IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

ASTELLAS PHARMA US, INC.
Three Parkway North
Deerfield, IL 60015-2548

Plaintiff,

v.

FOOD AND DRUG ADMINISTRATION
200 C Street, SW
Washington, DC 20240

MARGARET HAMBURG, MD,
Commissioner of Food and Drugs
Food and Drug Administration
200 C Street, SW
Washington, DC 20240

and

KATHLEEN SEBELIUS,
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Defendants.

Case: 1:09-cv-01511
Assigned To : Walton, Reggie B.
Assign. Date : 8/11/2009
Description: TRO/PI

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

Plaintiff, Astellas Pharma US, Inc. ("Astellas"), brings this Complaint against the Food and Drug Administration ("FDA"), the Commissioner of Food and Drugs, Margaret Hamburg, M.D., and the Secretary of Health and Human Services, Kathleen Sebelius, and alleges as follows:

NATURE OF ACTION

1. Ignoring its core statutory mandate of ensuring that drugs are safe and effective, FDA has approved a generic version of Prograf® (tacrolimus), an important drug used for preventing the rejection of transplanted organs. Astellas, a leading research-based pharmaceutical company, brings this action for declaratory and injunctive relief to direct FDA to take action necessary to comply with its statutory mandate. Prograf, marketed by Astellas, is a leading and widely used immunosuppressant drug prescribed to prevent rejection in patients receiving heart, kidney, and liver transplants. FDA's decision, based on inadequate data, to approve generic versions of Prograf, and its failure to impose adequate labeling requirements, if not remedied, would place in jeopardy the health -- and the lives -- of the tens of thousands of patients who live with transplanted organs and who take Prograf to prevent rejection.

2. In the past 25 years, transplantation has become the treatment of choice to address many failed organs. The success of transplantation has increased dramatically the demand for donated organs, which has led to a correlative scarcity of organs available to transplant. At any given time, nearly 100,000 patients are on a waiting list for transplanted organs. Patients with failing organs often must endure prolonged waits for compatible organs, and thousands die while waiting. Safe and effective immunosuppressant drug therapy designed to prevent rejection of these highly valuable transplanted organs is thus of critical importance.

3. Ensuring that transplant patients obtain the proper dosage of tacrolimus, including Prograf, is also critically important: even small dosing errors can have grave consequences. Tacrolimus is a drug characterized by a narrow therapeutic index ("NTI"). The term "narrow therapeutic index" applies to drugs for which small changes in systemic concentration can lead to a significant difference in pharmacodynamic and clinical response.

Prograf is also a "critical dose" drug, meaning that small changes in systemic concentration can lead to acute rejection, toxicities, or even death of the patient.

4. To ensure the setting and maintenance of proper dosage levels of tacrolimus -- and to avoid adverse events including rejection and death -- careful therapeutic drug monitoring of blood levels and clinical monitoring of each patient is necessary. If drug exposure levels are too high, there is a risk of significant toxicity. If the levels are too low, the patient may experience graft loss or organ rejection. As a result, dosing of tacrolimus is highly individualized, based on both therapeutic drug monitoring and clinical monitoring of each patient.

5. Given this extremely sensitive nature of tacrolimus and the significant human and economic costs associated with organ donation and transplantation, on September 21, 2007, Astellas filed a Citizen Petition with FDA, requesting that, prior to approving any generic version of tacrolimus, the agency take measures to ensure that it is safe and effective. Astellas asked FDA, among other things: (1) to require, before approval, that for orally administered immunosuppressants, bioequivalence studies be performed in transplant patients, not only in healthy patients; and (2) to require changes in the labeling for orally administered immunosuppressants used in the transplant population and characterized by a NTI, such as tacrolimus, that would ensure that physicians are aware of any switch in formulation of tacrolimus (both from Prograf to a generic and between two generic formulations of tacrolimus) or in manufacturing source.

6. On August 10, 2009, FDA denied the majority of Astellas' requests in its Citizen Petition. FDA denied Astellas' request for a requirement of bioequivalence studies in the transplant patient population, its request for labeling changes that would reduce the risks

associated with substituting alternate formulations of tacrolimus, its request for changes to the Orange Book discussion of immunosuppressants, and its request that FDA require differentiation between manufacturing sources of tacrolimus.

7. Simultaneously with this denial of Astellas' Citizen Petition, FDA approved the abbreviated new drug application ("ANDA") of Sandoz for a generic version of tacrolimus.

8. In denying the requests in Astellas' Citizen Petition, FDA relied on the appropriateness of its standard bioequivalence inquiries and the safeguards presented by the normal ANDA approval process. FDA thus imported standard bioequivalence and labeling requirements to an NTI drug that is used with an unusually sensitive population and that, as FDA acknowledges, requires "careful dosage titration and monitoring of patient blood levels." FDA's one-size-fits-all approach to bioequivalence is inconsistent with its own findings that bioequivalence can be affected by variability in pharmacokinetics based on differing patient states.

9. FDA's denial of Astellas' Citizen Petition and its approval of generic tacrolimus are arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with the law in that the FDA failed, in violation of the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 321, *et seq*, to require bioequivalence studies in the transplant patient population and to require labeling changes that would reduce the risks associated with substituting alternate formulations of tacrolimus.

10. Astellas is entitled to declaratory judgment and injunctive relief requiring FDA to revoke its approval of generic versions of Prograf until such time as FDA (1) requires for approval of generic tacrolimus that studies be performed in the transplant patient population

demonstrating bioequivalence with Prograf, (2) revises labeling requirements for Prograf to require warnings and precautions regarding substitution of formulations, and (3) requires manufacturers of substitute formulations of tacrolimus to designate clearly their manufacturing sources so that physicians and pharmacists know when the manufacturing source has changed.

11. In the absence of injunctive relief, not only the public, but also Astellas would suffer irreparable injury. Because of FDA's approval of generic versions of tacrolimus, generic manufacturers can launch their products immediately and market them as "bioequivalent" and fully "substitutable" for Prograf. In fact, on information and belief, Sandoz has already commenced such shipments. Any such marketing of generic versions of tacrolimus would cause irreparable injury to Astellas in the form of lost sales, price erosion, loss of good will, and harm to reputation, for which Astellas would have no remedy.

Parties

12. Plaintiff Astellas is a Delaware corporation with its principal place of business at Deerfield, Illinois.

13. Defendant FDA is an agency of the United States Government within the Department of Health and Human Services, with offices at 200 C Street, S.W., Washington, D.C., and 5600 Fishers Lane, Rockville, Maryland. The Secretary of Health and Human Services has delegated to FDA the authority to administer the relevant provisions of the FDCA.

14. Defendant Margaret Hamburg, M.D., is Commissioner of Food and Drugs and is the senior official of the FDA. She is sued in her official capacity. Dr. Hamburg maintains offices at 200 C Street, S.W., Washington, D.C., and 5600 Fishers Lane, Rockville, Maryland.

15. Defendant Kathleen Sebelius is Secretary of Health and Human Services and the official charged by law with administering the FDCA. She is sued in her official

capacity. Secretary Sebelius maintains an office at 200 Independence Avenue, S.W., Washington, D.C.

Jurisdiction and Venue

16. This action arises under the FDCA and the Administrative Procedure Act, 5 U.S.C. §§ 500 *et seq.* This Court has jurisdiction pursuant to 28 U.S.C. §§ 1331, 1361, and 2201–2202.

17. Venue is proper in this district pursuant to 28 U.S.C. § 1391(e).

Factual and Legal Background

I. Statutory and Regulatory Background

18. The FDCA requires that all drug manufacturers (or "sponsors") demonstrate the safety and effectiveness of their products for each intended use.

19. Brand name (or "pioneer") drug manufacturers, such as Astellas, demonstrate safety and effectiveness by conducting pre-clinical and clinical studies of their products, producing data which are submitted in new drug applications ("NDAs"). *See* 21 U.S.C. § 355(b)(1).

20. Generic drug manufacturers, in contrast, demonstrate safety and effectiveness by showing that their products are "the same as" already-approved brand name products.

21. Generic drug manufacturers do not typically conduct pre-clinical studies or clinical studies with efficacy endpoints, and do not submit NDAs; instead, they submit abbreviated new drug applications ("ANDAs") comparing their products to approved pioneer products, with clinical data limited to bioequivalence studies. *See id.* § 355(j)(2)(A).

22. The agency may approve an ANDA if, among other things, the generic product is determined to be bioequivalent to the pioneer product. *See id.* § 355(j)(2)(A)(iv); 21 C.F.R. § 314.127(a)(6)(i).

23. The FDCA defines bioequivalence to mean that "the rate and extent of absorption of the [proposed generic] drug do not show a significant difference from the rate and extent of absorption of the [approved pioneer] drug when administered . . . under similar experimental conditions." 21 U.S.C. § 355(j)(8)(B)(i); *see also* 21 C.F.R. § 320.1(e).

24. FDA requires a demonstration of bioequivalence based on "the thesis that, if a drug product contains a drug substance that is chemically identical and is delivered to the site of action at the same rate and extent as another drug product, then it is equivalent and can be substituted for that drug product." Food and Drug Administration, Center for Drug Evaluation and Research, *Approved Drug Products with Therapeutic Equivalence Evaluations*, 28th edition, at viii. In other words, the purpose of this demonstration of bioequivalence is to provide assurance that the generic drug product is equivalent to and can be substituted for the approved pioneer product. *Id.*

25. In order for an applicant to demonstrate bioequivalence of its generic product, FDA generally requires two types of studies. For oral tablets and capsules, for which the active ingredient circulates in the blood stream, FDA generally requires one single-dose study in the fasting state in healthy adults. This study measures the mean test reference ratio for two important pharmacokinetic parameters, AUC_{0-t} and C_{max}, which measure the extent and rate of the drug's absorption. A second test, administered to healthy adults in the fed state, is typically recommended for drugs whose pharmacokinetics are affected by the administration of food. For both studies, the data must demonstrate only that the 90% confidence intervals for

both AUC_{0-t} and C_{max} fall within the range of 80% to 125%. This combination of tests was approved in FDA guidance published in 1992 ("1992 Guidance").

26. Over the past ten years, FDA has acknowledged the limitations of its existing bioequivalence standards for NTI drugs like tacrolimus and has recognized that bioequivalence determinations for NTI drugs present unique issues.

27. As a condition of approval, in addition to showing bioequivalence, generic companies must also meet labeling requirements for their products. Except in limited circumstances, generic products must use the same labeling approved for the pioneer product. *See* 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iv).

II. Factual Background

A. Transplantation

28. Transplantation is a unique medical procedure; it requires either a living donor to consent or a deceased donor to have indicated a willingness to consent to donating an organ. In the past 25 years, there have been major advances in immunosuppression, surgical technique, allocation schema, and organ storage. As a result, transplantation has become the treatment of choice for many end-organ disease states.

29. Once patients receive a transplanted organ, their care is dedicated principally to maintaining the health of the new organ in order to prevent rejection, in addition to maintaining their overall health and survival.

30. There are few, if any, physical signs to indicate when a patient's body begins to reject a transplant. The initial stages of rejection can be detected only by blood tests. By the time a patient actually experiences and reports to his or her physician symptoms related to a rejection, the rejection episode typically has progressed to an advanced stage.

31. A rejection episode can occur at any time during the life of the graft. The rejection episode typically increases in severity as more time elapses from the date of the actual transplant, because the frequency of blood monitoring and hence the opportunity to detect signs of early rejection have decreased.

32. Despite advances in the treatment of transplant patients, acute rejection occurs in roughly 20 percent of kidney transplant recipients and between 20 to 70 percent of liver transplant recipients. The number of adult heart transplant recipients treated for rejection in the first year hovers around 30 to 40 percent.

33. Rejection carries with it serious costs. The cost of the transplant surgery and recovery is substantial. In 2005, the average charge in the first year for kidney transplantation was estimated at $210,000; the costs for liver and heart transplantation during the first year were significantly higher, with average billed charges of $392,800 and $478,000 respectively. The economic costs of treating acute rejection are significant, with estimated costs of approximately $3,300 for treatment with a course of corticosteroids and between $14,500 and $18,000 with a course of antilymphocyte therapy.

34. Because of the difficulty in obtaining a suitable organ for transplant, the human costs of rejection are even more significant. More than 96,000 people in the US with end state organ failure are currently waiting for an organ transplant with nearly 4,000 new patients added each month. There is a scarcity of organs available for kidney, liver or heart transplantation, with approximately 73,000 patients on the waiting list for a kidney and only approximately 8,300 kidney transplants performed in the first half of 2007. Almost 17,000 patients are on the waiting list for a donated liver, with only 3,260 liver transplants performed in the first half of 2007. Approximately 2,700 patients are waiting for a heart transplant, with

only 1,140 heart transplants performed in the first half of 2007. The number of deaths of patients on these waiting lists has increased steadily every year. In 2006 alone, more than 6,400 patients died while waiting for an organ transplant.

B. Prograf® and its Administration

35. Astellas holds an approved NDA for Prograf, a widely prescribed immunosuppressant that is used to help reduce the risk of rejection in transplant patients. Prograf is indicated for the prophylaxis of organ rejection in patients receiving liver, kidney, or heart transplants.

36. FDA approved the NDA for Prograf on April 8, 1994, and marketing of Prograf began soon thereafter. Prograf is available for oral administration as capsules containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus. (Prograf is also available in injectable form. That form is not relevant to this case.) In fiscal year 2008 (April 1, 2008 through March 31, 2009), Prograf accounted for nearly $885 million in U.S. sales for Astellas. This translates into approximately $74 million in sales per month.

37. Prograf is first administered to a patient at the hospital following transplantation of an organ. In the induction phase, roughly the first six months after surgery, patients are at particularly high risk for rejection, and higher doses of immunosuppressants are administered during this period.

38. Patients with transplanted organs are typically required to take Prograf (or other immunosuppressants) for the entirety of the life of the grafted organ. Drug exposure levels are monitored closely to ensure that immunosuppression is within appropriate limits. If the levels are too low, the patient may experience graft loss or organ rejection.

39. During the first year, blood levels are typically tested once a week. After the induction phase, the patient is maintained on long-term immunosuppression, which can

include two or three different immunosuppressant agents. Dosage levels generally are decreased, and monitoring frequency typically is reduced to once a month or, sometimes, once every three months. Monitoring will continue, however, as long as the patient is on immunosuppressant therapy -- in most cases, for the rest of the patient's life.

C. Astellas' Citizen Petition

40. On September 21, 2007, Astellas submitted to FDA, under Sections 505(b) and 505(j) of the FDCA, a citizen petition requesting that, prior to any ANDA approval, the agency take actions necessary to ensure the safety and effectiveness of generic tacrolimus in vulnerable transplant patients. *See* Citizen Petition of Astellas, FDA Docket No. 2007P-0358 (Sept. 21, 2007) ("Citizen Petition"). Astellas requested that FDA:

A. Require that for orally administered immunosuppressants used in the transplant population and characterized by a narrow therapeutic index, such as tacrolimus, bioequivalence studies in healthy subjects be supplemented by studies performed in the transplant patient population.

B. Require changes in the labeling for orally administered immunosuppressants used in the transplant population and characterized by a narrow therapeutic index, such as tacrolimus, as follows:

1. In the "Boxed Warning" section, add: "The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient and *should be consulted before converting a patient to a substitute oral formulation so that the physician may institute appropriate blood concentration monitoring.*"

2. In the "Dosage and Administration: Blood Concentration Monitoring" section, list change to substitute oral formulations as a factor influencing the frequency of monitoring. This section would state:
"Monitoring of tacrolimus blood concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially interacting drugs, the post-transplant time and *change to substitute*

oral formulations. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies."

3. In the "Precautions: Information for Patients" section, add: "Patients should be advised that any change of oral formulation should be made cautiously and only under physician supervision because it may result in the need for a change in dosage."

C. Require manufacturers of substitute oral formulations of narrow therapeutic index drugs for use in transplant, such as tacrolimus, to identify clearly the manufacturer of tacrolimus, so that physicians and pharmacists know when the manufacturing source has changed.

41. Astellas explained to FDA that, due to significant variability among patients in the pharmacokinetics of tacrolimus, meeting the FDA-established bioequivalence standards in studies with healthy volunteers only was unlikely to predict with sufficient accuracy the pharmacokinetics observed when tacrolimus is administered to individual transplant patients. As Astellas informed FDA, the pharmacokinetics of tacrolimus in healthy volunteers varies from that observed in kidney, liver, and heart transplant recipients. For example, adult kidney transplant recipients exhibit a higher rate of clearance of tacrolimus compared to healthy subjects. Similarly, the half-life of tacrolimus differs based on whether a healthy or transplant population is studied. Thus, Astellas explained that a demonstration of bioequivalence in healthy subjects only is inadequate to ensure patient safety.

42. In the Citizen Petition, Astellas relied on numerous scientific reports that recognized and discussed the need to supplement bioequivalence testing requirements for immunosuppressants. The Citizen Petition cited reports by both the National Kidney Foundation and the American Society of Transplantation that advocated for bioequivalence studies in at-risk patients.

43. Even if bioequivalence is demonstrated through tests on transplanted patients prior to approval, additional measures are required to ensure safety in substitutions

between Prograf and generic tacrolimus drugs and between different versions of generics. If FDA approves ANDAs for tacrolimus, pharmacies ordinarily -- and in the absence of a labeling requirement -- would then be free to substitute generic versions of tacrolimus for Prograf, without notice to the prescribing physician or the patient. As Astellas explained in the Citizen Petition, substituting formulations of tacrolimus -- both from Prograf to a generic formulation or from one generic to another -- without any notice to prescribing physicians raises unique concerns in post-transplant immunosuppression, where the patients must receive long-term therapy with an NTI and critical dose drug like tacrolimus.

44. Where the formulations have been switched, tacrolimus requires especially close patient monitoring to avoid serious adverse events, including organ rejection, organ loss, and death. But this need may go unnoticed if formulations are substituted without the knowledge of the prescribing physician.

45. Astellas requested, therefore, that FDA require in the label for all versions of tacrolimus -- Prograf and generic versions alike -- that physicians be notified if a pharmacist switches a patient from previously prescribed Prograf to a generic formulation of tacrolimus or from one generic formulation to another. Astellas also requested that FDA require generic manufacturers to specify the manufacturing source of tacrolimus. These notifications, as Astellas told FDA, would allow the physician to consider whether additional therapeutic blood concentration monitoring should be performed to ensure appropriate blood levels -- and to prevent rejection episodes or toxicity.

D. FDA's Denial of the Citizen Petition

46. On August 10, 2009, FDA denied all but one of Astellas' requests in its Citizen Petition.

47. FDA admitted that it "has not made a determination whether to characterize tacrolimus as a narrow therapeutic range drug product." It acknowledged, however, that tacrolimus "requires careful dosage titration and monitoring of patient blood levels[.]"

48. FDA supported its denial of Astellas' request for additional bioequivalence studies by stating, among other things, that "[b]ased on the current literature, the effects of the patient-related factors" Astellas had cited as a basis for requiring studies in transplant patients "on the pharmacokinetics of tacrolimus are related to the active ingredients in the drug product." FDA differentiated these factors from the effect of food on the basis that "the patient-related factors should not play a significant role in determining the bioequivalence of tacrolimus products because the generic tacrolimus product will contain the identical amount of the same active ingredient in the same dosage form as Prograf (the RLD)."

49. FDA cites no "current literature," and there is none, to support its conclusion.

50. FDA denied Astellas' request for labeling changes, asserting -- without explanation -- that the ANDA review process is "adequate to assure the interchangeability of generic versions of immunosuppressant drugs such as tacrolimus with their branded counterparts."

51. FDA denied the request that it require sellers of generic tacrolimus to differentiate among manufacturing sources so that patients, physicians, and pharmacists know when sourcing has changed. FDA based this decision on the conclusion that a generic version that is approved under the current ANDA review practice is "expected" to be substitutable for

its branded counterpart "with the full expectation" that the generic will have the same clinical effect and safety profile as the prescribed product.

E. FDA's Approval of Generic Tacrolimus

52. On August 10, 2009, FDA approved an application for a generic version of tacrolimus produced by Sandoz. On information and belief, Sandoz began shipping its generic tacrolimus to pharmacies and distributors on August 10, 2009.

53. FDA's denial of the Citizen Petition and approval of a generic tacrolimus product constitute final agency action for which Astellas has no other adequate remedy within the meaning of 5 U.S.C. § 704.

CLAIMS FOR RELIEF

Count I (Bioequivalence)
(Administrative Procedure Act: Violation of the FDCA and Applicable Regulations)

1. Paragraphs 1 through 53 are incorporated herein by reference.

2. FDA's denial of Astellas' Citizen Petition and its approval of Sandoz's ANDA for a generic tacrolimus product is arbitrary, capricious, an abuse of discretion, not in accordance with law, and in violation of the FDCA and the APA.

3. The FDCA and the agency's regulations provide that a sponsor seeking approval of a generic drug product must demonstrate, among other things, that the proposed product is bioequivalent to an approved pioneer product. *See* 21 U.S.C. § 355(j)(2)(A)(iv), 21 C.F.R. § 314.127(a)(6)(i).

4. FDA has violated the FDCA by failing to require bioequivalence testing in transplanted patients because meeting the FDA-established bioequivalence standards in studies with only healthy volunteers will not sufficiently predict the pharmacokinetics observed when tacrolimus is administered to transplant patients.

5. FDA's approval of a generic tacrolimus product was arbitrary, capricious, an abuse of discretion and not in accordance with law and therefore violates 5 U.S.C. § 706(2)(A).

6. There is no basis for FDA's statements that the patient-related factors "should not play a significant role in determining the bioequivalence of tacrolimus products[.]" FDA's denial of Astellas' request is inconsistent with its recognition that variability in pharmacokinetics between the fed and fasted state may affect the results of bioequivalence studies. In addition, it disregards the sensitivity of dosing for tacrolimus and the vulnerability of the transplant population. FDA's speculation that patient-related factors "should not" play a role is insufficient to protect the transplant population, particularly in light of FDA's recognition that tacrolimus "requires careful dosage titration and monitoring of patient blood levels[.]"

7. FDA's approval of a generic tacrolimus product constitutes agency action in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, in violation of 5 U.S.C. § 706(2)(C).

8. Astellas will be irreparably harmed if defendants are not required to revoke the approval of any ANDAs for generic tacrolimus until bioequivalence studies are conducted in the transplant patient population, the labeling for tacrolimus products is revised to include warnings and precautions regarding substitution of tacrolimus formulations, and manufacturers of substitute formulations of tacrolimus are required to identify the manufacturing source of their generic products so that physicians and pharmacists know when the manufacturing source has changed.

9. Astellas will suffer irreparable harm and has no adequate remedy at law because generic tacrolimus products that were approved based on inadequate grounds for a determination

of bioequivalence and in violation of federal law will compete with and, in many cases, be automatically substituted for, Astellas' Prograf.

Count II (Labeling and Differentiation)
(Administrative Procedure Act: Violation of the FDCA and Applicable Regulations)

10. Paragraphs 1 through 53 are incorporated herein by reference.

11. In the alternative, and in addition, FDA has violated the FDCA by failing to require that the label of Prograf and any approved generic alert physicians and patients to the risks associated with substituting formulations of tacrolimus and to any change in the source of manufacturing. Warnings and precautions regarding the substitution of formulations or manufacturing source are necessary to ensure the safe use of the drug, as the FDCA requires.

12. FDA's approval of a generic tacrolimus without these labeling and differentiation requirements was arbitrary, capricious, an abuse of discretion, and not in accordance with law and therefore violates 5 U.S.C. § 706(2)(A).

13. FDA's denial of Astellas' request for labeling changes for tacrolimus is based on the conclusory assertion that the current ANDA review process is adequate to assure interchangeability of generic versions of immunosuppressant drugs. FDA's decision does not address whether additional warnings and precautions are necessary in light of the potential interpatient and intrapatient variability prevalent in narrow therapeutic index drugs. Such analysis, rather than a conclusion that the current system is adequate across the board, is necessary in light of the special vulnerability of the transplant patient population, the scarcity or organs for transplant, and the NTI status of tacrolimus.

14. FDA's denial of the request to differentiate among manufacturing sources is based on the supposition that the generic is "expected" to be substitutable for its branded

counterpart. FDA thus relies on assumptions regarding substitutability in the normal context rather than relying on facts specific to the immunosuppressant context. FDA fails to address the argument that physicians and pharmacists would be better able to avoid medication errors through differentiation among manufacturing sources.

15. FDA's approval of generic tacrolimus products without these labeling and differentiation requirements constitutes agency action in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, in violation of 5 U.S.C. § 706(2)(C).

16. Astellas will suffer irreparable harm and has no adequate remedy at law because generic tacrolimus products that were approved without adequate labeling requirements and in violation of federal law will compete with and, in many cases, be automatically substituted for, Astellas' Prograf.

RELIEF REQUESTED

WHEREFORE, Astellas requests that this Court issue judgment in its favor and against Defendants and issue the following relief:

1. A declaratory judgment that Defendants acted unlawfully in approving an ANDA for generic tacrolimus;

2. A temporary restraining order and a preliminary injunction:

   a) Requiring FDA to supplement its existing bioequivalence standards for tacrolimus to require that bioequivalence studies be performed in the transplant patient population; and

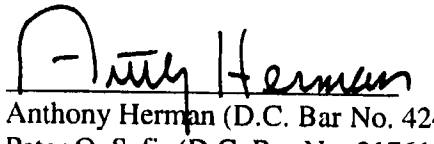
   b) Requiring FDA to revise labeling requirements for Prograf to add warnings and precautions to physicians patients regarding substitution of formulations; and

   c) Requiring producers of substitute formulations of tacrolimus to identify their manufacturing source so that patients, physicians, and pharmacists know when the source has changed; and

   d) Directing FDA to withdraw approval of any generic versions of Prograf until such time as the actions set forth above are complete;

3. An award of such other and further relief as this Court may deem just and proper.

Respectfully submitted,



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