**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

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

Plaintiff,

v.

Civ. No. _____

FOOD AND DRUG ADMINISTRATION
200 C Street, SW
Washington, D.C. 20240

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

and

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

Defendants.

**MEMORANDUM OF POINTS AND AUTHORITIES**
**IN SUPPORT OF APPLICATION OF PLAINTIFF ASTELLAS**
**FOR A TEMPORARY RESTRAINING ORDER AND**
**A PRELIMINARY INJUNCTION**

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Plaintiff Astellas Pharma US, Inc. ("Astellas") seeks a temporary restraining order ("TRO") and preliminary injunction requiring the Food and Drug Administration ("FDA") to comply with its statutory mandate to ensure that drugs are safe and effective. Disregarding this mandate, FDA has approved a generic version of Prograf® (tacrolimus) -- a leading drug prescribed to prevent rejection of organs in patients receiving heart, kidney, and liver transplants -- without imposing conditions necessary to ensure the health and safety of patients who will use these drugs. To ensure that FDA complies with its statutory mandate, the Court should require the agency to revoke its approval of generic versions of Prograf until such time as the agency (1) requires for approval of generic tacrolimus that studies demonstrating bioequivalence with Prograf be performed in the transplant population and (2) revises labeling requirements for Prograf and generic tacrolimus products to add warnings and precautions regarding substitution of formulations and related requirements.

FDA's approval of a generic form of tacrolimus sharply conflicts with its core statutory mandate of ensuring that drugs are safe and effective. In denying Astellas' request that FDA impose conditions in connection with approval of generic tacrolimus, the agency relied on conclusory propositions that lack support in the literature and that are at odds with evidence in the record (including labeling the agency previously approved). The decision reflects an arbitrary one-size-fits-all approach that fails to take proper account of the dosage sensitivity for immunosuppressant drugs and the highly vulnerable nature of transplant patients. If not remedied, FDA's decision to approve a generic version of Prograf without requiring appropriate clinical studies in transplant patients or imposing adequate labeling requirements will place in jeopardy the health -- and the lives -- of the tens of thousands of patients who live with transplanted organs and who currently take Prograf to prevent

rejection. In addition, the decision will cause irreparable injury to Astellas and seriously undermine the public interest in patient health and safety.

## INTRODUCTION

In the past 25 years, transplantation has become the treatment of choice for many cases of organ failure. The success of transplantation has increased the demand for donated organs, which has led in turn to a scarcity of organs available for transplantation. 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. If a patient is fortunate enough to receive a life-saving organ from a donor, it is critically important to make every effort to protect the transplanted organ from rejection and to maintain the health and life of the patient who has received this precious gift. Safe and effective immunosuppressant drug therapy designed to prevent rejection of these highly valuable transplanted organs is central to this effort.

Ensuring the appropriate dosage level of immunosuppressant drugs like Prograf is key to the survival and health of the transplanted organ and the transplant patient. 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.

Setting the proper dosage level for tacrolimus, however, is highly complex and quite variable, both from patient to patient ("inter-patient variability") and even for the same patient ("intra-patient variability"). Treating transplant patients is particularly complex, because they have multiple medical conditions, which may include the underlying disease that caused their organ failure. Such patients take multiple medications, which may interact with one another. Transplant patients are extremely vulnerable to medical complications

from changes in their medication, changes in their life style, and even changes in their diet. The proper dosage depends on a variety of factors -- including the particular tacrolimus formulation.

Dosing of tacrolimus must be highly individualized, tailored through both therapeutic drug monitoring and clinical monitoring of each patient for the life of the transplanted organ. Tacrolimus is characterized by a narrow therapeutic index ("NTI"); in other words, it is in the category of drugs for which small changes in concentration in the body can lead to a significant difference in pharmacodynamic and clinical response.[1] Tacrolimus is also 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. Moreover, studies show that the drug -- including different formulations of the drug at the same strength -- can have different clinical and pharmacodynamic effects on patients. As a consequence, 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.

Despite these unique features of the patient population and of tacrolimus -- and the high human stakes involved -- FDA has approved a generic version of the drug without requiring any studies in patients with transplanted organs. FDA also declined to require enhanced labeling to minimize the risks involved when patients take different formulations of tacrolimus. FDA's actions are arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with the law in that they violate the Food, Drug, and

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[1] Pharmacodynamics involves the effects of a drug on the body at specific sites.

Cosmetic Act ("FDCA"), 21 U.S.C. §§ 321 *et seq.* In view of FDA's unlawful actions, the irreparable harm to Astellas, and the serious harm the public would suffer as a result of FDA's action, the Court should enter a TRO and a preliminary injunction.

## STATUTORY AND REGULATORY BACKGROUND

### A. Approval of Prescription Drugs

The FDA must approve all new prescription drugs before they can be introduced into interstate commerce. 21 U.S.C. § 355(a). The FDCA requires that all drug manufacturers (or "sponsors") demonstrate the safety and effectiveness of their products for each intended use. *Id.* Brand name (or "pioneer") drug manufacturers, such as Astellas, must demonstrate safety and effectiveness by conducting pre-clinical and clinical studies of their products, producing data that are submitted in new drug applications ("NDAs"). *See* 21 U.S.C. § 355(b)(1). The manufacturer of the pioneer product (the "innovator") makes this showing in a new drug application ("NDA") submitted to FDA.

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

In addition to showing bioequivalence, as a condition of approval generic companies also must meet labeling requirements for their products. Except in limited

circumstances (not at issue here), 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).

**B. Bioequivalence**

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).

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 at viii (28th ed. 2008). In other words, the purpose of this demonstration of bioequivalence is to provide assurance that the generic drug product is therapeutically equivalent to and can be substituted for the approved pioneer product. *Id.*

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 ratio of test drug to reference drug for two important pharmacokinetic parameters, $AUC_{0\text{-}t}$ and $C_{max}$, which

measure the extent and rate of the drug's absorption.[2] A second test, administered to healthy adults in the fed (non-fasting) 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 the test-to-reference ratios 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. Guidance for Industry: Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design (July 1992) ("1992 Guidance"), at 9 (attached as Exhibit A).

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. In 1997, for example, FDA issued draft guidance addressing "individual bioequivalence" testing. FDA described "individual bioequivalence" for NTI drugs as the scaling of the 80% to 125% criteria to the variability of the reference product. Draft Guidance for Industry: In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches (October 1997), at 15 (attached as Exhibit B). The guidance, however, was never finalized. In 1999, a subsequent draft guidance document again recommended an individual bioequivalence approach for NTI drugs. Draft Guidance for Industry: Average, Population, and Individual

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[2] Pharmacokinetics involves the absorption, distribution, and elimination of a drug by the body, or the body's response to a drug. AUC, or area under the curve, refers to drug concentration over time and is a means of measuring bioavailability (the amount of a drug that reaches systemic circulation and is available at the site of action). $C_{max}$ refers to the peak concentration of a drug following its administration.

Approaches to Establishing Bioequivalence (August 1999), at 1, 5 (attached as Exhibit C). This guidance, likewise, was never finalized.

In a 2001 final guidance document on statistical methods for bioequivalence testing, which was intended to replace the two unfinalized draft guidance documents as well as the 1992 Guidance, FDA set out the "individual bioequivalence" approach in statistical terms, but offered no guidance as to the use of this approach for NTI drugs. Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (Jan. 2001), at 1, 6-7 (attached as Exhibit D). In a 2003 final guidance document on general bioavailability/bioequivalence issues, FDA recommended consideration of additional testing for NTI drugs to "provide increased assurance of interchangeability for drug products containing specified narrow therapeutic range drugs." Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (March 2003) at 20 (attached as Exhibit E).[3]

Despite FDA's history of concern about the adequacy of its standards for NTI drugs, in July 2006, without explanation, FDA published draft guidance on bioequivalence testing for tacrolimus that recommended adoption of the general standard (*i.e.*, the standard from the 1992 Guidance) for tacrolimus. Draft Guidance for Industry: Bioequivalence Recommendations for Specific Products; Draft Guidance on Tacrolimus (recommended July 2006; May 2007) (attached as Exhibit F).

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[3] The guidance document recommended that sponsors "consider additional testing and/or controls to ensure the quality of drug products containing [NTI] drugs," and that the "traditional [bioequivalence] limit of 80 to 125 percent" would "remain unchanged" for the AUC and $C_{max}$ bioavailability measures of these drugs. *Id.*

## FACTUAL BACKGROUND

### A. Prograf

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

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 also is available in injectable form.)

Prograf is first administered to a patient at the hospital following transplantation of an organ. Letter from D. Cronin, MD, FDA Docket Number FDA-2007-P-0111/C1 ("Dr. Cronin Letter") (attached as Exhibit G), at 2. For roughly the first six months after surgery (the "induction phase"), patients are at particularly high risk for rejection. Higher doses of immunosuppressants are administered during this period. *Id.*

Drug exposure levels are closely monitored to ensure that immunosuppression is within appropriate limits. *Id.* Because Prograf is a "critical dose" drug with an NTI, careful therapeutic drug monitoring of blood levels and clinical monitoring of each patient are critical to avoiding adverse events. *Id.* at 1. If drug exposure levels are too high, there is a risk of significant toxicity. *Id.* If the levels are too low, the patient may experience graft loss or organ rejection. *Id.*

During the three to six months following a transplant, blood levels are typically tested once a week. *Id.* at 2. Thereafter, the patient is maintained on long-term

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

In fiscal year 2008 (April 1, 2008 through March 31, 2009), Prograf accounted for nearly $885 million in North American sales for Astellas. This translates into approximately $74 million in sales per month. Declaration of P. Shea, attached as Exhibit H, ¶ 6.

### B. Sandoz's Application for a Generic Version of Prograf

Sandoz (and possibly other companies) filed an ANDA seeking approval to market generic tacrolimus. This application was based on the safety and effectiveness studies performed by Astellas. Instead of conducting bioequivalence studies in both healthy and transplant populations, Sandoz (and any other generic tacrolimus applicants) submitted bioequivalence studies only, comparing blood levels of their product in healthy patients with those of Prograf.

FDA's approved labeling for tacrolimus products does not include warnings and precautions regarding notification to the prescribing physician when a pharmacy substitutes formulations. As a result, there is no requirement that physicians be alerted that a switch to generic tacrolimus will occur nor that blood concentration monitoring should be considered to address the risks associated with a switch.

### C. Astellas' Citizen Petition

On September 21, 2007, Astellas submitted a Citizen Petition to FDA under sections 505(b) and 505(j) of the FDCA. *See* Exhibit I. In this petition, Astellas requested that FDA (1) supplement its existing bioequivalence standards for orally administered immunosuppressants used in the transplant population and characterized by a narrow therapeutic index, such as tacrolimus, to require that bioequivalence studies be performed in the transplant patient population (rather than solely in healthy patients) and (2) revise labeling requirements for all orally administered NTI immunosuppressant drugs to add warnings and precautions regarding substitution of formulations. *Id.* at 1-2.[4]

Astellas explained that, for a drug with high interpatient and intrapatient variability, like Prograf, bioequivalence studies limited to healthy patients do not adequately predict the pharmacokinetics observed when such drugs are administered to individual transplant patients and as a result approval of such drugs based on only such studies presents grave risks to patients. *Id.* at 12-19.[5] David C. Cronin, M.D., Ph.D, F.A.C.S., an Associate Professor of Surgery and Director of Liver Transplantation at the Medical College of Wisconsin, submitted a letter to FDA supporting Astellas on this point. (A copy of this letter is attached as Ex. G.) In his letter, Dr. Cronin, who is both a transplant surgeon and a

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[4] The Citizen Petition also requested that FDA require manufacturers of substitute oral formulations of NTI drugs for use in transplant patients, such as tacrolimus, to identify their manufacturing source, and to distinguish among dosage strengths by using different color capsules and container closures. *Id.* at 2, 21.

[5] Variability refers to the fact that clearance (rate of elimination) of the drug from the body varies from one patient to the next (interpatient variability) and even varies for a single patient, depending on, *e.g.*, age, state of health, or time elapsed since transplantation (intrapatient variability). *See id.* at 15-18.

pharmacist by training, noted his concerns about the impact of transplant patients' drug exposure levels and expressed the opinion "that FDA should require that applications for generic tacrolimus include bioequivalence studies in the transplant population as well as in healthy subjects." Ex. G, at 2. Dr. Cronin noted that, "due to significant intrapatient variability in the pharmacokinetics of tacrolimus, meeting the FDA-established bioequivalence standards in studies with healthy volunteers will likely not sufficiently predict the pharmacokinetics observed when tacrolimus is administered to individual transplant patients." *Id.*

Astellas also explained that, because of intrapatient variability, FDA's failure to mandate that the label require notification to the prescribing physician when there is a switch in tacrolimus formulation presents unnecessary risks to transplant patients. Ex. I, at 19-21. As a result of FDA's ANDA approvals, and in the absence of injunctive relief, pharmacies will substitute generic versions of tacrolimus for Prograf. Declaration of Heather Goodman, Esq. ("Goodman Decl."), attached as Ex. J, ¶¶ 8-9, 12-13.[6] When FDA has approved several generic drugs and deemed all of them therapeutically equivalent to a reference product, the pharmacist can substitute one generic formulation for another without notice of the substitution to the prescribing physician. *Id.* ¶¶ 12, 18, 20. These substitutions are driven not by any clinical factors but rather simply by the differences in price among manufacturers. *Id.* ¶ 17.

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[6] Heather Goodman, Esq., was formerly Senior Counsel, Customer & Vendor Relations, and Director, Rx Product Management, for Cardinal Health, Inc., one of the three largest national pharmaceutical wholesalers in the United States. *Id.* ¶ 2.

Thus, while bioequivalence studies in the transplant patient population would help quantify, and (if bioequivalence is demonstrated) reduce, the risks associated with substituting generic formulations of tacrolimus, additional measures are required to ensure safety in substitutions -- as between Prograf and generic tacrolimus drugs and as between different versions of generics. As Astellas explained in the Citizen Petition, substituting formulations of tacrolimus -- either 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 patients must receive long-term therapy with an NTI and critical-dose drug like tacrolimus.

Dr. Cronin also supported the Citizen Petition on this point. He explained that where tacrolimus formulations have been switched, there must be especially close patient monitoring to avoid serious adverse events, including organ rejection, organ loss, and death. Dr. Cronin Letter (Ex. G), at 3. Some studies have shown that where there is a switch to a different formulation, the same dosage level of the drug may affect the same patient differently. *See* Citizen Petition (Ex. I), at 9-10. But this difference -- which could have critical implications -- may go unnoticed if formulations are substituted without the knowledge of the prescribing physician, since rejection can begin to occur with no symptoms that are apparent to the transplant patient. Dr. Cronin Letter (Ex. G), at 2.

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, from one generic formulation to another, or from a generic formulation to Prograf. 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. Citizen Petition (Ex. I), at 1-2, 19-21. Dr. Cronin agreed that the FDA should require labeling with directions about substitution as well as physical indications of manufacturing source.

In support of its Petition, Astellas submitted a White Paper from the National Kidney Foundation and a Meeting Report from the American Society of Transplantation. *See* Tabs Y, EE to Citizen Petition (FDA Docket Number FDA-2007-P-0111/CP1), attached as Exhibit I.- The National Kidney Foundation raised concerns about the general application of the current FDA bioequivalence standards to special populations such as transplant recipients and the problems that may arise due to substitution of critical-dose immunosuppressive drugs, such as tacrolimus. *Id.*, Tab EE. The American Society of Transplantation urged in its report that bioequivalence studies performed in at-risk populations be incorporated into the generic drug approval process. *Id.*, Tab Y.

### D. FDA's Denial of Astellas' Citizen Petition and Approval of Sandoz's ANDA

On August 10, 2009, Astellas received notification from FDA that the agency had denied its Citizen Petition in almost all respects. *See* Letter from Janet Woodcock, M.D., dated August 10, 2009 (Exhibit L). In denying the request to require bioequivalence studies in transplant patients, FDA asserted -- without citation or explanation -- that patient-related factors that produced variable pharmacokinetic effects were related to the active ingredient of a drug product, not the formulation, and that such factors "should not play a significant role" in bioequivalence determinations for tacrolimus. *Id.* at 7-8. FDA denied the request for labeling requirements on the ground that it regards the current review process for ANDA as

sufficient to assure interchangeability of the generic and the branded product. *Id.* at 13. It rejected Astellas' request for differentiation of manufacturing sources on the ground that this was unnecessary if there is an "expectation" that the generic is substitutable for the branded product. *Id.* at 15.[7] FDA acknowledged that tacrolimus "requires careful dosage titration and monitoring of patient blood levels." *Id.* at 5 n.11. However, in its discussion of Astellas' requests, it made virtually no mention of these special features of tacrolimus or of the vulnerability of the patient population.

Simultaneous with its denial of Astellas' Citizen Petition, FDA approved Sandoz's ANDA for a generic version of tacrolimus. *See* Exhibits O, P. Based on this approval, Sandoz is now free to enter the market. Astellas understands that Sandoz began to ship its generic product on August 10.

## ARGUMENT

Rule 65 of the Federal Rules of Civil Procedure allows the Court to grant preliminary injunctive relief, including a TRO, prior to full adjudication. Astellas is entitled to both a TRO and a preliminary injunction.

The traditional test for a TRO weighs four factors:

> (1) whether there is a substantial likelihood that the plaintiff will prevail on the merits; (2) whether the plaintiff will suffer irreparable injury if the temporary restraining order does not issue; (3) the hardship to the defendants if the temporary restraining order is granted is balanced against the hardship to the plaintiff if the temporary restraining order is not granted;

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[7] FDA accepted the request to require differentiation between strengths, but suggested that documentation in the labeling (rather than use of unique colors) could be sufficient. *Id.*

> and (4) whether the public interest favors granting the preliminary relief requested.

*Boehringer Ingelheim Corp. v. Shalala*, 993 F. Supp. 1, 1 (D.D.C. 1997); *see also Virginia Petroleum Jobbers Ass'n v. Federal Power Comm'n*, 259 F.2d 921, 925 (D.C. Cir. 1958). A parallel four-pronged test governs the grant of a preliminary injunction. *See, e.g., Winter v. Natural Res. Def. Council*, 129 S. Ct. 365, 374 (2008) ("A plaintiff seeking a preliminary injunction must establish that he is likely to succeed on the merits, that he is likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in his favor, and that an injunction is in the public interest.").

These four factors interrelate on a sliding scale and should be balanced against each other. *Serono Labs., Inc.* v. *Shalala*, 158 F.3d 1313, 1318 (D.C. Cir. 1998). The D.C. Circuit has "recognized that injunctive relief may be justified, for example, 'where there is a particularly strong likelihood of success on the merits even if there is a relatively slight showing of irreparable injury.' " *CSX Transp., Inc. v. Williams*, 406 F.3d 667, 670 (D.C. Cir. 2005) (quoting *CityFed Fin. Corp. v. Office of Thrift Supervision*, 58 F.3d 738, 747 (D.C. Cir. 1995)); *see also Cuomo v. Nuclear Regulatory Comm'n*, 772 F.2d 972, 974 (D.C. Cir. 1985).

Each of these four factors weighs heavily in favor of issuing an injunction here. Unless the Court intervenes, substantial and imminent harm will flow from FDA's wrongful decision to deny Astellas' Citizen Petition and to approve generic tacrolimus. Generic market entry will have an immediate, significant and irreparable effect on Prograf sales, goodwill, and reputation -- and will place at risk the tens of thousands of patients who rely on tacrolimus to prevent rejection of their transplanted organs.

## II. Astellas Is Likely to Prevail on the Merits.

It is likely that Astellas will prevail on the merits. FDA denied virtually all of Astellas' requests for conditions designed to ensure the safety and effectiveness of generic tacrolimus, based on propositions that are not supported by the evidence and on conclusory statements. FDA repeatedly rested on speculation, rather than reasoned consideration of reliable evidence or scientific opinion. Moreover, the agency disregarded its own prior expressions of concern about the adequacy of its standards for drugs such as tacrolimus. It failed to take account of what it recognized to be special features of tacrolimus that require particularly careful dosing and blood level monitoring, as well as the highly vulnerable patient population for those vital immunosuppressant drugs. FDA's decision is plainly arbitrary and capricious and inconsistent with the agency's mandate to ensure the safety and effectiveness of drugs.

Section 706(2)(A) of the Administrative Procedure Act ("APA"), 5 U.S.C. § 706(A)(2), instructs that a reviewing court must "hold unlawful and set aside agency action" where -- as here -- it is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." Agency action is arbitrary and capricious when "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 the 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 Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Ins. Co.*, 463 U.S. 29, 43 (1983). An agency must have examined the relevant information and "articulate[d] a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'" *Id.* (quoting *Burlington*

*Truck Lines, Inc. v. United States*, 371 U.S. 156, 168 (1962)). The "agency must cogently explain why it has exercised its discretion in a given manner," and that explanation must be "sufficient to enable us to conclude that the [agency's action] was the product of reasoned decisionmaking." *Id.* at 48, 52. A reviewing court must strike down and set aside an agency decision if there has been a "clear error in judgment." *Id.* at 43 (quoting *Bowman Transp., Inc. v. Arkansas-Best Freight Sys., Inc.*, 419 U.S. 281, 285 (1974)) (internal quotation marks omitted).

The review of agency action requires a "searching and careful" inquiry into the basis for the agency's decision. *Zotos Int'l, Inc. v. Young*, 830 F.2d 350, 352 (D.C. Cir. 1987) (quoting *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971)) (internal quotation marks omitted). While the reviewing court may give deference to an agency's "scientific" judgments, the Court does "not hear cases merely to rubber stamp agency actions. To play that role would be 'tantamount to abdicating the judiciary's responsibility under the Administrative Procedure Act.'" *Natural Res. Def. Council, Inc. v. Daley*, 209 F.3d 747, 755 (D.C. Cir. 2000) (quoting *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1491 (D.C. Cir. 1995)). Here, a "searching and careful" examination of FDA's action shows that Astellas is likely to prevail on the merits.

### A. FDA's Failure to Require Testing In Transplant Patients is Arbitrary and Capricious.

FDA's approval of generic tacrolimus products without requiring adequate testing -- in transplant patients -- is unlawful, arbitrary, and capricious. Under the FDCA, FDA may approve a drug only if it has been shown to be safe and effective. As described above (pages 6-7), over the course of many years FDA has acknowledged the limitations of its existing bioequivalence standards for NTI drugs and has recognized that bioequivalence

determinations for such drugs present unique issues. Now, brushing those concerns aside, FDA has decided not to require bioequivalence studies of the use of generic tacrolimus in transplant patients.

FDA has taken this action despite the compelling case for requiring such studies. As the administrative record reflects, the effect of tacrolimus, an NTI drug, is highly sensitive to a number of interpatient and intrapatient variables. For example, the expression of certain enzymes in patients taking tacrolimus can vary dramatically.[8] Moreover, the clearance from the body and half-lives of tacrolimus vary considerably among different transplant patients. The Citizen Petition (and the FDA-approved Prograf label) list various factors (such as organ type and time after transplant) that are associated with variable effects in transplant patients. *See* Citizen Petition (Ex. I), at 14-18; 2006 Prograf Label at 3-10, 15-16, Tab KK to Citizen Petition (FDA Docket Number FDA-2007-P-0111/CP1), attached as Exhibit I. And, studies submitted to FDA show that "[t]he pharmacokinetics of tacrolimus in healthy volunteers varies from that observed in kidney, liver and heart transplant patients." Citizen Petition (Ex. I), at 15. In these circumstances, it is not enough to conclude that generic tacrolimus is bioequivalent to Prograf in healthy individuals. Tests in transplant patients are essential to show that the generic is therapeutically equivalent to Prograf.

FDA's basis for rejecting Astellas' argument is conclusory and unsupported. FDA asserts that bioequivalence studies of transplant patients are unnecessary because, "[b]ased on current literature," a number of what it calls "patient-related factors" that show

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[8] "Expression" refers to the process by which gene information is made into a functional gene product, such as a metabolizing enzyme. Differences in the expression of enzymes can cause marked variability in patients' drug response. Citizen Petition (Ex. I) at 15.

variability among transplant patients are related to the active ingredient of the product, not the formulation. Ex. L at 7. The agency cites no such literature, and Astellas is aware of none. *See* Declaration of William Fitzsimmons ("Fitzsimmons Decl.") ¶ 9, attached as Exhibit M.[9]

Furthermore, FDA's comments about the so-called "patient-related factors" are inconsistent with the position it takes regarding another factor -- effect of food on drug absorption. FDA recognizes that studies of food effects (fed or fasting state) should be conducted because the food effect can potentially affect the outcome of bioequivalence studies where formulations differ. Ex. L at 7. But it cites no reason for singling out food effects and asserting that they differ from the "patient-related factors" in this respect; its conclusion regarding the "patient-related factors" is simply inconsistent with its position on food effects. *See* Fitzsimmons Decl. ¶¶ 8, 10 . The arbitrary nature of FDA's comments is reinforced by the fact that one of the factors Astellas cited was concomitant medications, including antacid. There is no reasoned basis for concluding that different drug formulations may produce different pharmacokinetic effects depending on food intake but clearly would not depending on the individual's use of an antacid. *See id.* at ¶ 10.

FDA assertions regarding the "patient-related factors" do not support its conclusion that studies of transplant patients are unnecessary. For all of the factors Astellas cited, studies suggest that variability may be associated with different formulations, and thus a generic could produce different pharmacokinetic effects. *Id.* ¶ 6; Citizen Petition (Ex. I), at

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[9] Dr. Fitzsimmons is Senior Vice President U.S. Development and Global Group Therapeutic Area Head of Astellas Pharma Global Development, Inc., an affiliate of Astellas Pharma US, Inc.

14-18. Because several of the "patient-related factors" (such as time following transplant) are present only in transplant patients, there is plainly a need for studies in this population. Without such studies, there is a risk that the generic formulation will produce different pharmacokinetic effects in a patient than the reference drug when one or more of the factors differs. FDA's failure to offer support for its contrary conclusion renders its decision arbitrary and capricious. *See FCC v. Fox Television Stations, Inc.*, 129 S.Ct 1800, 1839 (2009).

In fact, the only evidence in the record shows that the factors Astellas cited are related to formulation, rather than active ingredient, of tacrolimus. Astellas submitted information in its Citizen Petition on studies of Advagraf, a product with the same active ingredient as Prograf and that met the bioequivalence standard when compared with Prograf. For certain kidney and liver transplant patients, these studies showed different pharmacokinetic effects for Advagraf and Prograf associated with time following transplant (one of FDA's "patient-related factors"), despite the same active ingredient for these two products (and their bioequivalence). *See* Citizen Petition (Ex. I), at 18. Yet, without cogent explanation, FDA failed to acknowledge that these studies show that "patient-related factors" may be related to formulation of a drug. *See* Fitzsimmons Decl. ¶ 12. FDA also disregarded the fact that the Prograf label, which it had approved earlier, states that the various factors Astellas cited may affect pharmacokinetics of the drug. FDA's failure to address this relevant evidence is arbitrary and capricious. *See Morall v. DEA*, 412 F.3d 165, 178 (2009).

FDA recognizes that expert organizations support Astellas' position, but it also brushes aside these expert views. For example, the American Society of Transplant Surgeons takes the position that there is a need to conduct bioequivalence studies in organ-

specific transplant patients. *See* Ex. Lat 11. FDA states that it disagrees with this position, and it objects that ASTS has not provided data to support its position. *Id.* at 11-12. But FDA itself has no data to support its conclusions that factors such as organ type are related only to the active ingredient. Its offhand dismissal of the views of authoritative experts is clearly arbitrary.

Moreover, FDA fails to take into account a particularly important factor -- the risks presented by tacrolimus and the vulnerability of the patient population. At critical points, FDA relies merely on supposition. It states that patient-related factors "should not" play a significant role in determining bioequivalence of tacrolimus products (Ex. L at 7) (emphasis added), and that in the absence of data, "it is expected" that a comparison of various results for test and reference products would yield certain relationships. *Id.* at 12 (emphasis added). FDA simply fails to explain why this sort of supposition or "expectation" is sufficient when dealing with such a vulnerable patient population. It relies instead on a one-size-fits-all approach. If any question deserves a hard look by the agency, it is protection of such vulnerable patients. But FDA has largely glossed over the question here with exactly the type of baseless speculation that the case law forbids. *See Natural Res. Def. Council v. E.P.A.*, 859 F.2d 156, 210 (D.C. Cir. 1988) (agency actions based upon speculation are arbitrary and capricious).

FDA asserts that experience with cyclosporine, another immunosuppressant drug used for transplant patients, shows that differences among pioneer and generic formulations of such drugs are not therapeutically significant and that bioequivalence testing in transplant patients is therefore unnecessary for approval of generic tacrolimus. Ex. L at 8. This logic is fundamentally flawed. In the first place, the results of tests on the effects of

switching among different formulations of cyclosporine are inconclusive at best. *See* Citizen Petition (Ex. I), at 7-10.[10] Moreover, in pointing to individual aspects of the cited studies, FDA disregards the broader point -- that, taken as a whole, the studies suggest that pharmacokinetic effects of immunosuppressant drugs on transplant patients can differ significantly compared with healthy patients.

Even if the cyclosporine studies FDA cites were definitive, they would not prove that using different formulations of tacrolimus would yield similar results. While cyclosporine and tacrolimus are both immunosuppressants and NTI drugs, FDA fails to establish that the two drugs are similar chemical entities with similar pharmacokinetic properties, or that there is otherwise a sound scientific basis for expecting different formulations to have the same clinical consequences for the two drugs. FDA's failure to address an essential basis for its conclusion is fatal as a matter of law. *See, e.g., American Rivers v. U.S. Army Corps of Engineers*, 271 F. Supp. 2d 230, 251 (D.D.C. 2003); *Carlton v. Babbitt*, 900 F. Supp. 526, 533 (D.D.C. 1995).

Based on the compelling data presented in the Citizen Petition, there is no rational basis for FDA's failure to require bioequivalence studies in transplant patients as a condition of generic approval. Bioequivalence studies in transplant patients as well as healthy subjects are necessary to help determine whether a generic formulation of tacrolimus can be safely substituted for Prograf and whether additional monitoring and dose adjustments will be required in order to minimize the chance of acute rejection or toxicities for patients

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[10] Two of the studies (Taber et al. and Qazi et al.) suggested that tests of cyclosporine in healthy subjects and transplant patients might yield different results. *See* Citizen Petition (Ex. I) at 9-10. Several other tests were insufficiently powered to reveal meaningful differences. *See id.* at 7-8.

using a generic product. FDA's response to the Citizen Petition is not supported by the evidence; it is inadequate to the point of being arbitrary and capricious. It fails to establish that the current FDA bioequivalence standard provides a sufficient basis for determining the safety and effectiveness of such products.

### B. FDA's Failure to Require Labeling to Warn of Switches in Formulation is Arbitrary and Capricious.

FDA also violated the FDCA by denying Astellas' requests to revise the approved labeling of Prograf (and consequently, the labeling of any approved generic versions of tacrolimus) to include warnings and precautions when pharmacists substitute formulations of tacrolimus. The existing labeling requirements do not ensure safe administration of the drug in light of the risk that doctors will be unaware when pharmacies substitute generic products for Prograf, or substitute one generic product for another.[11]

The FDCA requires that a drug be safe and effective when used under the conditions described in the labeling. 21 U.S.C. § 355 (b), (d). Because the existing labeling fails to ensure safe and effective use of tacrolimus once generic products enter the market, the FDCA requires enhancement of the labeling before a generic version is approved.

Tacrolimus has a narrow therapeutic index; small changes in the systemic concentration of tacrolimus can lead to significant differences in pharmacodynamic and clinical responses. Dr. Cronin Letter (Ex. G) at 1. Both subtherapeutic and elevated blood levels of tacrolimus can lead to serious adverse events. As a result, dosing is highly

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[11] The labeling also does not ensure safe administration of the drug when the manufacturing source for a generic product has changed. FDA's rejection of a requirement that producers differentiate manufacturing sources relies simply on an "expectation" that the substituted product will be equivalent to the branded product. Ex. L at 15.

individualized, tailored through both therapeutic drug monitoring and clinical monitoring of each patient. Studies have shown that different formulations of tacrolimus can vary in their absorption in the body. *See* Citizen Petition (Ex. I) at 18-19. Such variations have also been observed in studies comparing branded and generic versions of another immunosuppressant drug. *See id.* at 11-14. Thus, where there is a change in strength or sourcing of such drugs, physicians should consider increased monitoring to protect against adverse events. As noted above, FDA acknowledged in its response to the Citizen Petition that tacrolimus requires careful dosage measurements and monitoring of blood levels. *See* Ex. L at 5 n.11

In the absence of a restriction described in the labeling, pharmacies are free to substitute generic versions of tacrolimus for Prograf, or to substitute one generic product for another, without notice to the prescribing physician. Goodman Decl. ¶¶ 12, 18, 20. Such substitution places transplant patients at high risk due to several factors, including the decrease in frequency of monitoring as time passes after transplantation, the absence of early physical signs that a patient's body is rejecting a transplant, and the severity and speed of rejections. Citizen Petition (Ex. I), at 5-6; Dr. Cronin Letter (Ex. G), at 2, 3. If prescribing physicians are not aware that a switch has been made, they are not alerted to the potential for a change in blood levels and the need to increase therapeutic monitoring to ensure that the patient's drug exposure remains within appropriate limits. *Id.* at 3. Changes to the labeling that require the pharmacist to alert physicians that a switch to generic tacrolimus (or to a different generic product) has occurred and the risks associated with a switch would alert physicians to increase therapeutic drug monitoring, thereby minimizing the threat of outcomes such as neurotoxicity, nephrotoxicity, graft loss, and rejection. *See* Citizen Petition (Ex. I), at 20.

FDA's position that tacrolimus can be freely substituted without any notice to the prescribing physician is inexplicable, given the recent enhancement to the agency's authority to mandate labeling that will maximize the safety of patients who take prescription drugs.[12] FDA simply asserts -- without explanation -- that additional warnings and precautions are not needed because the review process is sufficient to assure interchangeability of tacrolimus products. Ex. L at 13. This conclusory rejection of a common sense measure (notifying health professionals of a change in drug product) is simply insufficient, given FDA's own recognition of the careful dosing measures and monitoring required for transplant patients. Moreover, FDA failed even to mention Astellas's request for warnings regarding the need for extra blood level monitoring when formulations are changed. In light of its acknowledgment of the importance of such monitoring, that omission is clearly arbitrary. *See Wedgewood Village Pharmacy v. DEA*, 509 F.3d 541, 549 (D.C. Cir. 2007).

The changes to the labeling that Astellas proposed would ensure that tacrolimus continues to be safe and effective when used under the conditions described in the labeling, as required by the FDCA. FDA's failure to give serious consideration to the risks faced by vulnerable transplant patients, who may not appreciate the possible medical consequences of taking a drug that is cheaper but potentially less safe and effective due to incomplete testing and labeling, is arbitrary and capricious. *See id.*

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[12] *See* 21 U.S.C. § 355(o)(4) (authorizing FDA to mandate labeling changes to address new safety information about a drug).

FDA's failure to require bioequivalence studies in transplant patients and enhanced labeling to ensure that physicians are notified of any change in formulation is unlawful, arbitrary, and capricious and thus should be reversed under the APA. Accordingly, Astellas is likely to prevail on the merits.

## III. Astellas Will Suffer Irreparable Injury in the Absence of Injunctive Relief.

In the absence of preliminary relief, Astellas faces irreparable injury. As a result of FDA's unlawful ANDA approval for tacrolimus, generic manufacturers immediately can launch their products and market them as "bioequivalent" and "substitutable" for Prograf. *See* Goodman Decl. ¶¶ 8, 12. Astellas understands that Sandoz shipped its generic product on August 10, the day FDA approved its ANDA. FDA's final approvals of these ANDAs without sufficient bioequivalence testing or adequate labeling will cause irreparable injury to Astellas in the form of lost sales, price erosion, loss of goodwill, and harm to reputation.

Prograf is Astellas' leading drug in the United States. Declaration of Patrick Shea ("Shea Decl.") ¶ 5.[13] Revenues from sales of Prograf represented approximately half of Astellas' total U.S. revenue for the 2008 fiscal year. *Id.* In its financial report for fiscal year 2008, Astellas Pharma Inc., the parent company of Astellas, reported $884 million in North American sales, including the U.S. and Canada. *Id.* As a result of FDA's wrongful approval of generic tacrolimus products, in the absence of an injunction Astellas will begin losing sales immediately. *Id.* ¶¶ 6-7.

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[13] Patrick Shea is Astellas' Senior Vice President of Marketing and Sales.

Experience in similar situations in which FDA has approved for marketing generic versions of drugs rated as therapeutically equivalent shows that Astellas can expect to lose a very substantial percentage of its sales of Prograf in the months following introduction of generic tacrolimus. It is well established in the pharmaceutical industry that a generic entrant has an immediate impact on the marketplace because pharmacists generally are permitted, and in some instances are required, to substitute lower-priced generic drugs for the branded innovator drug. *Id.* ¶ 6. Certain third-party payers of prescription drugs encourage, and in some cases insist on, the use of the generic drug instead of the brand name drug, because the generic drug has a cheaper acquisition price. Thus, rapid erosion in market share and price of the branded drug sales typically occurs when a generic drug enters the market. *Id.* For example, following the entry of a generic form of Norvasc® (used to treat hypertension) in March 2007, the branded drug's share of prescriptions dropped from 100 percent to less than 20 percent within three months and to less than five percent within a year. *Id.* ¶ 7.

Experience also shows that entry of a generic drug into the market causes the brand drug to suffer financial injury that is irreversible. Such entry creates an immediate incentive for health maintenance organizations (HMOs) and other third-party payors to direct consumer demand toward the cheaper generic drug, ordinarily by adjusting reimbursement tiers to charge consumers a higher co-payment for selecting the brand drug. To avoid being downgraded to a less favorable tier, the brand drug manufacturer must offer rebates and other pricing concessions to the HMOs. Once given, these concessions are near-impossible to take away. In these circumstances, the brand drug manufacturer suffers irreparable harm that supports grant of a temporary restraining order and preliminary injunction. *See Sanofi-*

*Synthelabo v. Apotex, Inc.*, 488 F. Supp. 2d 317, 342-44 (S.D.N.Y.) (describing this sequence of events and noting the Federal Circuit's recognition that "irreversible price erosion . . . is a legitimate basis for a finding of irreparable harm"), *aff'd*, 470 F.3d 1368 (Fed. Cir. 2006); *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1368 (Fed. Cir. 2001) ("Given the testimony of the likelihood of price erosion and loss of market position . . . , we see no deficiency in the district court's finding of irreparable harm."); *see also* Goodman Decl. ¶¶ 11-14; Shea Decl. ¶ 8.

In addition to lost sales, Astellas would suffer a loss in goodwill resulting from generic entry into the market. The entry of generic versions of tacrolimus immediately would devalue the Prograf brand as the innovative form of tacrolimus. Shea Decl. ¶ 9. Astellas would suffer irreparable harm to its reputation with patients and health care professionals to the extent a generic product that is substituted for Prograf fails to provide the expected therapy or safety profile, as physicians and patients would likely associate these failures with Prograf. *Id.* ¶ 10. Physicians prescribe Prograf with the expectation of safe and effective treatment, and patients have corresponding expectations. If a generic product is substituted for Prograf, and it fails to provide the expected result, physicians and patients will tend to associate substandard results with Prograf; as a result, they may switch to a different immunosuppressant. *Id.*

It is settled that injury to goodwill and reputation constitutes irreparable harm sufficient to support the entry of a TRO and preliminary injunction. *See Patriot, Inc. v. United States Dep't of Housing & Urban Dev.*, 963 F. Supp. 1, 5 (D.D.C. 1997) (finding irreparable harm based, in part, on plaintiffs' showing of damage to their business reputation); *Honeywell, Inc. v. Consumer Prod. Safety Comm'n*, 582 F. Supp. 1072, 1078

(D.D.C. 1984) (finding irreparable harm based on plaintiff's showing that, without a preliminary injunction, it would suffer injury to "corporate goodwill and reputation and its competitive position"); *see also Multi-Channel TV Cable Co. v. Charlottesville Quality Cable Operating Co.*, 22 F.3d 546, 552 (4th Cir. 1994) ("[W]hen the failure to grant preliminary relief creates the possibility of permanent loss of customers to a competitor or the loss of goodwill, the irreparable injury prong is satisfied.").

There can be no doubt that Astellas lacks an adequate remedy at law to recover for these losses. Astellas would have no private right of action against FDA to recover damages resulting from improper approval of an ANDA. *See Woerner v. United States Small Bus. Admin.*, 739 F. Supp. 641, 650 (D.D.C. 1990) ("[Plaintiffs] claim, persuasively, irreparable injury because the government is immune from damage suits"); Shea Decl. ¶ 8. Nor would Astellas have a cognizable claim against ANDA filers that market generic versions of tacrolimus. *See* Shea Decl. ¶ 8. Accordingly, the harm to Astellas is irreparable. *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 29 (D.D.C. 1997) (finding irreparable harm where, although injury is "'admittedly economic,' there is 'no adequate compensatory or other corrective relief' that can be provided at a later date, tipping the balance in favor of injunctive relief.") (quoting *Hoffmann-LaRoche Inc. v. Califano*, 453 F. Supp. 900, 903 (D.D.C. 1978)).

## IV. The Balance of Harm Favors Astellas.

FDA would not be harmed by a requirement that it revoke the approval of ANDAs for generic tacrolimus until bioequivalence studies are conducted in the transplant population or by a requirement that the labeling for tacrolimus products be revised to include warnings and precautions regarding substitution of tacrolimus formulations. To the contrary,

as the agency has recognized, the public interest is served by a regulatory regime that ensures the safety and efficacy of drug products. It would make a mockery of that regime, and would greatly lessen the extent to which the public could rely on it in the future, if Astellas were unable to secure the preliminary relief necessary for meaningful judicial review of FDA's decision not to require bioequivalence studies in transplant populations and not to ensure safe prescription of generic products by adding appropriate labeling warnings and precautions.

Further, the harm Astellas would suffer in the absence of a TRO and preliminary injunction far outweighs any harm to the generic drug applicants from such relief. There is no prospect that a limited delay in entering the market for tacrolimus will destroy Sandoz's business. In 2008, Sandoz had worldwide sales of $7.6 billion. *See* NOVARTIS AG-NVS, Form 20-F, at 59 (Jan. 28, 2009) (Exhibit N). IMS Health has identified Sandoz as the No. 2 company in worldwide generic sales. *See id.* at 60. Moreover, Sandoz and other generic applicants have been on notice for years that bioequivalence standards for orally administered immunosuppressants are matters of regulatory and scientific debate. *See* pages 6-7 above. FDA itself raised the bioequivalence issues associated with orally administered immunosuppressants in a guidance document issued in 1997. *See* Exhibit B. Astellas' Citizen Petition has been a matter of public record since September 2007. Yet Sandoz chose not to submit such data. As noted in Sandoz's parent company's financial statement, "research and development costs associated with generic pharmaceuticals are much lower than those of the established counterparts[.]" Ex. N at 64. In this case, the low investment in research and development that Sandoz has undertaken is insufficient to prevent harm, and it should be required to do additional studies that are supported by scientific necessity.

Finally, the additional burdens associated with the labeling requirements Astellas seeks are not substantial. And, of course, they will weigh equally on Astellas and the generics.

In short, injunctive relief would cause no harm to FDA, and the limited harm that a generic manufacturer of tacrolimus may incur due to an injunction would be outweighed by the irreparable harm Astellas would suffer in the absence of injunctive relief.

## V. The Public Interest Favors Grant of Injunctive Relief.

Injunctive relief is plainly in the public interest. As a threshold matter, the public interest would be served by requiring the FDA to comply with the law. *See, e.g., Fund for Animals v. Espy*, 814 F. Supp. 142, 152 (D.D.C. 1993) ("There is a strong public interest in meticulous compliance with law by public officials."); *see also Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1066-67 (D.C. Cir. 1998) (discussing the district court's determination that "the public's interest in the 'faithful application of the laws' outweighed its interest in immediate access to the generic product"); *id.* at 1066 n. 6 (regardless of any public interest in the entry of generic drugs to the marketplace, "this factor alone cannot support denying an injunction").

Moreover, the public interest mandates assurances that any generic versions of tacrolimus be demonstrably safe and effective. This requires thorough testing to ensure that any generic is in fact bioequivalent to Prograf when taken by transplant patients, not just healthy subjects. In addition, steps must be taken to ensure that patients will be monitored to determine the effects of any change in formulation of the drug. If the dosage is too high, there is a risk of significant toxicity. If the required dosage level is underestimated, and not sufficiently monitored, the result could be rejection of a transplanted liver, kidney or heart.

*See* Citizen Petition (Ex. I), at 5. 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. 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 transplant, because the frequency of blood monitoring and hence the opportunity to detect signs of early rejection have decreased. Dr. Cronin Letter (Ex. G), at 2.

Rejection carries with it serious costs -- in both human and financial terms. As explained in the Citizen Petition, because of the difficulty in obtaining a suitable organ for transplant, the human costs of rejection are high. As of 2007, more than 96,000 people in the United States with end-stage organ failure were waiting for an organ transplant, with nearly 4,000 new patients added each month. There is a serious shortage of organs available for kidney, liver or heart transplantation. Approximately 73,000 patients were on the waiting list for a kidney, and only approximately 8,300 kidney transplants were performed in the first half of 2007. Almost 17,000 patients were 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 were 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. *See* Citizen Petition (Ex. I), at 3. Thus, there are potentially grave consequences associated with organ rejection that could have been prevented with suitable drug therapy and monitoring.

The Citizen Petition also described the high economic costs associated with organ rejection that could otherwise have been prevented. For the first year alone, the average billed charge for a heart transplant patient is nearly $500,000; the average charge for a liver transplant patient is approximately $400,000; and the average charge for a kidney transplant patient is over $200,000. *See id.* If a transplanted kidney fails, and the patient must return to dialysis, the cost in the first year alone is nearly $135,000. *See id.* The costs of transplant failure are thus quite considerable.

This is too high a price to pay. The FDA must take the necessary steps to ensure that transplant patients are treated with tacrolimus in a safe and effective manner. Until FDA has taken these steps, FDA must be ordered to withdraw approval of any generic versions of Prograf .

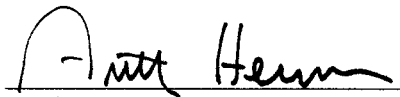
In determining whether to vacate an agency's decision, the D.C. Circuit has instructed that courts should consider "the seriousness of the...[action's] deficiencies (and thus the extent of doubt whether the agency chose correctly)," and "the disruptive consequences of an interim change that may itself be changed." *Allied-Signal, Inc. v. USNRC*, 988 F. 2d 146, 150-51 (D.C. Cir. 1993) (quoting *International Union, UMW v. FMSHA*, 920 F. 2d 960, 967 (D.C.Cir. 1990)); *see also A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1492 (D.C. Cir. 1995). In view of FDA's failure to consider the serious safety and effectiveness concerns articulated by Astellas and the fact that vacatur will cause no disruption but instead will ensure that the status quo ante is maintained, FDA's decision to accept the Sandoz ANDA for filing should be vacated. *See American Bioscience, Inc. v. Thompson,* 269 F.3d 1077, 1078, 1086 (D.C. Cir. 2001) (vacating the FDA's approval of an ANDA after finding it arbitrary and capricious).

An injunction compelling FDA to withdraw its ANDA approvals until it takes the necessary steps to ensure that transplant patients are treated with tacrolimus in a safe and effective manner is unquestionably in the public interest.

## CONCLUSION

For the reasons stated above, Astellas' Application for a Temporary Restraining Order and a Preliminary Injunction should be granted. The Court should order FDA to vacate its approval of Sandoz's ANDA and any other ANDAs it has granted for a generic tacrolimus product.

Respectfully submitted,



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