstanding this well-established doctrine, mere economic loss is precisely the type of harm that Cobalt alleges it will suffer in the absence of a TRO. See Pl. TRO Mem. at 30-35. In its attempt to demonstrate irreparable harm, Cobalt alleges, in general terms, that "[i]f deprived of exclusivity, Cobalt believes that its profitability and market share will plummet dramatically." Id. at 31. Cobalt's alleged "profitability" loss would not cause its business to collapse, let alone have a severe detrimental impact. Allegations of lost sales and a lost opportunity to gain certain market advantages are a far cry from the required demonstration of a "serious" and "irretrievable" loss that "would significantly damage its business above and beyond a simple diminution in profits." Mylan Pharm. Inc. v. Thompson, 139 F. Supp. 2d 1, 27 (D.D.C. 2001), rev'd on other grounds, 268 F.3d 1323 (Fed. Cir. 2001); Mylan (terazosin), 81 F. Supp. 2d at 42. Cobalt has failed to even allege, much less demonstrate, that its alleged smaller

market position would result in economic injury "sufficiently large in proportion to [its] operations that the loss of the amount of money involved would also cause extreme hardship to [its] business, or even threaten destruction of [its] business." Gulf Oil, 514 F. Supp. at 1025. Thus, the alleged loss of potential sales that may result from competition with other generic versions of acarbose do not constitute irreparable harm. See Amtote Int'l, Inc. v. PNGI Charles Town Gamming LLP, 998 F. Supp. 674, 678 (N.D. W. Va. 1998) (citing Wisconsin Gas, 758 F.2d at 674) ("Such extraordinary circumstances have been found to exist if the denial of injunctive relief would likely cause the business to collapse."); see also Varicon Int'l v. Office of Personnel Mgmt., 934 F. Supp. 440, 447-48 (D.D.C. 1996) (finding no irreparable harm due to lost contract where movant's revenue would decline by 10%); TGS Tech., Inc. v. United States, Civ. No. 92-0062, 1992 U.S. Dist. LEXIS 195, at *10 (D.D.C. Jan. 14, 1992) (finding no irreparable harm where lost contract constituted 20% of movant's business).

The cases that Cobalt claims support its contention that the loss of exclusivity alone suffices to show irreparable harm actually belie this argument. Pl. TRO Mem. at 32. In Mova, for example, the district court granted a preliminary injunction both because Mova would be harmed by the loss of its exclusivity and because "Mova's small size put it at a particular disadvantage." Mova, 140 F.3d at 1066 n.6. The D.C. Circuit affirmed, noting that both of those factors sufficed to show a "severe economic impact to Mova." Id.; see also Bracco Diagnostics v. Shalala, 963 F. Supp. 20, 28-29 (D.D.C. 1997) (finding that FDA's disparate treatment of plaintiff and its competitor's products during the approval process, as well as plaintiff not being the first approved, demonstrated irreparable harm). Furthermore, this is not a case in which Cobalt is being denied entrance into the market to compete with other generic companies, as in

Torpharm, Inc. v. Shalala, 1997 U.S. Dist. LEXIS 21983, *13-*15 (D.D.C. Sept. 15, 1997). Rather, Cobalt must simply enter the market at the same time as any other company with an approved acarbose ANDA.

Nor does the likelihood that Cobalt's alleged money damages may not be recovered from the government translate into irreparable harm. This court has held that "the injury must be more than simply irretrievable; it must also be serious in terms of its effect on the plaintiff. Under this standard, it is apparent that [plaintiff] will not suffer irreparable harm even if the monetary loss is irretrievable." Gulf Oil Corp. v. Dep't of Energy, 514 F. Supp. 1019, 1025 (D.D.C. 1981); see also Sandoz, 439 F. Supp. 2d at 31-32 (same). Cobalt's claim of being unable to collect lost revenue from FDA simply does not suffice to establish irreparable harm.

Because Cobalt has not shown that it will suffer an irretrievable loss that would significantly damage its business, its allegations fall well short of the showing necessary to support a finding of irreparable injury.

C. The Requested Relief Will Not Serve The Public

Finally, Cobalt has also failed to show that any potential harm to its interests in the absence of injunctive relief outweighs the potential harm to other parties, or that the entry of the relief it seeks would further the public interest – the third and fourth requirements for preliminary injunctive relief. Although FDA has no commercial stake in the outcome of this litigation, FDA is the government agency charged with implementing the statutory scheme governing exclusivity and the approval of generic drugs. As such, FDA's interest coincides with the public interest. See Serono Labs. Inc. v. Shalala, 158 F.3d 1313, 1326 (D.C. Cir. 1998); Mylan (terazosin), 81 F. Supp. 2d at 44-45.

In enacting the Hatch-Waxman Amendments, "Congress sought to get generic drugs into the hands of patients at reasonable prices – fast." In re Barr Labs., Inc., 930 F.2d 72, 76 (D.C. Cir. 2006). Moreover, "the public has a 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." Apotex Inc. v. FDA, 508 F. Supp. 2d 78, 88 (D.D.C. 2007). Giving Cobalt 180 days of exclusivity after Cobalt forfeited its exclusivity by failing to being marketing its product within 75 days of the NDA-holder withdrawing the '769 patent from the Orange Book unnecessarily delays competition for generic acarbose for at least 180 days. This harms both Roxane, the other generic drug manufacturer with an ANDA that is ready for approval and the public, who benefit from competition by lower generic drug prices.

As explained above, FDA's interest and the public's interest are the same. See Serono, 158 F.3d at 1326 (determining that the public interest is "inextricably linked" to Congress's purpose in passing the Hatch-Waxman Amendments). FDA must implement the statutory scheme governing exclusivity determinations and the approval of generic drugs. For the reasons stated above, FDA has concluded that Cobalt forfeited its exclusivity under the plain language of the statute, 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb), and that in vitro studies properly establish bioequivalence. Because Cobalt has failed to establish that it has any rights at issue that are being threatened, public interest "would be better served by denying [Cobalt's] motion." Boehringer Ingelheim Corp. v. Shalala, 993 F. Supp. 1, 3 (D.D.C. 1997).

CONCLUSION

For the foregoing reasons, Cobalt's motion for a temporary restraining order should be denied.

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