UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

ASTELLAS PHARMA US, INC.,	:	
	:	
Plaintiff,	:	Civil Action No.: 09-1511 (RMU)
	:	
v.	:	Re Document No.: 3
	:	
FOOD AND DRUG ADMINISTRATION *et al.*,	:	
	:	
	:	
Defendants.	:	

MEMORANDUM OPINION

DENYING THE PLAINTIFF'S MOTION FOR A TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION

I. INTRODUCTION

This matter is before the court on the plaintiff's motion for a temporary restraining order and preliminary injunction requiring the Food and Drug Administration ("FDA") to withdraw its approval of any generic version of the immunosuppressant tacrolimus. The plaintiff, which pioneered the development of tacrolimus and markets it under the brand name Prograf®, contends that the FDA acted in an arbitrary and capricious manner in approving a generic version of the drug for distribution in the U.S. market. Because the plaintiff has failed to demonstrate a likelihood of success on the merits, has not demonstrated that it will suffer irreparable harm absent interim injunctive relief and has failed to show that the public interest favors withdrawing the FDA's approval of the generic drug, the court denies the plaintiff's motion.

II. FACTUAL & PROCEDURAL BACKGROUND

A. Framework Governing the Approval of New Drugs

The Food, Drug, and Cosmetic Act ("FDCA") provides that before any new drug can be introduced into the U.S. market, the FDA must determine that it is safe and effective. 21 U.S.C. § 355(a). The first, or "pioneer," applicant for a given drug must submit to the FDA a new drug application ("NDA"), containing, among other things, "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use . . . a full list of the articles used as components of such drug . . . [and] a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drugs." *Id*. § 355(b). Once approved, the pioneer drug is referred to as a "listed" drug. *Id*.

Recognizing that the NDA process is costly and time-consuming, Congress amended the FDCA in 1984 pursuant to the "Hatch-Waxman Amendments." *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1316 (D.C. Cir. 1998) (citing H.R. Rep. No. 98-857, pt. 1 at 14 (1984)). In an effort "to make available more low cost drugs," *id*., the amended FDCA permits the manufacturer of a generic version of a listed drug to obtain FDA approval through a far simpler, abbreviated new drug application ("ANDA") containing a more limited set of information than that required for an NDA. 21 U.S.C. § 355(j). Rather than requiring the applicant to make an independent showing that the proposed generic is itself safe and effective, the amended statute requires a showing that the proposed generic operates in the same manner as the pioneer drug on which it is based – its reference listed drug ("RLD"). Thus, the FDA's approval of a new generic drug relies on its prior determination that the RLD is safe and effective. *See id*.

Specifically, the FDCA provides that an ANDA must contain "information to show that the new drug is bioequivalent" to the RLD.[1] *Id.* § 355(j)(2)(A)(iv); 21 C.F.R. § 314.127(a)(6)(i) (stating that the FDA will refuse approval of an ANDA if the information submitted "is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the abbreviated new drug application"). The FDA must approve an ANDA unless the information submitted in the ANDA is insufficient to meet the statutory requirements. 21 U.S.C. § 355(j)(4).

The FDCA further provides that a generic drug is considered to be "bioequivalent" to an RLD 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 when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses." *Id.* § 355(j)(8)(B)(i); *see also* 21 C.F.R. § 320.1(e). The applicable regulations identify several methodologies for testing bioequivalency, including 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).

B. Approval of Prograf® and Generic Tacrolimus

In April 1994, the FDA approved the plaintiff's NDA for the immunosuppressant tacrolimus, which it markets under the brand name Prograf®. Pl.'s Mot. at 8. Prograf® is indicated for the prophylaxis of organ rejection in patients receiving liver, kidney and heart transplants. *Id.* Typically, the drug is administered orally. *Id.* The plaintiff states that in fiscal year 2008, sales of Prograf® constituted roughly half of the plaintiff's total U.S. revenues of $884 million. *Id.* at 9, 26.

[1] The ANDA must also contain information sufficient to show that the proposed generic drug has the same active ingredient, indications for use, route of administration, dosage form and labeling as the RLD. 21 U.S.C. § 355(j)(2)(A).

The plaintiff notes that tacrolimus is characterized as a narrow therapeutic index ("NTI") drug, meaning that it is the type of drug for which "small changes in concentration in the body can lead to significant difference in pharmacodynamic and clinical response." *Id*. at 3. The plaintiff also asserts that tacrolimus is a "critical dose" drug, meaning that "small changes in concentration in the body can lead to acute rejection, toxicities, or even death of the patient." *Id*. As a result, "careful therapeutic monitoring of blood levels and clinical monitoring of each patient is necessary." *Id.*

In 2006, the FDA published draft guidelines for establishing the bioequivalency of generic tacrolimus. *Id*., Ex. L (Letter from Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research, Department of Health & Human Services) ("Woodcock Letter") at 3-4. The FDA recommended the following studies to establish bioequivalency: (1) a single-dose, two-treatment *in vivo* study of individuals in a fasting state and (2) a single-dose, two-treatment *in vivo* study of individuals in a fed state. *Id*.

The plaintiff states that over the past decade, the FDA has acknowledged the limitations of its existing bioequivalency guidelines for NTI drugs like tacrolimus. *Id*. at 6. The plaintiff asserts that on multiple occasions, the FDA has considered amending its bioequivalency guidelines for NTI drugs but, inexplicably, has never implemented those changes. *Id*. at 6-7.

In September 2007, the plaintiff submitted a "Citizen Petition" to the FDA. *Id*. at 10. In the petition, the plaintiff requested that the FDA (1) require that bioequivalence studies be performed in transplant populations (rather than solely in healthy populations) for orally administered NTI immunosuppressants like tacrolimus and (2) revise labeling requirements for all orally administered NTI immunosuppressants to add warnings notifying physicians about the substitution of the generic for the name brand. *Id*. In support of its petition, the plaintiff offered

a letter authored by Dr. David C. Cronin, a transplant surgeon and pharmacist, stating that due to the significant intrapatient variability in the pharmacokinetics of tacrolimus, the FDA's existing bioequivalency standards would not sufficiently predict the effects of the generic when administered to individual patients. *Id*. at 11. Cronin also supported the plaintiff's petition for revising the label requirement, asserting that where tacrolimus formulations have been switched, physicians must be particularly vigilant in monitoring their patients to avoid serious adverse effects. *Id*. at 12. The plaintiff also submitted a white paper from the National Kidney Foundation and a meeting report from the American Society of Transplantation, both of which expressed concerns about the general application of the FDA's current bioequivalence standards to special populations such as transplant recipients. *Id*. at 13.

On August 10, 2009, the FDA denied the plaintiff's Citizen Petition in all relevant respects. *Id*. at 13; Woodcock Letter at 6-15. The FDA concluded that additional bioequivalence studies conducted in transplant populations were not warranted:

> We note that single-dose bioequivalence studies are generally more sensitive at detecting formulation or other product-related characteristics that may affect bioequivalences 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 bioequivalence outcomes. 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.

Woodcock Letter at 6-7. The FDA noted that the same bioequivalency testing framework was successfully employed in connection with generic versions of cyclosporine, another NTI immunosuppressant which, like tacrolimus, is a calcineurin inhibitor and which shares with tacrolimus a common mechanism of action. *Id*. at 3.

In response to the plaintiff's assertion that tacrolimus can have varying effects on patients, which purportedly underscored the need for additional bioequivalency studies, the FDA stated that based on the current literature, this variability "[is] related to the active ingredient in the drug product." *Id*. at 7. Because the generic version of tacrolimus "will contain the identical amount of the same active ingredient in the same form as Prograf," patient variability did not justify additional studies in transplant populations. *Id*. at 7-8. Finally, the FDA addressed the various studies included by the plaintiff in support of its petition and concluded that they did not justify additional bioequivalency testing. *Id*. at 8-10.

The FDA also rejected the plaintiff's request for revised labeling requirements. *Id*. at 12-13. The FDA concluded that based upon its current knowledge and prior experience with similar drugs, additional warnings were unnecessary because "[t]he 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*. at 13.

On August 10, 2009, the same day that it denied the plaintiff's Citizen Petition, the FDA approved the ANDA for a generic version of tacrolimus submitted by Sandoz, a leading manufacturer of generic drugs.[2] *Id*. at 14 & Ex. P. The next day, Sandoz announced the launch of its generic version of tacrolimus in the U.S. market. Pl.'s Mot., Ex. P. At the same time, the plaintiff filed the instant motion for a temporary restraining order and preliminary injunction. *See generally* Pl.'s Mot. The court set an expedited briefing schedule, and the FDA submitted its opposition on August 12, 2009.

[2] Sandoz's ANDA had been pending for more than two years. Defs.' Opp'n at 2.

II. ANALYSIS

A. Legal Standard for Interim Injunctive Relief

This court may issue interim injunctive relief only when the movant demonstrates "[1] that he is likely to succeed on the merits, [2] that he is likely to suffer irreparable harm in the absence of preliminary relief, [3] that the balance of equities tips in his favor, and [4] that an injunction is in the public interest." *Winter v. Natural Res. Def. Council, Inc.*, 129 S. Ct. 365, 374 (2008) (citing *Munaf v. Geren*, 128 S. Ct. 2207, 2218-19 (2008)). It is particularly important for the movant to demonstrate a likelihood of success on the merits. *Cf. Benten v. Kessler*, 505 U.S. 1084, 1085 (1992) (per curiam). Indeed, absent a "substantial indication" of likely success on the merits, "there would be no justification for the court's intrusion into the ordinary processes of administration and judicial review." *Am. Bankers Ass'n v. Nat'l Credit Union Admin.*, 38 F. Supp. 2d 114, 140 (D.D.C. 1999) (internal quotation omitted).

The other critical factor in the injunctive relief analysis is irreparable injury. A movant must "demonstrate that irreparable injury is *likely* in the absence of an injunction." *Winter*, 129 S. Ct. at 375 (citing *Los Angeles v. Lyons*, 461 U.S. 95, 103 (1983)). Indeed, if a party fails to make a sufficient showing of irreparable injury, the court may deny the motion for injunctive relief without considering the other factors. *CityFed Fin. Corp. v. Office of Thrift Supervision*, 58 F.3d 738, 747 (D.C. Cir. 1986). Provided the plaintiff demonstrates a likelihood of success on the merits and of irreparable injury, the court "must balance the competing claims of injury and must consider the effect on each party of the granting or withholding of the requested relief." *Amoco Prod. Co. v. Gambell*, 480 U.S. 531, 542 (1987). Finally, "courts of equity should pay particular regard for the public consequences in employing the extraordinary remedy of injunction." *Weinberger v. Romero-Barcelo*, 456 U.S. 305, 312 (1982).

As an extraordinary remedy, courts should grant such relief sparingly. *Mazurek v. Armstrong*, 520 U.S. 968, 972 (1997). The Supreme Court has observed that a preliminary injunction "is an extraordinary and drastic remedy . . . that should not be granted unless the movant, *by a clear showing*, carries the burden of persuasion." *Id.* Therefore, although the trial court has the discretion to issue or deny a preliminary injunction, it is not a form of relief granted lightly. In addition, any injunction that the court issues must be carefully circumscribed and "tailored to remedy the harm shown." *Nat'l Treasury Employees Union v. Yeutter*, 918 F.2d 968, 977 (D.C. Cir. 1990).

B. The Court Denies the Plaintiff's Motion for a Temporary Restraining Order and Preliminary Injunction

1. The Plaintiff Has Not Demonstrated a Likelihood of Success on the Merits

a. Legal Standard for Judicial Review of Agency Action

The Administrative Procedure Act ("APA") entitles "a person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action . . . to judicial review thereof." 5 U.S.C. § 702. Under the APA, a reviewing court must set aside an agency action that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." *Id.* § 706; *Tourus Records, Inc. v. Drug Enforcement Admin.*, 259 F.3d 731, 736 (D.C. Cir. 2001). In making this inquiry, the reviewing court "must consider whether the [agency's] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Marsh v. Oregon Natural Res. Council*, 490 U.S. 360, 378 (1989) (internal quotations omitted). At a minimum, the agency must have considered relevant data and articulated an explanation establishing a "rational connection between the facts found and the choice made." *Bowen v. Am. Hosp. Ass'n*, 476 U.S. 610, 626 (1986); *Tourus Records*, 259 F.3d at 736. An agency action usually is arbitrary or capricious if

> the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.

Motor Veh. Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983); *see also County of L.A. v. Shalala*, 192 F.3d 1005, 1021 (D.C. Cir. 1999) (observing that "[w]here the agency has failed to provide a reasoned explanation, or where the record belies the agency's conclusion, [the court] must undo its action").

As the Supreme Court has explained, however, "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." *Motor Veh. Mfrs. Ass'n*, 463 U.S. at 43. Rather, the agency action under review is "entitled to a presumption of regularity." *Citizens to Pres. Overton Park, Inc. v. Volpe*, 401 U.S. 402, 415 (1971), *abrogated on other grounds by Califano v. Sanders*, 430 U.S. 99 (1977).

b. The Plaintiff Is Not Likely to Show that the FDA Acted in an Arbitrary or Capricious Manner by Refusing to Require Additional Bioequivalency Testing

The plaintiff contends that it is likely to prevail on the merits because the FDA acted in an arbitrary and capricious manner in denying the plaintiff's Citizen Petition and approving Sandoz's ANDA without requiring additional bioequivalency studies. Pl.'s Mot. at 17-26. The plaintiff asserts that despite the fact that the FDA has acknowledged the limitations of its current bioequivalence guidelines with respect to NTI drugs, and despite the obvious significance of testing generic NTI immunosuppressants on transplant populations, the FDA did not require bioequivalency testing on transplant patients prior to approving Sandoz's ANDA for generic tacrolimus. *Id*. at 17-18. The plaintiff asserts that in the Woodcock Letter, the FDA cites no literature justifying its conclusion that variability among transplant patients is related to the active ingredient of tacrolimus. *Id*. at 18-19. Indeed, the plaintiff contends that this conclusion

is contradicted by several studies, cited by the plaintiff in its Citizen Petition, which suggest that variability may be associated with different formulations of an NTI immunosuppressant drug, such that a generic could produce different effects on patients despite having an identical amount of the same active ingredient. *Id*. at 19-20. For instance, the plaintiff points to a study showing that Advagraf® may have different effects on patients than Prograf® despite the fact that the two drugs contain the same active ingredient. *Id*. at 20.

The plaintiff notes that although the FDA's bioequivalence guidelines acknowledge that tacrolimus can have differing effects depending on whether the individual is fed or fasting when ingesting the drug, it cites no reason for singling out food effects. *Id*. at 19. The FDA's recognition that food effects can have an effect on bioequivalency contradicts the FDA's assertion that variability among effects is related to the active ingredient of tacrolimus. *Id*.

In addition, the plaintiff asserts that in approving Sandoz's ANDA without requiring a bioequivalency study on a transplant population, the FDA ignored the unique vulnerability of transplant patients, who are often on multiple medications and face unique risks. *Id*. at 21. The plaintiff also asserts that the FDA's reliance on its experience testing generic cyclosporine is inapposite, as the FDA has presented no evidence that cyclosporine and tacrolimus are similar chemical entities with similar properties. *Id*. at 22. Furthermore, the plaintiff contends that the FDA's experience with cyclosporine fails to establish that the effects of immunosuppressant drugs on transplant patients can differ significantly as compared with healthy patients. *Id*.

The defendants respond that the FDA considered the plaintiff's challenges regarding the adequacy of its bioequivalency testing guidelines and, applying its scientific and technical expertise, concluded that additional bioequivalency testing was not warranted. Defs.' Opp'n at 9-13. The defendants note that the reasoning underlying the FDA's determination was set forth

in great detail in its response to the plaintiff's Citizen Petition. *See id*. For instance, the FDA noted that single-dose bioequivalence studies, like the ones called for in the FDA's draft guidelines for generic tacrolimus, "are more sensitive [than multi-dose, in-patient tests] at detecting formulation or other product-related characteristics that may affect bioequivalence to the RLD," precisely the concern cited by the plaintiff in its petition. *Id*. at 13 (quoting Woodcock Letter at 7). In addition, the FDA concluded that "there [was] 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 would not be detected by bioequivalence studies in healthy subject." *Id*. at 13 (quoting Woodcock Letter at 6-7). Moreover, the FDA noted that the then-current scientific literature indicated that the patient variability cited by the plaintiff was related to the active ingredient in tacrolimus, which is identical in Prograf® and the proposed generic. *Id*. at 13-14. The FDA reasoned that while food effects are known to vary based on a drug's formulation, the plaintiff failed to explain how patient-specific factors, such as organ-type transplanted, current medications and the time elapsed after transplant, would lead to different effects based on different formulations. *Id*. at 13-14. In short, the FDA concluded that the plaintiff's call for additional bioequivalency testing was based on nothing more than conjecture and was not supported by the scientific literature. *Id*. at 9-13.

The Circuit has noted that the FDA's "evaluations of scientific data within its area of expertise . . . [are] entitled to a 'high level of deference.'" *Serono*, 158 F.3d at 1320; *Int'l Fabricare Inst. v. Envtl. Prot. Agency*, 972 F.2d 384, 389 (D.C. Cir. 1992) (observing that the rationale for deference is "particularly strong" when an agency evaluates scientific evidence within its technical expertise); *see also Zeneca, Inc. v. Shalala*, 213 F.3d 161, 170 (4th Cir.

2000); *Henley v. Food & Drug Admin.*, 77 F.3d 616, 621 (2d Cir. 1996) (noting that the FDA is entitled to deference insofar as it "possesses the requisite know-how to conduct such analyses, by sifting through the scientific evidence to determine the most accurate and up-to-date information regarding a particular drug, and how those data affect human usage"); *Schering Corp. v. Food & Drug Admin.*, 51 F.3d 390, 399 (3d Cir. 1995). The Circuit has stated that the FDA's "judgment as to what is required to ascertain the safety and efficiency of drugs falls squarely within the ambit of the FDA's expertise and merit deference" from the courts. *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995) (quoting *Schering*, 51 F.3d at 399).

This high degree of deference has been applied to the FDA's determinations regarding which methodologies it determines are needed to test the bioequivalency of a given generic. *See Serono*, 158 F.3d at 1325 (holding that an RLD manufacturer was unlikely to succeed on its challenge to the FDA's reliance on animal studies to establish the bioequivalency of a proposed generic because courts "are bound to show deference to the agency's fact-finding in this area of its technical expertise"); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 2d 212, 217-18 (D.D.C. 1996) (holding that the plaintiff demonstrated no likelihood of success in its challenge to the FDA's reliance on *in vitro* testing to establish bioequivalence because "there is nothing in the legislative history [to the Hatch-Waxman Amendments] to indicate that Congress intended to restrict FDA's historical discretion to decide how that requirement would be met"); *Somerset Pharm., Inc. v. Shalala*, 973 F. Supp. 443, 453 (D. Del. 1997) (rejecting the plaintiff's contention "that the FDA failed to adhere to its own regulations requiring the use of 'the most accurate, sensitive, and reproducible approach available' to establish bioequivalence" because "the determination of *which* method is the 'most accurate sensitive, and reproducible' for measuring bioequivalence is a matter of scientific judgment, falling squarely within the FDA's discretion").

Indeed, the applicable regulations expressly permit the FDA to employ "any . . . approach deemed adequate by [it] to measure bioavailability or establish bioequivalence." 21 C.F.R. § 320.24(b); *see also A.L. Pharma*, 62 F.3d at 1491 (observing that the court "must defer to an agency's interpretation of its own regulations 'unless it is plainly erroneous or inconsistent with the regulation'").

In the instant case, the FDA produced a comprehensive response to the plaintiff's Citizen Petition, in which it specifically addressed the plaintiff's arguments and provided a detailed justification for its conclusion that additional bioequivalency testing was not needed. *See generally* Woodcock Letter. The Woodcock Letter indicates that the testing guidelines established for generic tacrolimus were based on the guidelines used to gauge the bioequivalency of generic cyclosporine, a similar NTI immunosuppressant which shares with tacrolimus a common mechanism of action. *Id*. at 3. The FDA asserted – and the plaintiff has not disputed – that single-dose studies, like the ones called for in the bioequivalency guidelines at issue, are more sensitive than multi-dose, in-patient studies at predicting differences resulting from differences in formulation. *Id*. at 6-7. The FDA asserted that the current scientific literature indicated that the effects of characteristics specific to transplant patients were related to the drug's active ingredient, and thus the FDA's conclusion that testing on transplant patients was not required appears to have been reasonable. *Id*. at 7-8. Furthermore, the FDA specifically addressed the numerous studies relied on by the plaintiff and explained why each did not, in the FDA's view, justify additional bioequivalency testing. *Id*. at 8-9.

The plaintiff has identified no studies or other evidence demonstrating that the FDA's conclusion was irrational, implausible or contrary to existing scientific consensus. *See generally* Pl.'s Mot. The letter submitted by Cronin on behalf of the plaintiff reiterates that tacrolimus is

an NTI, "critical dose" drug, but fails to explain why the FDA's bioequivalency guidelines for generic tacrolimus do not adequately address his concerns regarding patient variability. *See* Pl.'s Mot., Ex. G. Furthermore, as the FDA points out, the comment filed by the American Society of Transplantation provided no new scientific or clinical data to support its position. Woodcock Letter at 6. In short, although the plaintiff provides ample support for the uncontroversial proposition that supplemental testing could reveal additional information pertinent to bioequivalency, it has made no showing that the testing guidelines established by the FDA were insufficient to meet its statutory obligation to ensure the safety and efficiency of new drugs. *See generally* Pl.'s Mot.

Given the high level of deference that must be afforded to the FDA in choosing which methodologies to employ to test bioequivalency for a given drug, *see Somerset*, 973 F. Supp. at 453; 21 C.F.R. § 320.24(b), the court concludes that the plaintiff has presented insufficient evidence to suggest that the FDA acted in an arbitrary and capricious manner in setting the bioequivalency guidelines for generic tacrolimus. Accordingly, the plaintiff has failed to demonstrate a likelihood of success on the merits with respect to its request for additional bioequivalency testing.

c. The Plaintiff Is Unlikely to Demonstrate that the FDA Acted in an Arbitrary or Capricious Manner in Rejecting its Request for Revised Labeling Requirements

The plaintiff also contends that the FDA acted in an arbitrary and capricious manner in rejecting its request to revise the labeling requirements for tacrolimus. Pl.'s Mot. at 23. The plaintiff asserts that because tacrolimus is an NTI drug, physicians should be made aware of the switch to a generic version because increased patient monitoring may be needed when there is a "change in strength or sourcing of such drugs." *Id*. at 24. Accordingly, the plaintiff argues that

the label requirements for tacrolimus should be revised to notify physicians of the potential switch to a generic version of the drug. *Id*. at 24-25.

The defendants respond that the FDA properly concluded that labeling changes were not needed and that the current labeling requirements appropriately described the need for physicians to closely monitor transplant patient when using immunosuppressant drugs. Defs.' Opp'n at 14-15 (citing Woodcock Letter at 13). As the defendants note, the FDA explained that "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*. at 15 (quoting Woodcock Letter at 13). Accordingly, the FDA concluded that there was no need for the additional notices requested by the plaintiff.

The "high degree" of deference afforded to the FDA in assessing scientific data applies to the FDA's determinations regarding labeling requirements for drugs. *See Henley*, 77 F.3d at 620 (holding that the FDA did not act in an arbitrary or capricious manner in refusing to require that a requested warning be placed on a drug label because "the FDA's determination of what labeling best reflects current scientific information regarding the risks and benefits of [the drug] involves a high degree of expert scientific analysis"); *Biovail Corp. v. Food & Drug Admin.*, 519 F. Supp. 2d 39, 47 (D.D.C. 2007) (maintaining that the FDA's determination regarding the adequacy of a label for a generic drug fell within its area of technical expertise and was entitled to a high level of deference from the court).

In this case, the analysis of whether the FDA acted arbitrarily and capriciously in refusing to revise the labeling requirement for tacrolimus is intertwined with the adequacy of the agency's bioequivalency guidelines. Given the FDA's determination that its ANDA testing guidelines were sufficient to ensure the bioequivalency of generic tacrolimus, and the plaintiff's failure to

demonstrate that that determination was arbitrary or capricious, the court cannot conclude that the FDA acted arbitrarily or capriciously in concluding that additional warnings were not necessary. Indeed, the plaintiff has not identified any basis for concluding that physicians who prescribe generic tacrolimus must be more vigilant than physicians who prescribe Prograf® to similarly situated patients. *See generally* Pl.'s Mot. Accordingly, the plaintiff is unlikely to succeed on this claim as well.

2. The Plaintiff Has Failed to Demonstrate Irreparable Harm Absent Interim Injunctive Relief[3]

The plaintiff contends that it will suffer irreparable harm without a temporary restraining order and preliminary injunction. Pl.'s Mot. at 26-29. The plaintiff states that Prograf® is its top-selling drug in the United States and that sales of Prograf® constituted approximately half of its total U.S. revenue for the 2008 fiscal year. *Id*. at 26. The plaintiff asserts that once the generic form of tacrolimus enters the market, the plaintiff's revenues from the sale of Prograf® will rapidly diminish and force the plaintiff to lower the price it charges for Prograf®. *Id*. at 26-28. The plaintiff further asserts that it will suffer a loss of goodwill and reputation as a result of the entry of the generic on the market to the extent that the generic product fails to provide the safe and effective treatment that physicians have come to expect from Prograf®. *Id*. at 28-29. The plaintiff contends that it lacks an adequate remedy at law for these losses, because it would have no legal claim against the FDA or any generic drug manufacturer acting pursuant to an ostensibly valid FDA approval. *Id*. at 29. The defendants respond that the injuries identified by the plaintiff are speculative and do not constitute irreparable harm. Defs.' Opp'n at 15-18.

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[3] Although the plaintiff's failure to demonstrate a likelihood of success on the merits is sufficient grounds to deny its motion for injunctive relief, *Am. Bankers Ass'n v. Nat'l Credit Union Admin.*, 38 F. Supp. 2d 114, 140 (D.D.C. 1999), the court nonetheless turns to an examination of irreparable harm and the public interest, as the plaintiff has failed to satisfy these requirements for interim injunctive relief as well.

Turning first to the plaintiff's allegations of potential lost sales resulting from the introduction of generic tacrolimus into the market, it is well-settled that economic loss alone will rarely constitute irreparable harm. *Wis. Gas Co. v. Fed. Energy Regulatory Comm'n*, 758 F.2d 669, 674 (D.C. Cir. 1985); *Mylan Pharm., Inc. v. Shalala*, 81 F. Supp. 2d 30, 42-43 (D.D.C. 2000) (observing that "[c]ourts within the Circuit have generally been hesitant to award injunctive relief based on assertions about lost opportunities and market share"). *Barton v. District of Columbia*, 131 F. Supp. 2d 236, 247 (D.D.C. 2001). Indeed, "financial harm alone cannot constitute irreparable injury unless it threatens the very existence of the movant's business." *Sociedad Anonima Vina Santa Rita v. Dep't of Treasury*, 193 F. Supp. 2d 6, 14 (D.D.C. 2001); *Gulf Oil Corp. v. Dep't of Energy*, 514 F. Supp. 1019, 1026 (D.D.C. 1981) (noting that to constitute irreparable harm, 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 . . . cause extreme hardship to the business, or even threaten destruction of the business").

In the instant case, although the plaintiff has indicated that sales of Prograf® account for a sizable percentage of its U.S. revenues, Pl.'s Mot. at 26, it has failed to demonstrate how the introduction of generic tacrolimus would cause extreme hardship to the business or threaten its very existence, *see Gulf Oil*, 514 F. Supp. at 1026. The plaintiff has not indicated to what extent it predicts its revenues will decline following the introduction of generic tacrolimus or how such a decline would affect its overall business operations. *See Mead Johnson Pharm. Group v. Bowen*, 655 F. Supp. 53, 56 (D.D.C. 1986) (holding that a drug manufacturer failed to demonstrate irreparable harm because its "claim that it will suffer a loss of sales should an ANDA be approved and drug product marketed before this case is disposed of on the merits is pure speculation" as it had "failed to provide any proof of economic loss and merely states that it

would probably lose 20 to 30 percent of its market during the first year"); *see also Mylan Pharm.*, 81 F. Supp. 2d at 42-43 (holding that a drug manufacturer failed to establish irreparable harm because it "all but conceded" that its estimated lost revenues would not cause serious damage to the company); *Bristol-Meyers*, 923 F. Supp. at 221 (holding that a drug manufacturer failed to establish irreparable harm because its claim that it would lose between fifty and seventy percent of its market share upon the introduction of the competing drug on the market was based on mere speculation). Nor has the plaintiff indicated why it will be unable to recover its lost market share through competition. *See Cent. & S. Motor Freight Tariff Ass'n v. United States*, 757 F.2d 301, 308-09 (D.C. Cir. 1985) (observing that "revenues and customers lost to competition which can be regained through competition are not irreparable"); *see also Gulf Oil*, 514 F. Supp. at 1026 (observing that the plaintiff must show that it will suffer harm that is "more than simply irretrievable"). Accordingly, the plaintiff has failed to demonstrate that the potential loss of sales and market share rises to the level of irreparable harm.

The plaintiff's concerns about the potential loss of goodwill and reputation are founded entirely on its belief that the approved generic tacrolimus may be more harmful than Prograf®, a belief that, as has already been discussed, lacks evidentiary support and is entirely speculative. *See Bristol-Myers*, 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"). For these reasons, the court concludes that the plaintiff has failed to demonstrate that it will be irreparably harmed by the introduction of generic tacrolimus on the market during the pendency of this litigation.

3. The Public Interest Favors Denying the Plaintiff's Motion

The plaintiff contends that the public interest would be served by restraining the FDA from approving any generic versions of tacrolimus without adequate testing. Pl.'s Mot. at 31-32. The plaintiff points out that there are enormous health risks associated with organ transplantation, and that organ rejection can result in the death of a transplant patient. *Id*. Given these grave consequences, the plaintiff argues that the FDA should be required to withdraw its approval of any generic versions of tacrolimus until proper bioequivalency testing has been performed. *Id*. at 31-33. The defendants contend that delaying the introduction of a safe generic on the market will merely result in higher prices for transplant patients seeking needed drugs. Defs.' Opp'n at 19.

The public interest factor is inextricably linked with the merits of the plaintiff's claim and, accordingly, provides no support for the plaintiff. *See Serono*, 158 F.3d at 1326. As the Circuit reasoned in *Serono*,

> If, as we have held, [the movant] is not likely to establish that [the] ANDA was wrongly approved, then public interest considerations weigh against an injunction. The purpose of the Hatch-Waxman Amendments was, after all, 'to increase competition in the drug industry by facilitating the approval of generic copies of drugs.' Congress expected that competition 'to make available more low cost generic drugs.'

Id.; *see Boehringer Ingelheim Corp. v. Shalala*, 993 F. Supp. 1, 3 (D.D.C. 1997) (noting that "there is [a] public interest in receiving generic competition to brand-name drugs as soon as is possible" and that "[i]n light of the Court's view regarding the plaintiff's likelihood of success on the merits, it is clear to the Court that this particular public interest would be better served by denying the plaintiff's motion"); *see also Biotechnology Indus. Org. v. District of Columbia*, 505 F.3d 1343, 1347 (Fed. Cir. 2007) (noting that one of the purposes of the Hatch-Waxman

Amendments was to "increase[] price competition in the drug marketplace by simplifying the approval process for generic drugs") (quoting 130 Cong. Rec. 23058-59).

Here, the plaintiff has failed to demonstrate that the FDA wrongfully approved Sandoz's ANDA for generic tacrolimus. Indeed, the evidence presented to the court strongly suggests that the interests of the public, and of transplant patients more specifically, will be served by permitting generic competition with the name brand version of tacrolimus. Accordingly, the court concludes that the public interest weighs in favor of denying the plaintiff's motion.

IV. CONCLUSION

For the foregoing reasons, the court denies the plaintiff's motion for a temporary restraining order and preliminary injunction. An Order consistent with this Memorandum Opinion was issued on the 12th day of August, 2009.

RICARDO M. URBINA
United States District Judge