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BY UPS OVERNIGHT MAIL AND TELEFAX (301-827-6870)

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Docket Number 2007D-0168: Draft Guidance for Industry
Describing Product-Specific Bioequivalence Recommendations
for Tacrolimus**

Dear Mr. Nguyen:

Astellas Pharma US, Inc. ("Astellas"), the NDA-holder for Prograf® (tacrolimus), submits these comments to the recently published draft guidance from FDA regarding bioequivalency testing requirements for the development of generic tacrolimus. FDA's draft guidance recommends that bioequivalence be demonstrated in two single-dose studies, one in fed state and one in fasted state, in healthy volunteers using FDA's standard bioequivalence criteria of 80-125% for both C_{max} and AUC at the 90% confidence interval.¹ Although requiring studies in both a fed and fasted state is more than the minimum routinely required by FDA, this standard is not adequate to ensure the safe and effective use of orally administered, narrow therapeutic index immunosuppressants used in the transplant population. FDA bioequivalence standards for these products should require studies in transplant patients in the immediate post-transplant period.

In addition to these comments, Astellas has filed a Citizen Petition with FDA requesting that FDA take action to ensure the safe and effective use of orally administered immunosuppressant drugs that are used in the transplant population and are characterized by a narrow therapeutic index.

¹ See FDA Draft Guidance on Tacrolimus (July 2006), published on May 31, 2007, 72 Fed Reg 30386 (May 31, 2007).

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2007D-0168

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1. Transplant Patients and Immunosuppression

a) *Transplantation*

Transplantation is a unique area of medicine because it requires either a living donor to consent or a deceased donor to indicate a willingness to consent to donating an organ. Fifty years ago, end stage organ disease was a terminal illness and transplant was available only to those with an identical twin who agreed to donate one of their kidneys. In the past 25 years, there have been major advances in immunosuppression, surgical technique, allocation schema, and organ storage and transplantation has become the treatment of choice for many end-organ disease states. The success of transplantation has increased the demand for donated organs and this has led to the current imbalance of organs available to transplant versus the number of people waiting.

More than 96,000 people in the US with end organ failure are currently waiting for an organ transplant with nearly 4,000 new patients added each month. (www.optn.org/latestData/rptData.asp 9/19/07.) 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 1140 heart transplants performed in the first half of 2007. Death on the waiting list has steadily increased every year and in 2006 more than 6400 patients died while waiting for an organ transplant (www.optn.org/latestData/rptData.asp 9/19/07).

Every day, 17 people die waiting for a transplant of a vital organ (heart, liver, kidney, pancreas, lung, or bone marrow). (National Kidney Foundation, 25 Facts About Organ Donation (www.kidney.org/news/newsroom/fsitem.cfm?id=30 9/19/07). As of July 1, almost 2900 patients waiting for an organ transplant have died in 2007. (www.optn.org/latestData/rptData.asp 9/19/07).)

In addition to the scarcity of organs available for transplant, the costs of transplant are substantial. In 2005, the average billed 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 \$478,900, respectively, over the same duration. (Ortner NJ. Milliman Research Report: 2005 US organ and tissue transplant cost estimates and discussion. June 2005.

(www.transplantliving.org/ContentDocuments/2005_Milliman_Report.pdf 9/20/07). Following the first posttransplant year, the average cost associated with maintaining a functioning organ is approximately \$13,000 annually. By contrast, the average cost of graft failure and return to dialysis is almost \$135,000 for the year following graft failure (Yen EF, Hardinger K, Brennan DC, et al. Cost-effectiveness of extending Medicare coverage of immunosuppressive medications to the life of a kidney transplant. *Am J Transplant.* 2004;4:1703-1708).

Once patients receive a transplanted organ, their care is dedicated to maintaining the health of their new organ in order to prevent rejection, in addition to maintaining the overall health and survival of the patient. A rejection episode can occur at any time during the life of the graft. Despite advances in the treatment of transplant patients, acute rejection still occurs in roughly 20% of kidney transplant recipients (Bresnahan B, Pascual M. Understanding the impact of calcineurin inhibitor-based immunosuppression on renal allograft function and survival. *Nephrology Updates* 2004; 1:1-10) and 20-70% in liver transplant recipients (Weisner RH, Demetris AJ, Belle SH, et al., Acute hepatic allograft rejection: incidence, risk factors, and impact on outcome. *Hepatology* 1998;28:638-645), and the number of adult heart transplant recipients treated for rejection in the first year hovers around 30-40% (Taylor D, Edwards LB, Boucek MM, et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-third Official Adult Heart Transplantation Report – 2006. *J Heart Lung Transplant.* 2007;25:869-879). Preventing acute rejection must remain a top priority in the lifelong management of transplant recipients as it impacts not only short term results but also long term outcomes. Acute rejection is linked to greater incidence of kidney graft dysfunction and is detrimental to long term graft survival. (Cosio FG, Pelletier RP, Falkenhain ME et al. Impact of acute rejection and early allograft function on renal allograft survival. *Transplantation.* 1997;63:1611-1615, Rush DN, Karpinski ME, Nickerson P et al. Does subclinical rejection contribute to chronic rejection in renal transplant patients. *Clin Transplant.* 1999; 13:441-446, Shishido S, Asamuna H, Nakai H et al. The impact of repeated subclinical acute rejection on the progression of chronic allograft nephropathy. *J Am Soc Nephrol.* 2003;14(4):1046-1052, Hariharan S, Johnson CP, Bresnahan BA et al. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med.* 2000;342(9):605-612.)

A key to successful outcomes is patient adherence to their prescribed medication regimen. In a prospective study, 146 kidney transplant recipients were followed for 5 years. (Vlaminck H, Maes B, Evers E et al. Prospective study on late consequences of subclinical non-compliance with

immunosuppressive therapy in renal transplant patients. *Am J Transplant* 2004;4(9): 1509-1513). The incidence of late acute rejection and changes in serum creatinine between patients who adhered to treatment versus those who were non-adherent were compared. In this study, Kaplan-Meier survival analysis revealed a significant negative impact on graft survival with treatment non-adherence; $p=0.03$. Treatment related risk factors for non-adherence are dosing frequency, number of prescribed medications, pill characteristics, and unwanted drug side effects and level of symptom distress (Laederach-Hofmann K, Bunzel B, et al. Noncompliance in organ transplant recipients: a literature review. *Gen Hosp Psychiatry*. 2000;22(6):412-424. Weng FL, Israni AE, Joffe MM et al. Race and electronically measured adherence to immunosuppressive medications after deceased donor renal transplantation. *J Am Soc Nephrol*. 2005; 16(6): 1839-1848. De Geest S, Moons P, et al. The patient's appraisal of side effects: the blind spot in quality-of-life assessments in transplant recipients. *Nephrol Dial Transplant*. 2000; 15(4):457-459).

Given the significant need and the human and economic costs required to support organ donation and transplantation, maximum effort needs to be made to ensure the survival and health of the transplanted organ and the transplant patient.

b) Treatment of Transplant Recipients

Following organ transplant surgery, patients must be treated with immunosuppressants to prevent rejection of the allograft. In the induction phase, roughly the first six months after surgery, higher doses of immunosuppressants are administered. Drug exposure levels are closely monitored to ensure that immunosuppression is within appropriate limits. During this time patients are at a particularly high risk for opportunistic infection. After the induction phase, the patient is maintained on long-term immunosuppression, which might include two or three different immunosuppressant agents. Dosage levels are generally decreased and monitoring frequency is typically reduced to once a month. Monitoring will continue, however, as long as the patient is on immunosuppressant therapy -- in most cases, for the rest of the patient's life. If drug exposure levels are too high, there is a risk of significant toxicity. If the levels are too low, the patient could experience graft loss or organ rejection.

The calcineurin inhibitors tacrolimus and cyclosporine, which are considered to be the cornerstone of current immunosuppressive therapy in organ transplant recipients, are characterized by a narrow therapeutic index (NTI). The term "narrow therapeutic index" is generally understood to apply to

drugs for which small changes in systemic concentration can lead to a significant difference in pharmacodynamic and clinical response. Therapeutic drug monitoring of blood levels (TDM) is critical to avoiding adverse effects.² With both cyclosporine and tacrolimus, for example, subtherapeutic blood levels may result in rejection of the graft, loss of the transplanted organ, or even patient death. (Levy GA. Relationship of pharmacokinetics to clinical outcomes. *Transplant Proc* 1999;31:1654-8; Dansirikul C, Staats E, Duffull SB, et al. Relationships of tacrolimus pharmacokinetic measures and adverse outcomes in stable adult liver transplant recipients. *J Clin Pharm Ther* 2006;31:17-25; Winkler M, Wonigeit K, Undre N, et al. Comparison of plasma vs whole blood as matrix for FK 506 drug level monitoring. *Transplant Proc* 1995;27:822-5; Kershner RP, Fitzsimmons WE. Relationship of FK506 whole blood concentrations and efficacy and toxicity after liver and kidney transplantation. *Transplantation* 1996;62:920-6; Staats C, Taylor P, Tett S. Low tacrolimus concentrations and increased risk of early acute rejection in adult kidney transplantation. *Nephrol Dial Transplant* 2001;16:1905-9.) Elevated levels of these agents may lead to adverse events associated with toxicity such as renal impairment and neurotoxicity. (Dansirikul 2006; Kershner 1996) Therefore, with such agents, dosing is highly individualized based on both therapeutic drug monitoring and clinical monitoring of each patient. Narrow therapeutic index drugs, together with drugs that have a high potential for toxicity in therapeutic use, are sometimes referred to as "critical dose drugs."³

In the immunosuppressive regimen for many organ transplant recipients, calcineurin inhibitors are typically administered in combination with an antimetabolite such as azathioprine or mycophenolate mofetil, and/or a corticosteroid such as prednisone. In addition to immunosuppressants, transplant patients are generally prescribed a number of medications to address their weakened immune state, toxicities associated with immunosuppressants and their underlying disease state. These may include medications to provide prophylaxis against bacterial, fungal, and viral infections, as well as medications needed for the management of chronic conditions, such as hypertension,

² FDA has used the term "narrow therapeutic range" and has defined "narrow therapeutic range drug products" as those containing "certain drug substances subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin." See FDA Guidance, *Bioavailability and Bioequivalence Studies For Orally Administered Drug Products -- General Considerations* (March 2003), at 20.

³ See, e.g., Health Canada Therapeutic Products Directorate, Guidance: *Bioequivalence Requirements: Critical Dose Drugs* (May 31, 2006), at 1.

hypercholesterolemia, and diabetes. On average, transplant patients take 10 different medications and must maintain compliance to avoid acute rejection and toxicities. (Friedman AL, Geoghegan SR, Sowers NM, et al. Medication errors in the outpatient setting. Arch Surg 2007;142:278-83.)

Monitoring of blood concentrations in conjunction with other laboratory and clinical parameters is an essential aid to transplant patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. The costs of treating acute rejection are substantial, with estimated costs of approximately \$3,300 for treatment with a course of corticosteroids and \$14,500-\$18,000 with a course of antilymphocyte therapy (Lake KD. Pharmacoeconomic and outcomes analyses in solid organ transplantation. Graft 2001;4:544-557; Young M, Plosker GL. Mycophenolate mofetil: a pharmacoeconomic review of its use in solid organ transplantation. Pharmacoeconomics 2002;20:675-713).

2. Clinical Experience in the Transplant Population Since the Introduction of Generic Cyclosporine

FDA has approved generic versions of cyclosporine based on the standard bioequivalence criteria in healthy volunteers. However, despite demonstration of bioequivalence in healthy volunteers, clinical study data suggest that these standards do not necessarily translate to clinical equivalence when comparing both generic and branded cyclosporine in transplant patients. A review of the available published literature reveals that studies evaluating the use of generic cyclosporine oral capsules in the transplant patient population are limited and inconclusive. Under these circumstances, questions arise as to whether the current standard for bioequivalence is sufficient to support indiscriminate substitution of alternate formulations of immunosuppressants in vulnerable transplant patients. (Roza A, Tomlanovich S, Merion R, et al. Conversion of stable renal allograft recipients to a bioequivalent cyclosporine formulation. Transplantation 2002;74:1013-7; Carnahan W, Cooper TY. Neoral-to-Gengraf conversion in renal transplant recipients. Transplant Proc 2003;35:1308-13; Taber DJ, Baillie GM, Ashcraft EE, et al. Does bioequivalence between modified cyclosporine formulations translate into equal outcomes? Transplantation 2005;80:1633-5; Fradette C, Lavigne J, Waters D, Ducharme MP. The utility of the population approach applied to bioequivalence in patients: comparison of 2 formulations of cyclosporine. Ther Drug Monit 2005;27:592-600; Qazi YA, Forrest A, Tornatore K, Venuto RC. The clinical impact of 1:1 conversion from Neoral to a generic cyclosporine (Gengraf) in

renal transplant recipients with stable graft function. Clin Transplant 2006;20:313-7.)

The first pharmacokinetic study of generic cyclosporine in stable kidney transplant recipients was published by Roza and colleagues in 2002 (Roza 2002). In this 7 week, multicenter, open-label study, 50 patients maintained on stable doses of Neoral ("branded cyclosporine") were converted to a generic cyclosporine formulation on a dose-for-dose basis; after 2 weeks of treatment with the generic cyclosporine, patients were converted back to the branded cyclosporine. During this study, no dosing adjustments were required following conversion between formulations of cyclosporine. Based on mean C_{max} , AUC, T_{max} , and C_{min} , there were no differences detected between the two formulations of cyclosporine. This published report did not state the distribution range of values observed for each of the pharmacokinetic parameters in this group of patients so the pharmacokinetic variability is not known. The authors reported that there were no differences in the pharmacokinetics of cyclosporine based on gender, race, or presence of diabetes with either formulation of cyclosporine, however, this study was not powered to show statistical differences between these patient subpopulations.

In 2003, Carnahan and colleagues presented the findings of a single center, open-label conversion from a branded cyclosporine to a generic cyclosporine formulation in 41 kidney transplant recipients (Carnahan 2003). As directed in the study protocol, cyclosporine trough levels obtained throughout the study were classified as therapeutic (within ± 25 ng/mL of the designated cyclosporine trough concentration), subtherapeutic, or suprathreshold. Using these criteria, no significant differences were observed in the proportion of patients who were classified as having therapeutic blood levels during treatment with the two cyclosporine formulations. The mean cyclosporine trough concentrations observed after the administration of either cyclosporine formulation were also not significantly different, and no changes in dose were necessary due to the conversion of patients to the generic formulation. Neither the standard deviation nor the range of values for the mean cyclosporine trough concentration were reported and the study was not designed to establish bioequivalence in kidney transplant patients using the bioequivalence criteria established by FDA. The study duration (mean follow-up was 18 weeks) makes it difficult to draw meaningful conclusions with regard to graft rejection.

In 2005, Fradette and colleagues sought to evaluate the pharmacokinetics of a branded cyclosporine and generic cyclosporine in 37 stable kidney transplant recipients (Fradette 2005). In this 7 week, multicenter,

open-label study, patients maintained on stable doses of branded cyclosporine were converted to a generic cyclosporine formulation on a dose-for-dose basis; after 2 weeks of treatment with the generic cyclosporine, patients were converted back to the branded cyclosporine. On average, the C_{max} and AUC observed after the administration of brand or generic cyclosporine were not statistically different. However, these comparisons were made based on mean population data, and the range of values observed for each of these pharmacokinetic parameters is not presented. In addition, although statistical significance was not observed, greater intrasubject variability in both C_{max} and AUC values was observed after patients were treated with the generic cyclosporine compared with the branded cyclosporine formulation.

Taber and colleagues published the findings of a single-center retrospective review of patient outcomes associated with treatment with either a branded cyclosporine or a generic cyclosporine after kidney transplantation (Taber 2005). In this study, 100 patients transplanted between January 1999 and May 2001 were treated with the branded cyclosporine, and 88 patients transplanted between May 2001 and July 2002 were treated with the generic cyclosporine. Both groups received the same initial dose of cyclosporine and targeted the same cyclosporine trough levels in the blood. Adjunctive agents used in both groups included mycophenolate mofetil and prednisone. At 6 months after transplant, acute rejection occurred in a significantly higher proportion of patients treated with the generic cyclosporine (39%), compared with the brand cyclosporine (25%); $p=0.04$. Based on multivariate regression analysis, immunosuppression with the generic cyclosporine formulation was found to be a significant independent risk factor for the development of acute rejection. Additionally, patients treated with the generic cyclosporine were also more likely to have a second acute rejection episode or have more treatment-resistant acute rejection; $p=0.03$ and $p=0.02$, respectively. The differences in the incidence and severity of acute rejection observed between treatment groups in this study are clinically significant, since the occurrence of acute rejection is correlated with an increase in graft loss and patient mortality.

In a randomized, prospective study, Qazi and colleagues evaluated the dose-for-dose (1:1) conversion from a branded cyclosporine to a generic cyclosporine formulation in 82 stable kidney transplant recipients (Qazi 2006). Seventy-three patients were randomized to convert from a stable dose of branded cyclosporine to a generic cyclosporine formulation, while 9 patients were randomly selected to remain on the branded cyclosporine and serve as the control group. In both cyclosporine groups, the cyclosporine trough levels were obtained at baseline, after two weeks, and again after four weeks. An adjustment in dosing was allowed for patients in either group if the cyclosporine

trough levels changed by $\geq 20\%$ from the level at baseline. Of the 73 patients converted to generic cyclosporine, nearly one-fifth (18%) required a dosage change after the dose-for-dose conversion; in these patients, the cyclosporine trough level at baseline was 234 ± 96 ng/mL compared with 289 ± 102 ng/mL after conversion; $p < 0.05$. After dose adjustment, cyclosporine trough levels returned to 239 ± 151 ng/mL, comparable to baseline levels. None of the 9 patients randomized to remain on branded cyclosporine required a dosage change. The findings regarding dosage changes in this study suggest that the bioequivalence established in pharmacokinetic evaluations in healthy volunteers may not be sufficient in the transplant population. The authors conclude that "All patients irrespective of their risk, subsequent to being switched to a generic [cyclosporine] should have additional drug monitoring to ensure that the new steady states fall within the intended target range. Although this may offset some cost savings in the short term, the significant risk of jeopardizing graft function could be avoided."

Thus, the few studies evaluating generic cyclosporine in transplant patients that have been published are inconclusive and there are outstanding concerns regarding the use of generic narrow therapeutic index immunosuppressants in transplant recipients. These concerns have been expressed by experts in the transplantation community, particularly regarding indiscriminate substitution of generic immunosuppressants, without notification to the prescribing physician and patient.

In 1999, the National Kidney Foundation published a White Paper consensus document to develop recommendations for the safe and effective use of generic immunosuppressants based on the expert opinion of a multi-disciplinary group of participants and their review of the literature (Sabatini S, Ferguson RM, Helderman JH, et al. Drug substitution in transplantation: a National Kidney Foundation White Paper. *Am J Kidney Dis* 1999;33:389-97). While committee participants generally acknowledged that the presence of generic immunosuppressant agents in the marketplace is beneficial, concerns were raised about the exclusion of certain immunosuppressive agents from classification as critical dose drugs. Additional concerns of the committee were raised in regards to the general application of currently used bioequivalence standards to special populations such as transplant recipients, along with the potential for problems that may arise due to the indiscriminate substitution of critical dose immunosuppressive agents. Recommendations for improving the approval standards for generic immunosuppressants included: (a) the establishment of an official critical dose drug designation; (b) the inclusion of certain immunosuppressants, such as cyclosporine and tacrolimus, into such a critical dose drug category; (c) the use of pharmacokinetic studies with replicate

study design for establishing bioequivalence to critical dose drugs; (d) the inclusion of studies evaluating bioequivalence in the transplant population and subpopulations (eg., pediatric, African-American, or diabetic patients). Further recommendations were proposed related to the safe and effective use of generic immunosuppressant agents, including: (a) the need for states to develop greater consistency on regulations pertaining to generic medications; (b) the importance of patient education related to the proper identification of prescribed medications; (c) the need for physician and patient notification when the prescribed immunosuppressant for a transplant patient is to be switched by the pharmacist; (d) the need for careful evaluation of bioequivalence data by physicians for the drugs that they prescribe, so that appropriate prescribing decisions can be made related to generic substitution; (e) the need to consider appropriate monitoring if patients are switched from one formulation to another (eg., innovator to generic, generic to generic); (e) the importance of documenting and reporting adverse events with innovator and generic drugs.

The American Society of Transplantation published a similar report in 2003 on the use of generic immunosuppressants in the transplant setting (Alloway 2003). In general, experts who participated in this conference were supportive of efforts to introduce generic alternatives for immunosuppressants, stating that FDA-approved generics for narrow therapeutic index drugs appeared to provide adequate immunosuppression when accompanied with appropriate therapeutic drug monitoring in patients with low immunologic risk. However, several issues were raised during this meeting, including the lack of clinical studies and long-term follow-up data for generic immunosuppressants in transplant recipients as well as the unquantified risk and concerns of therapeutic failure due to switches between immunosuppressive agents under uncontrolled circumstances. As a result of this meeting, the group proposed several recommendations, including: (a) maintaining consistency with regards to the variables that may affect target blood levels, including the consistent use of the selected immunosuppressant brand, formulation, and timing of doses; (b) notification of physicians and patients for any switch in the brand of medications dispensed; (c) pill and container uniqueness among generics; (d) patient education to ensure that physicians are informed when a switch occurs so that the appropriate follow-up, including monitoring of blood levels, can take place; (e) avoidance of the use of different formulations in combination, due to the lack of data in this area. In addition, the group advocated for the incorporation of bioequivalence studies performed in at-risk patient populations into the generic drug approval process.

As supported by the concerns raised by both the National Kidney Foundation and the American Society of Transplantation, and the limited

published data currently available, indiscriminate substitution of formulations of narrow therapeutic index immunosuppressants -- without any notice required to prescribing physician or patient -- can result in significant risks to transplant patients, especially once a patient has been started on a particular immunosuppressant. The fact that each new formulation may have been shown to be bioequivalent in healthy volunteers, under current FDA criteria, may not operate to prevent these harms to patients.

3. FDA's bioequivalence standards are not sufficient to control switch-associated risks for transplant patients treated with narrow therapeutic index drugs

Over the past ten years, FDA has periodically acknowledged the limitations of its existing bioequivalence standards for narrow therapeutic index drugs, but to date has not reached any determination that general bioequivalence criteria should be narrowed for these drugs, or that the generally required bioequivalence studies should be supplemented.⁴ In a 2003 final guidance on general bioavailability/bioequivalence issues, FDA recognized the need to "provide increased assurance of interchangeability for drug products containing [NTI] drugs."⁵ The guidance merely recommended, however, that sponsors "consider additional testing and/or controls to ensure the quality of drug product containing [NTI] drugs," indicating that the "traditional [bioequivalence] limit of 80 to 125 percent" would "remain unchanged" for these drugs.⁶

- a) *High variability of pharmacokinetics in individual patients.*

⁴ Canada has taken more specific action by issuing in 2006 a final guidance document recommending that for critical dose drugs (a category that includes narrow therapeutic index drugs), bioequivalence be demonstrated by a showing that the 90% confidence interval of the relative mean AUC test:reference ratio falls between 90% and 112%, and that the 90% confidence interval of the relative mean C_{max} test:reference ratio falls between 80% and 125%. The guidance further recommended that these criteria be met under both fasted and fed conditions, and stated that "due to the nature of [critical dose drugs], it may be necessary to conduct [bioequivalence] studies in patients rather than in healthy subjects." Health Canada Therapeutic Products Directorate, Guidance: *Bioequivalence Requirements: Critical Dose Drugs* (May 31, 2006).

⁵ See FDA Guidance, *Bioavailability and Bioequivalence Studies For Orally Administered Drug Products -- General Considerations* at 20.

⁶ See *id.*

For a drug with high inpatient variability, bioequivalence established using mean pharmacokinetic data from the healthy volunteer study population may not sufficiently predict the pharmacokinetics observed when such drugs are administered to individual patients. In the analysis by Taber and colleagues discussed previously, no significant difference was observed in mean cyclosporine trough concentrations. However, when individual bioequivalence was evaluated using the percent coefficient of variation (CV), a significantly higher proportion of patients treated with the generic cyclosporine formulation had CVs >40% (40% of patients treated with generic cyclosporine compared with 25% of patients treated with Neoral; $p=0.03$). Similarly, the percentage of patients with CVs >50% and >60% were significantly greater for the patients treated with generic cyclosporine ($p=0.04$ and $p=0.017$, respectively). As evidenced by the higher CVs observed in patients treated with generic cyclosporine, bioequivalence established based on mean values did not correlate with individual bioequivalence. Furthermore, low trough levels after the administration of generic cyclosporine, as well as immunosuppression with the generic cyclosporine formulation itself, were each determined to be a significant independent risk factors for the development of acute rejection.

In another study, comparing the bioequivalence of branded cyclosporine and a generic cyclosporine in 34 healthy volunteers, underexposure to cyclosporine following the administration of the generic formulation was reported in 18% of subjects based on AUC and 38% of patients based on C_{max} . The study nevertheless satisfied FDA bioequivalence criteria. (Johnston A, Belitsky P, Frei U, et al. Potential clinical implications of substitution of generic cyclosporine formulations for cyclosporine microemulsion (Neoral) in transplant recipients. *Eur J Clin Pharmacol* 2004;60:389-95.)

b) High interpatient and inpatient variability in the pharmacokinetics of tacrolimus.

Tacrolimus has demonstrated interpatient and inpatient variability in extensive testing of its pharmacokinetics. Following oral administration, the mean bioavailability of tacrolimus is approximately 25%, with a range of 4-93% (Scott LJ, McKeage K, Keam SJ, Plosker GL. Tacrolimus: a further update of its use in the management of organ transplantation. *Drugs* 2003;63:1247-97.) The peak concentration of tacrolimus is generally achieved 0.5-1 hour after the oral dose. (Venkataramanan R, Swaminathan A, Prasad T, et al. Clinical pharmacokinetics of tacrolimus. *Clin Pharmacokinet* 1995;29:404-30.) Although tacrolimus is extensively metabolized by the CYP3A isoenzyme in the liver and small intestine, along with p-glycoprotein present in the lumen of the small intestine, the expression of these enzymes may vary between individuals

(Staatz). Furthermore, the clearance of tacrolimus is also highly variable. For most patients, the half-life of tacrolimus is between 12-24 hours; however, the half-life may range from 4-41 hours.

The pharmacokinetics of tacrolimus in healthy volunteers varies from that observed in kidney, liver, and heart transplant recipients, as well as that observed in the early post-transplant period. Compared with healthy volunteers, adult kidney transplant recipients exhibit a higher rate of clearance of tacrolimus. In pharmacokinetic studies, the mean clearance after the IV administration of tacrolimus was 0.083 L/hr/kg in adult kidney transplant recipients compared with 0.040 L/hr/kg in healthy volunteers (Prograf Prescribing Information April 2006 ("PI")). In contrast, the rate of clearance for adult liver transplant patients and adult heart transplant patients were comparable to that reported for healthy volunteers. Similarly, the half-life of tacrolimus differs based on the population studied. In healthy volunteers, the mean half-life of tacrolimus is 35 hours. In contrast, the mean half-life of tacrolimus in kidney, liver, and heart transplant patients is 19 hours, 12 hours, and 23 hours, respectively.

In transplant patients, the pharmacokinetics of tacrolimus observed also differs based on the transplanted organ. In addition to differences noted above in regards to the clearance and half-life of tacrolimus in kidney, liver, and heart transplant recipients, the C_{max} and AUC for tacrolimus in kidney transplant recipients is lower than that observed in liver transplant recipients. After the oral administration of tacrolimus 0.3 mg/kg/day in adult kidney transplant recipients, the C_{max} was 24.2 ng/mL and the AUC was 288 ng*h/mL. In comparison, the C_{max} and AUC for tacrolimus was 68.5 ng/mL and 519 ng*h/mL, respectively, following the administration of the same dose of tacrolimus in adult liver transplant recipients.

The time elapsed since transplantation is also a factor that may affect the pharmacokinetics of tacrolimus in transplant patients (Pou L Brunet M, Andres I, et al. Influence of posttransplant time on dose and concentration of tacrolimus in liver transplant patients. *Transpl Int* 1998;11:s270-1; Undre NA, Schafer A. Factors affecting the pharmacokinetics of tacrolimus in the first year after kidney transplantation. *European Tacrolimus Multicentre Renal Study Group. Transplant Proc* 1998;30:1261-3). Over the first year posttransplant, the dose required to maintain a given tacrolimus trough concentration decreases with time.

Another factor that can impact the pharmacokinetics of tacrolimus is the administration of oral tacrolimus with meals, as both the content and timing of

meals have been shown to impact the rate and extent of tacrolimus absorption (Prograf PI; Bekersky I, Dressler D, Mekki Q. Effect of time of meal consumption on bioavailability of a single oral 5mg tacrolimus dose. *J Clin Pharmacol* 2001;41:289-97; Bekersky I, Dressler D, Mekki QA. Effect of low- and high-fat meals on tacrolimus absorption following 5mg single oral doses to healthy human subjects. *J Clin Pharmacol* 2001;41:176-82). In a pharmacokinetic study, the impact of time of meal consumption on the bioavailability of orally administered tacrolimus was evaluated at different times in relation to the administration of breakfast (Bekersky#1). The absorption of tacrolimus was highest in the fasted state, with the bioavailability of tacrolimus significantly higher when fasted compared with all other time points. The administration of tacrolimus immediately after the meal, or 1.5 hours after the meal, had a profound impact on the rate and extent of absorption. In comparison with tacrolimus administered in the fasted state, tacrolimus taken immediately after a meal resulted in a 70.6% reduction in C_{max} and 34.4% reduction in AUC. Similarly, when tacrolimus was taken 1.5 hours after a meal, a 63.0% reduction in C_{max} and 34.9% reduction in AUC took place. In another study, a single 5 mg dose was administered under fasted conditions, with a high fat meal, and with a meal containing low fat and high carbohydrate (Bekersky#2). The rate and extent of absorption of tacrolimus was highest under fasted conditions, while the presence of food significantly reduced these pharmacokinetic parameters. Compared with the fasted state, the reduction in mean C_{max} after the ingestion of a high fat meal was 77.1%, and the reduction in mean AUC was 36.9%. Similarly, the ingestion of a low fat and high carbohydrate meal resulted in a 64.7% reduction in the C_{max} and a 27.8% reduction in the AUC. Absorption was significantly delayed following the oral administration of tacrolimus with a meal; compared with the fasted state, the T_{max} was 373% and 134% greater after a high fat meal and after a low fat and high carbohydrate meal, respectively. As a result of the significant changes in tacrolimus pharmacokinetics in the presence of food, patients are typically advised to maintain a stable diet and to keep the timing of doses of tacrolimus consistent in regards to meals.

Age of the recipient has been identified as a factor that influences the pharmacokinetics of tacrolimus (Prograf PI). In comparison to adult transplant recipients, pediatric patients exhibit a higher rate of clearance following the administration of tacrolimus (Prograf PI; Venkataramanan; Staatz; McDiarmid SV, Colonna JO, Shaked A, et al. Differences in oral FK 506 dose requirements between adult and pediatric liver transplant patients. *Transplantation* 1993;55:1328-32; MacFarlane GD, Venkataramanan R, McDiarmid SV, et al. Therapeutic drug monitoring of tacrolimus in pediatric liver transplant patients. *Pediatr Transplant* 2001;5:119-24; Kim JS, Aviles DH, Silverstein DM, et al.

Effect of age, ethnicity, and glucocorticoid use on tacrolimus pharmacokinetics in pediatric kidney transplant patients. *Pediatr Transplant* 2005;9:162-9). In a one year study, no significant differences in the tacrolimus trough concentrations were observed between pediatric and adult liver transplant recipients; however, pediatric patients required a mean dose of 0.4 ± 0.04 mg/kg/day compared with the mean adult dose of 0.13 ± 0.01 mg/kg/day (McDiarmid). In a study of pediatric kidney transplant patients, the mean tacrolimus dose required to maintain similar AUC was higher in younger patients on a milligram-per-kilogram basis (Kim). On average, the dose of tacrolimus in children <5 years of age was 2.7 times higher than children greater >12 years of age. Similarly, the average daily dose of tacrolimus in children 5-12 years of age was 1.9 times greater than children >12 years of age. The difference in the metabolism and elimination of tacrolimus observed between these two patient groups is primarily attributed to the age dependent change in the CYP3A expression. As a result, pediatric transplant recipients typically require two- to four-fold higher doses of tacrolimus to maintain similar target trough concentrations.

Race is another source of variability in the pharmacokinetics of tacrolimus (Prograf PI; Staatz; Neylan JF. Racial differences in renal transplantation after immunosuppression with tacrolimus versus cyclosporine. FK506 Kidney Transplant Study Group. *Transplantation* 1998;65:515-23; Fitzsimmons WE, Bekersky I, Dressler D, et al. Demographic considerations in tacrolimus pharmacokinetics. *Transplant Proc* 1998;30:1359-64; Felipe CR, Silva HT, Machado PGP, et al. The impact of ethnic miscegenation on tacrolimus clinical pharmacokinetics and therapeutic drug monitoring. *Clin Transplant* 2002;16:262-72). An analysis of a large, randomized, multicenter, clinical study in kidney transplant patients showed that on average, African-American patients required doses of tacrolimus that were 37% higher than Caucasian patients to maintain comparable tacrolimus trough levels throughout the study (Neylan). In a retrospective analysis, the bioavailability of tacrolimus, following oral administration, was only 9.9% in African-American patients compared with 19.0% in non-African-American patients. (Fitzsimmons). In another study, there was significantly greater variability in tacrolimus blood levels observed in nonwhite patients in relation to white patients (Felipe). The study also found that 62% of nonwhite patients exhibited tacrolimus trough levels <10ng/mL in the time period immediately after transplant, compared with 24% of white patients. In addition, nonwhite transplant patients had significantly lower exposure to tacrolimus than white patients, as demonstrated by the AUC of 66.9 ± 67.1 ng*h/mL in nonwhite patients and 229.4 ± 55.5 ng*h/mL in white patients. The differences in pharmacokinetics observed between African-American and non-African-American patients is believed to result from higher

concentrations of p-glycoprotein and CYP3A expression in the small intestine, thereby decreasing the absorption and bioavailability of tacrolimus (Staatz). Therefore, higher milligram-per-kilogram doses of tacrolimus are typically required to achieve therapeutic tacrolimus trough levels in African-American patients compared with non-African-American patients.

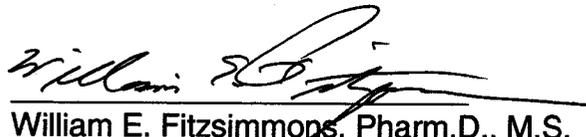
Other comorbidities that have been associated with changes in the pharmacokinetics of tacrolimus include diabetes, hepatitis C virus infection, and liver impairment (Prograf PI; Staatz). In addition, transplant patients are typically treated with many medications for both the prophylaxis of infections, as well as the management of chronic comorbid conditions before and after transplant. FDA clearly recognizes that variability in pharmacokinetics between the fed and fasted state requires additional testing of formulations and has proposed that both conditions be studied in the draft bioequivalence guidance for tacrolimus. Variability in pharmacokinetics of tacrolimus occurs with the transplanted organ, time after transplant, age, race and presence of co-morbid conditions and concurrent medications, and these factors should also be considered.

There is evidence to suggest that changes in the pharmacokinetics of tacrolimus may occur during the period immediately following solid organ transplantation. Astellas has developed an extended-release formulation of tacrolimus (Advagraf), with the objective of allowing once-daily maintenance immunosuppression using the same total daily dose as immediate-release tacrolimus while maintaining comparable exposure, using the same AUC criteria established to demonstrate generic drug bioequivalence. (European Public Assessment Report - Scientific Discussion (August 16, 2007)). In order to show that the same total daily dose of extended-release tacrolimus and immediate-release tacrolimus result in the same degree of exposure over a 24 hour period, the studies conducted in the development program for extended-release tacrolimus required that the mean AUC test:reference ratio be between 80-125% using a 90% confidence interval. Both the multiple-dose pharmacokinetic studies conducted in healthy volunteers, as well as conversion studies conducted in stable kidney and liver transplant recipients, demonstrated that the AUC observed following the administration of extended-release tacrolimus was the same as that observed following the administration of immediate-release tacrolimus. However, when both tacrolimus formulations were studied in de novo kidney and liver transplant patients, exposure to tacrolimus was significantly reduced on day 1 in patients treated with extended-release tacrolimus, demonstrated by AUC test:reference ratios of 67.6% and 50.3% in the de novo kidney and liver transplant patient populations, respectively.

It is significant that despite meeting the applicable bioequivalence standard in healthy volunteers as well as stable kidney and liver transplant recipients, the findings of these pharmacokinetic studies did not successfully predict the pharmacokinetics in de novo kidney or liver transplant patients during the immediate post-transplant period. While the reasons for this are unclear, the finding illustrates that there can be differences between the bioequivalence results for different formulations of tacrolimus in healthy volunteers as compared to transplant patients early after surgery.

As discussed above, the proposed FDA bioequivalence standards for tacrolimus cannot adequately ensure predictable pharmacokinetics in the individual patient. Given the potential deleterious effect in transplant patients and the consequences of losing a transplanted organ, FDA bioequivalence standards should require the evaluation of pharmacokinetics in transplant patients in the immediate post-transplant period.

Respectfully submitted,



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