UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

ASTELLAS PHARMA US, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No.1:09-cv-01511
	)	
FOOD AND DRUG ADMINISTRATION, *et al*.,	)	
	)	
	)	
Defendants.	)	
	)	

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

INTRODUCTION

At issue in this case is plaintiff Astellas' attempt to reverse a decision made by the United States Food and Drug Administration ("FDA") in order to preserve Astellas' own profits, while decreasing the availability of a low-cost, safe and effective pharmaceutical that has gone through FDA's thorough drug approval process. FDA has approved a generic version of tacrolimus, an immunosuppressant used in transplant patients. Plaintiff manufactures the brand name version of tacrolimus under the name Prograf®.

FDA's decision to approve a generic version of tacrolimus and the methods it applied are governed by statute and falls squarely within the agency's scientific and technical expertise. FDA's approval means that FDA has found the generic version to be bioequivalent with Prograf, as required under the Food, Drug, and Cosmetic Act ("FDCA"). Astellas does not argue that the bioequivalence findings made by FDA are inaccurate; rather, it asserts that FDA should require more testing on the product. Also, under the statute, the labeling of the generic will be

essentially the same as that of Prograf. Astellas' attempt to have FDA require different labeling on the generic would be inconsistent with the statutory scheme applicable to generic drugs.

It is the government's understanding that Sandoz, which received FDA approval of its abbreviated new drug application ("ANDA") on Monday, August 10, 2009, has already commercially launched its generic product, and granting the temporary or preliminary relief sought by Astellas would, in fact, alter the status quo. For these reasons, Astellas must establish a very strong likelihood of success on its claim that FDA's approval of generic tacrolimus must be set aside – a burden Astellas has failed to meet. Contrary to Astellas' contentions, FDA's method for approving generic tacrolimus uses appropriate bioequivalence standards and is based upon a thorough and rigorous review of the scientific evidence. Thus, Astellas has no likelihood of success on the merits of its contention that ANDA filers should conduct an additional clinical trial to provide evidence of bioequivalence for their generic product.

Sandoz' application for approval of this generic product was pending for over two-and-one-half years. At least part of this period was directly attributable to the need to evaluate and respond to a citizen petition submitted by Astellas, raising the same objections to the approval standards for generic tacrolimus it has asserted in this lawsuit. That petition, and this lawsuit, represent yet another instance in which a manufacturer of a pioneer drug product in fear of losing its lucrative monopoly has attempted to block generic competition by challenging the scientific basis for FDA's approval of the generic. *See, e.g.*, *Schering Corp. v. FDA*, 51 F.3d 390 (3d Cir. 1995); *Glaxo Group v. Leavitt*, AMD 06-469 (D. Md., Mar. 6, 2006) (Davis, J.); *Schering Corp. v. Sullivan*, 782 F. Supp. 645 (D.D.C. 1992), *vacated as moot sub nom., Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993); *Somerset Pharms., Inc. v. Shalala*, 973 F. Supp. 443

(D. Del. 1997); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212 (D.D.C. 1996); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994). All of these challenges failed, as should this one. The courts in the cited cases unequivocally held that scientific determinations as to the appropriate methodology required for approval of a generic drug product falls squarely within the broad discretion of FDA, which Congress has determined is in the best position to make such complex and technical scientific decisions.

Contrary to Astellas' contentions, FDA's method for approving generic tacrolimus uses appropriate bioequivalence standards and is based upon the statute, regulations, and a thorough and rigorous review of the scientific evidence. Thus, Astellas has no likelihood of success on the merits of its contention that ANDA filers should conduct an additional clinical trial to provide evidence of bioequivalence for their generic product. In addition, Astellas has failed to establish that it would suffer irreparable harm in the absence of emergency injunctive relief. Plaintiff's assertion of irreparable harm is based on unsupported speculation. Also, its speculative claim that it may lose "goodwill" and suffer a damaged reputation *if* a generic product should fail was specifically rejected by this Court in *Bristol-Myers*. Moreover, the public interest favors getting generic drugs to market, as this Court also recognized in *Bristol-Myers*. For these reasons, the Court should deny Astellas' request for a TRO and preliminary injunction.

BACKGROUND

I. Statutory and Regulatory Framework

A. New Drug Applications and Abbreviated New Drug Applications

Under the FDCA, 21 U.S.C. § 301 *et seq.*, pharmaceutical companies seeking to market "pioneer" or "innovator" drugs must first obtain FDA approval by filing a new drug application

("NDA"). 21 U.S.C. § 355(a), (b). The NDA must contain a wealth of scientific data and other information including investigative reports demonstrating the drug's safety and effectiveness, a statement of the drug's components, and specimens of proposed labeling for the packaging of the drug. 21 U.S.C. § 355(b)(1).

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 the submission of abbreviated new drug applications ("ANDAs") for approval of generic versions of drug products with approved NDAs. 21 U.S.C. § 355(j).[1] The Hatch-Waxman Amendments were intended to balance encouraging innovation in drug development with accelerating the availability of lower cost generic alternatives to innovator drugs. *See* H.R. Rep.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 Tri-Bio Labs., Inc. v. United States*, 836 F.2d 135, 139 (3d Cir. 1987).

B. Bioequivalence and the Requirements for ANDA Approval

To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA cites to a drug named in an earlier-approved NDA (the reference listed drug, or "RLD") and relies on FDA's previous finding that the RLD is safe and effective. To rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD. 21 U.S.C. § 355(j)(2)(A)(iv). Bioequivalence testing is designed to test formulations to ensure that when two products have the same active drug ingredient,

[1] Congress amended 21 U.S.C. § 355(j) in 2003. *See* The Access to Affordable Pharmaceuticals provisions of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003) (the "MMA").

differences in formulation do not adversely affect the rate and extent to which the active drug ingredient reaches the site of action. The statute, regulations, and case law give FDA considerable flexibility in determining how ANDA applicants can meet the requirement referenced above for establishing bioequivalence. The FDCA states that a generic drug is bioequivalent to the RLD if the following conditions exist:

> 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 when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either single or multiple doses.[1]

21 U.S.C § 355(j)(8)(B)(I). FDA's regulations identify acceptable methodologies for determining the bioequivalence of drug products. 21 C.F.R. Part 320. These methodologies include pharmacokinetic studies, pharmacodynamic studies, comparative clinical trials, *in vitro* studies and "any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence." 21 C.F.R. 320.24(b)(6). FDA determines which study design to require based on the design's ability to compare the amount of drug delivered by the two products at the drug's particular site of action. The selection of the method used to establish bioequivalence depends on "the purpose of the study, the analytical methods available, and the nature of the drug product." 21 C.F.R. 320.24(a).

In addition, an ANDA must contain, with certain exceptions not relevant here, information to show that the proposed drug has the same active ingredient, indications for use, route of administration, dosage form, strength, and labeling as the RLD. 21 U.S.C. § 355(j)(2)(A). FDA must approve an ANDA unless the information submitted in the ANDA is insufficient to meet these requirements for sameness (also known as demonstrating pharmaceutical equivalence) and/or demonstrate bioequivalence. 21 U.S.C. § 355(j)(4).

Generally, FDA will consider generic drug products that meet the approval requirements under 21 U.S.C. § 355(j) to be "therapeutically equivalent" to the RLD. *See* Approved Drug Products With Therapeutic Equivalence Evaluations, 29th ed., at vii (hereinafter the "Orange Book"). To be approved as an ANDA, a drug product does not necessarily contain the same inactive ingredients and they may also differ in characteristics such as shape, scoring, release mechanism, and, within certain narrow limits, labeling. *See* 21 C.F.R. § 320.1; Orange Book at vi, *et seq*. Products classified as therapeutically equivalent can be substituted with the expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. *See* Orange Book at vii.

II. Factual Background

A. Prograf

Astellas is the holder of the NDA for Prograf (tacrolimus) (NDAs 50-708 and 50-709). Prograf is an immunosuppressant used in transplant patients. It is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants. The labeling for Prograf contains a boxed warning indicating that only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Prograf, that patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources, and that physicians responsible for maintenance therapy should have complete information requisite for the follow-up of the patient administered Prograf. As stated in the warnings section of its labeling, patients administered a Prograf injection should be under continuous observation for at least the first 30 minutes following the start of infusion and at frequent intervals thereafter. In addition, the dosage and

administration section of the labeling states that monitoring of tacrolimus blood concentration with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments, and compliance.

B. Draft Guidance on Tacrolimus

In 2006, FDA published a draft guidance on tacrolimus. *See* Individual Bioequivalence Recommendations for Specific Products (Tacrolimus), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In that draft guidance, FDA recommend the following studies to establish bioequivalence for generic tacrolimus products referencing Prograf oral capsules:

1. A fasting single-dose, two-treatment, two-period crossover in vivo bioequivalence study comparing tacrolimus capsules, 5 mg, to the RLD.

2. A fed single-dose, two-treatment, two-period crossover in vivo bioequivalence study comparing tacrolimus capsules, 5 mg, to the RLD.

The draft guidance also stated that tacrolimus capsules, 0.5 mg and 1 mg, can be considered for a waiver of *in vivo* bioequivalence testing based on (1) acceptable bioequivalence studies on the 5 mg strength, (2) proportional similarity in the formulations of the 0.5 mg, 1 mg, and 5 mg strengths, and (3) acceptable *in vitro* dissolution testing of the 0.5 mg, 1 mg, and 5 mg strengths.

C. Astellas' Citizen Petition

Astellas filed a citizen petition on September 21, 2007, asking FDA to require that for ANDAs relying on Prograf as the RLD, bioequivalence studies in healthy subjects be supplemented by studies performed in the transplant patient population. *See* Citizen Petition, Pl.

Ex. I at 1. Astellas also requested that FDA take the following actions for Prograf: require specific labeling changes (including changes to the WARNINGS and PRECAUTIONS section); make specific changes to FDA's Orange Book; and require drug product differentiation for any future narrow therapeutic index ("NTI") immunosuppressant generic drug products.

Astellas filed a supplement to its citizen petition on September 11, 2008. The supplement asked FDA to consider, in the context of its citizen petition, the comments of the American Society of Transplant Surgeons (ASTS) submitted to the docket for the agency's draft guidance on the bioequivalence testing of tacrolimus.

On August 10, 2009, FDA issued a detailed response to the citizen petition, granting it in part and denying it in part. Pl. Ex. L. That same day, FDA approved Sandoz' ANDA for generic tacrolimus upon the agency's determination that Sandoz' product met the statutory and regulatory requirements for approval set forth at 21 U.S.C. § 355(j).

ARGUMENT

I. Legal Standard

In order to obtain a temporary restraining order or 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.* Indeed, "[w]ithout any probability of prevailing on the merits, the Plaintiffs' purported injuries, no matter how compelling, do not

justify preliminary injunctive relief." *Am. Bankers Ass'n v. Nat'l Credit Union Admin.*, 38 F. Supp. 2d 114, 140 (D.D.C. 1999). As the Supreme Court recently made clear, "a party seeking a preliminary injunction must demonstrate . . . 'a likelihood of success on the merits,'" not merely the existence of "questions 'so serious, substantial, difficult and doubtful, as to make them fair ground for litigation[.]'" *Munaf v. Geren*, 128 S. Ct. 2207, 2219 (2008) (citations omitted).

In this case, Astellas is seeking not to preserve the status quo, but to obtain an order requiring Sandoz to withdraw its generic version of tacrolimus from the market and directing FDA to use a specific methodology when evaluating ANDAs referencing Prograf. This exceptional request for relief presents an additional and very high hurdle for Astellas. A court's power to issue such an injunction "should be sparingly exercised." *Mylan Pharm., Inc. v. Shalala*, 81 F. Supp.2d 30, 36 (D.D.C. 2000). *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,* at 215.

II. Astellas Is Not Entitled to a Temporary Restraining Order or a Preliminary Injunction

A. Astellas Is Not Likely to Succeed on the Merits

1. FDA's Scientific Determinations, Particularly as They Concern Appropriate Measurements of Bioequivalence, Are Due Substantial Deference

FDA's administrative decisions are subject to review by this Court under the Administrative Procedure Act, 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). It starts with "a presumption in favor of the validity of the administrative action," *Bristol-Myers*, 923 F. Supp. at 216, and requires the Court to uphold the action so long as it 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).

When, as here, an agency's decision is based on evaluation of scientific information within the agency's area of technical expertise, the degree of deference is even greater. *International Fabricare Inst. v. EPA*, 972 F.2d 384, 389 (D.C. Cir. 1992) ("The rationale for deference is particularly strong when [the agency] is evaluating scientific data within its technical expertise."). Courts "review scientific judgments of the agency 'not as the chemist, biologist, or statistician that [they] are qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality.'" *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (quoting *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976)). Accordingly, courts, recognizing that "FDA possesses the requisite know-how to conduct such [scientific] analyses, by sifting through the scientific evidence to determine the most accurate and up-to-date information regarding a particular drug," routinely "defer to its reasonable findings." *Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996). *See also Schering Corp. v. FDA*, 51 F.3d at 399 (FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us."); *Tri-Bio Laboratories, Inc.*, 836 F.2d at 142 ("in evaluating

scientific evidence in the drug field, the FDA possesses an expertise entitled to respectful consideration by this court.").

The argument favoring deference is stronger yet in this case, where Astellas is challenging FDA's choice of a scientific methodology to evaluate bioequivalence. Courts have repeatedly upheld FDA's scientific judgment in determining appropriate measurements of bioequivalence.

In *Bristol-Myers*, for instance, an innovator drug manufacturer sought a preliminary injunction against FDA's approval of a generic competitor, arguing that FDA had impermissibly determined bioequivalence based solely on *in vitro* testing rather than requiring both *in vivo* and *in vitro* testing as it had required in the past. 923 F. Supp. at 216. The Court, however, denied the preliminary injunction request, recognizing FDA's broad discretion in making bioequivalence determinations and holding that FDA may, "as part of its expertise and exercise of discretion, . . . waive certain testing procedures." *Id.* at 217. The court went on to explain that while "the 1984 amendments did make the bioequivalence requiement mandatory . . . there is nothing in the legislative history to indicate that Congress intended to restrict FDA's historical discretion to decide how that requirement would be met." *Id.* at 218 (quoting *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 649-50 (D.D.C. 1992)).

Similarly, in *Fisons Corp. v. Shalala*, an innovator drug manufacturer's request for a preliminary injunction against approval of generic competitors also was denied. Like the manufacturer in *Bristol-Myers,* the manufacturer in *Fisons* contended that FDA could not waive *in vivo* testing to demonstrate bioequivalence with an RLD. The court held, however, that FDA had broad discretion in making bioequivalence determinations and could, "as part of its expertise

or discretion in making that bioequivalence finding, . . . elect to waive certain testing procedures where the make-up of pioneer and generic products are similar in all pertinent ways." 860 F. Supp. at 865. Once again, the court found nothing in the statute or legislative history "that mandates that the FDA undertake a given methodology" in determining bioequivalence. *Id.* at 866. Thus, it concluded that FDA was free to exercise its discretion "based on a reasonable and scientifically supported criterion, whether [FDA] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs or dosage forms." *Id.* (internal quotation omitted). *See also Somerset Pharms., Inc. v. Shalala*, 973 F. Supp. 443, 453 (D. Del. 1997) ("measuring bioequivalence is a matter of scientific judgment, falling squarely within the FDA's discretion.").

Schering Corp. v. FDA, also addressed a challenge to an FDA regulation concerning methods of determining bioequivalence. The innovator manufacturer contended that the regulation impermissibly construed the FDCA by permitting FDA to determine bioequivalence by examining the availability of the drug at the site of application, rather than by examining absorption. 51 F.3d at 393. The court rejected this argument, finding "no evidence that Congress intended to limit the discretion of the FDA in determining when drugs were bioequivalent for purposes of ANDA approval." *Id.* at 399. As the court forcefully explained, "[t]he FDA is the agency charged with implementing the [FDCA]. Its judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us." *Id.*

The central thrust of Astellas' challenge to FDA's determination about the appropriate bioequivalence measure for generic tacrolimus is its insistence that FDA require ANDA filers to

conduct studies in transplant patients. *See* Pl. Mem. at 16-22. FDA, however, carefully considered the scientific merits of this argument, and rejected it. As FDA explained in its response to Astellas' citizen petition:

> [F]or systemically acting drugs, bioequivalence studies are used to assess differences in formulation and other product-related characteristics on the release of the drug substance from a drug product into the systemic circulation. We note that single-dose bioequivalence studies are generally more sensitive at detecting formulation or other product-related characteristics that may affect bioequivalence to the RLD than multiple-dose (steady-state) bioequivalence studies. In addition, such multiple-dose studies are generally conducted in patients and hence may include sources of variability related to the disease state, which may confound the bioequivalence outcome. Moreover, with regard to tacrolimus, there is insufficient scientific evidence to suggest that the use of specific patient population(s) in bioequivalence studies would detect differences in formulation that might have clinical significance and that would not be detected by bioequivalence studies in healthy subjects. Therefore, additional bioequivalence studies conducted in transplant patients are not justified.

See Citizen Petition Response, Pl. Ex. L at 6-7.[2]

More specifically, Astellas claims that FDA failed to adequately explain how patient-related factors (such as organ-type transplanted, current medications, and time after transplant) do not have the same impact on bioequivalence testing for tacrolimus as food. To the contrary, however, the burden was on Astellas, as petitioner, to provide evidence to FDA to support its challenge to FDA's bioequivalence determination, which Astellas failed to do. *See* Ex. L to Pl. Mem. at 8 ("you [Astellas] have not provided evidence to show that the patient-related factors you cite would identify differences in formulation that might have clinical significance and that

[2] FDA obviously has not had time to compile the Administrative Record, but its citizen petition response is part of the Record.

would not be identified in the testing of healthy subjects").[3] Moreover, FDA reasoned that because the current literature indicates that the effects of patient-related factors are due to the active ingredient in the drug product, and because ANDAs will contain the same amount of the same active ingredient as the RLD, formulation differences between drug products should not significantly affect product performance. This is in contrast to the effects of food, however, which as indicated in the Prograf labeling, have been shown to have a considerable effect on the bioavailability, and hence bioequivalence, of the tacrolimus products and which are known to differ due to differences in formulation. *See* Ex. L to Pl. Mem. at 11 ("Since a generic product will contain identical amounts of the same active ingredient in the same dosage form at the RLD, the impact of patient-related factors on drug exposure is not expected to differ between the test and reference products.").

In sum, FDA's determination as to the appropriate measure of bioequivalence is due extraordinary deference and should only be disturbed if the agency entirely failed to consider relevant factors and reached a decision devoid of rational justification. Astellas has not and cannot come close to making such a showing here.

2. FDA Properly Determined That a Change in the Labeling for Tacrolimus was not Justified

Astellas contends that FDA violated the FDCA by failing to revise the approved tacrolimus labeling as requested in Astellas' citizen petition, and that such refusal was arbitrary and capricious. *See* Pl. Mem. at 23-25. As explained in the response to the citizen petition, FDA

[3] *See also id.* at 8-9 (discussing the flaws in the studies relied on by Astellas in its citizen petition); at 11 (discussing the ASTS submission).

concluded that labeling changes were not needed, and that the current labeling appropriately describes the need for physicians to closely monitor transplant patients when using immunosuppressant drug products. *See* Ex. L to Pl. Mem. at 13. More specifically, FDA explained, "the current review process for ANDAs is adequate to assure the interchangeability of generic versions of immunosuppressant drugs such as tacrolimus with their branded counterparts." *Id.* As with its arguments regarding bioequivalence, Astellas has failed to demonstrate that FDA's decision regarding the tacrolimus labeling is in any way arbitrary, capricious, or otherwise not in accordance with law. Astellas therefore has wholly failed to make a showing of likelihood of success on the merits and, for that reason alone, neither a temporary restraining order nor a preliminary injunction is warranted here.

B. Astellas Will Not Suffer Irreparable Injury 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 Astellas is not likely to succeed on the merits, it "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). "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*, 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 in this Circuit that mere economic loss in and of itself does not constitute irreparable harm. "Mere injuries, however substantial, in terms of money, time and energy necessarily expended" are inadequate. *Bristol Myers*, 923 F. Supp. at 220, quoting *Wisconsin Gas*, 758 F.2d at 674. Allegations of lost sales must be "sufficiently large in proportion to the plaintiff's operations that the loss of the amount of money involved would also cause extreme hardship to the business, or even threaten destruction of the business." *Gulf Oil*, 514 F. Supp. at 1025. *See also 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*, 81 F. Supp.2d at 42 ("Because Mylan is alleging a non-recoverable monetary loss, it must demonstrate 'that the injury [is] more than simply irretrievable, it must also be serious in terms of its effect on the plaintiff.'") (quoting in part *Gulf Oil Corp.*, 514 F. Supp. at 1026).

Astellas alleges it will suffer irreparable harm "in the form of lost sales, price erosion, loss of goodwill, and harm to reputation" in the absence of preliminary injunctive relief. *See* Pl. Mem. at 26. This Court has flatly rejected claims virtually identical to Astellas' assertions about the loss of "goodwill" and "reputation." In *Bristol-Myers*, plaintiff alleges that FDA had used an improper method to determine the bioequivalence of a generic drug, and as a result its reputation would suffer if use of the generic resulted in any adverse health effect. 923 F. Supp. at 221. This Court noted: "There is nothing before the court which would lead it to conclude that [the generic] will cause any harmful health effects." *Id.* Similarly, here Astellas' claim of the loss of goodwill is based on bald assertions – without support – in a declaration: "Astellas will suffer harm to its reputation with patients and health care professionals to the extent a generic product

is substituted for Prograf and the generic substitute fails to provide the expected therapy." Pl. Ex. H ¶ 10. Also, "*if* a generic product is substituted for Prograf and the generic product fails. . . ." *Id.* (emphasis added). Thus, Astellas' assertion that it will lose "goodwill" and "reputation" is based entirely on the unsubstantiated assertion that the generic product *might be* substituted for its product, and it *might* fail, and should be rejected by this Court as it was in *Bristol-Myers*.

Plaintiffs' allegations about loss of sales are similarly speculative. This Court has held that "demanding scrutiny must be applied to claims of irreparable injury." *Bristol-Myers*, 923 F. Supp. at 220. While Astellas claims that Prograf is its leading drug in the United States, it does not provide information about the sales figures for Prograf. Pl. Ex. H ¶ 5. It claims that Astellas' parent company had North American sales of $884 million in 2008, but there is no indication of how much of this was the sales of Prograf. *Id.* In sum, Astellas' allegations amount to "mere speculation concerning the encroachment of [the generic] into its market share." *Bristol-Myers*, 923 F. Supp. at 222. Moreover, Astellas bases its allegations of loss on a comparison to other products' loss figures for several months or years. Ex. H. ¶ 7. However, the correct time period for calculating loss is the period until the merits of the case can be resolved, which will not be many months or years. *Bristol-Myers*, 923 F. Supp. at 222.

Also, while Astellas argues that it "lacks an adequate remedy at law to recover for these losses," Pl. Mem. at 29, this Court has rejected that contention: "Bristol's argument that if it prevails on the merits it will be unable to recover damages is inconsequential." *Bristol-Myers*, 923 F. Supp. at 222.

Thus, Astellas' claims of irreparable harm are based on speculation, and fail to show meet the "demanding scrutiny" required by this Court. *Bristol-Myers*, 923 F. Supp. at 220. In *Bristol-*

Myers, the Court noted that a loss of 20 to 30 percent of market share had been "inadequate to establish irreparable harm" in *Mead Johnson Pharmaceutical Group v. Bowen*, 655 F.Supp. 53 (D.D.C. 1986). *See Bristol-Myers*, 923 F. Supp. at 221. *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 when movant's revenue would decline by 10 percent); *TGS Tech., Inc. v. United States*, Civ. No. 92-0062, 1992 WL 19058, at *4 (D.D.C. Jan. 14, 1992) (finding no irreparable harm where lost contract constituted 20 percent of movant's business); *Experience Works, Inc.*, 267 F. Supp. 2d at 96 ($21.1 million reduction in funding is a serious financial blow, but one frequently faced by other similar entities, and not an economic loss that threatens survival of the business).

C. The Requested Relief Will Not Serve the Public Interest

Finally, plaintiff 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. The FDCA requires generic drugs to be approved when FDA determines, among other things, that the product is bioequivalent to the brand product. 21 U.S.C. § 355(j)(4). As such, FDA's interest coincides with the public interest. *See Virginian Ry. Co. v. System Federation No. 40*, 300 U.S. 515, 552 (1937) (Congressional purpose "is in itself a declaration of public interest and policy which should be persuasive" to courts).

Astellas contends that the public interest is furthered by "requiring FDA to comply with the law." Pl. Mem. at 31. However, FDA has complied with the law, and that law requires FDA to approve generic products when they meet the requirements for approval. 21 U.S.C. § 355(j)(4). Astellas' assertions of "public interest" are based on its erroneous application of the law. The public interest depends on the faithful application of the statute, not a particular result to a particular company, *i.e.*, maintaining exclusivity for Astellas if the statute does not support that result. In this case, FDA is charged with administering the statute and does so responsibly and in accordance with its mission. *Cf. Citizens to Preserve Overton Park,* 401 U.S. at 415 (courts afford administrative agencies a "presumption of regularity").

Moreover, Astellas cannot show that the public interest would be served by delaying approval for ANDAs. Such an injunction would result in higher prices for consumers until other ANDAs could be approved and introduce full competition into the market. "The using public will therefore now benefit from increased competition." *Bristol-Myers*, 923 F. Supp. at 222. *See also Hi-Tech Pharmacal Co. v. FDA*, 587 F. Supp.2d 1, 12-13 (D.D.C. 2008); *Biovail*, 448 F. Supp. 2d at 166 (discussing the public interest in "'receiving generic competition to brand-name drugs as soon as is possible'" (quoting *Boehringer Ingelheim Corp. v. Shalala*, 993 F. Supp. 1, 3 (D.D.C. 1997), and "'in reduced prices'" (quoting *Schering Corp. v. Sullivan*, 782 F. Supp. at 652. Because Astellas has failed to establish that it has any rights at issue that are being threatened, public interest "would be better served by denying plaintiff's motion." *Boehringer Ingelheim*, 993 F. Supp. at 3.

CONCLUSION

For the foregoing reasons, Astellas' motion for a temporary restraining order and preliminary injunction should be denied.

Of Counsel:

DAVID S. CADE
Acting General Counsel
U.S. Dept. of Health & Human Services

MICHAEL M. LANDA
Acting Associate General Counsel
Food and Drug Division

ERIC M. BLUMBERG
Deputy Chief Counsel, Litigation

JOHN H. FUSON
Associate Chief Counsel, Litigation
Office of the General Counsel
5600 Fishers Lane, GCF-1
Rockville, MD 20857
301-827-1190
john.fuson@fda.hhs.gov

August 12, 2009

Respectfully submitted,

TONY WEST
Assistant Attorney General

ANN M. RAVEL
Deputy Assistant Attorney General

EUGENE M. THIROLF
Director

/s/
DRAKE CUTINI
Attorney
Office of Consumer Litigation
U.S. Department of Justice
P.O. Box 386
Washington, D.C. 20044
202-307-0044
Fax: 202-514-8742
drake.cutini@usdoj.gov