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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this petition pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.* (the "Act"), and in accordance with the procedural requirements specified in 21 C.F.R. § 10.30, to request that the Commissioner of the Food and Drug Administration ("FDA" or "the Agency") take the actions requested below with respect to any new drug application that seeks approval of an immunosuppressant indicated for maintenance therapy following renal transplantation.

A. ACTION REQUESTED

Petitioner respectfully requests that FDA, with limited exceptions, utilize a standard approach to all applications for new, modified or reformulated immunosuppressants indicated for maintenance therapy following renal transplantation. Specifically, petitioner requests that all primary and adjunctive drugs in this class be required to successfully complete at least one 12-month, double-blind clinical trial.[1]

B. STATEMENT OF GROUNDS

I. Maintenance Immunosuppressants are the "Backbone" of the Conventional Immunosuppressive Regimen.

Long-term patient and graft survival is the ultimate goal of drug therapy following a renal transplant. Although the exact approach varies with each individual patient, the current immunosuppressive protocol for most kidney transplant patients begins with a "four-drug

[1] As detailed in Section B.III.D, petitioner acknowledges that in some narrow circumstances it may be technically infeasible to conduct a double-blind clinical trial.

regimen":[2] (1) an induction agent; (2) a primary immunosuppressant, usually a calcineurin inhibitor ("CNI"); (3) an adjunctive immunosuppressant; and (4) steroids.[3]

The action requested in this petition is limited to new drug applications ("NDAs") for new, modified or reformulated immunosuppressant primary or adjunctive therapies. Primary immunosuppressants represent the "backbone" of the post-transplant drug regimen.[4] Adjunctive agents enhance the potency of the primary immunosuppressant and significantly improve transplant outcomes.[5] Primary and adjunctive immunosuppressants are usually long-term post-operative therapies and are referred to herein as maintenance immunosuppressants.

II. NDAs Based on Less Than 12 Months of Data Fail to Demonstrate the Efficacy Needed to Support Approval.

A. FDA Precedent Requires at Least One, 12-Month Clinical Trial to Demonstrate Efficacy.

FDA has consistently imposed – and should continue to require – a 12-month clinical trial standard for all NDAs that seek approval of a maintenance immunosuppressant. As detailed below, of the eight maintenance immunosuppressants approved in the last three decades, it appears that the only maintenance immunosuppressant approved following clinical trials with durations of less than 12 months was mycophenolate mofetil ("MMF" or CellCept®), an adjunctive therapy that demonstrated superior efficacy in three separate 6-month studies.

To date, all primary immunosuppressants have been approved following 12 months of clinical trial data. In 1983, FDA approved cyclosporine (Sandimmune® or "CsA"), the first CNI indicated as a primary immunosuppressant for use in renal transplantation. The approval followed a 12-month clinical trial in which the cyclosporine-steroid regimen was shown to be superior to the azathioprine-steroid regimen.[6] The cyclosporine trial (and follow-up study)

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[2] Transcript of FDA Meeting on Endpoints in Clinical Trials of Kidney Transplantation (excerpt), at 49:9-11 (Sept. 10, 2012) (Exhibit 1) (hereinafter, "FDA Transcript").

[3] *See* Gabriel M. Danovitch, *Immunosuppressive medications for renal transplantation: A multiple choice question*, 59 Kidney Intl. 388, 389-90 (2001) (Exhibit 2) (describing the evolution of the immunosuppressive regimen); KDIGO, *Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Care of Kidney Transplant Recipients*, 9 Am. J. of Transplantation (excerpt) (Supplement 3) at S6-S15 (2009) (Exhibit 3) (providing an overview of induction, initial maintenance and long-term maintenance immunosuppressive medications).

[4] *See* KDIGO, *supra* note 3, at S17 ("Calcineurin inhibitors currently form the backbone of immunosuppressive regimens."); *see also* Julie M. Yabu & Flavio Vincenti, *Kidney Transplantation: The Ideal Immunosuppression Regimen*, 16 Advances in Chronic Kidney Disease, 226, 227-29 (2009) (Exhibit 4) (noting that "cyclosporine and tacrolimus have been the mainstay of maintenance immunosuppression for the last 1 and a half to 2 decades," but acknowledging efforts to limit patient exposure to CNIs and thereby reduce negative side effects like hypertension and hyperlipidemia).

[5] *See, e.g.*, KDIGO, *supra* note 3, at S10 ("Agents are used in combination to achieve sufficient immunosuppression, while minimizing the toxicity associated with individual agents").

[6] *See* Herwig-Ulf Meier-Kriesche & Sundus A. Lodhi, *30-Year Retrospective on Organ Transplant Immunosuppression in the Era of Calcineurin Inhibitors*, Medscape CME Monograph, tbl 2 (2010) (Exhibit 5).

revolutionized renal transplant outcomes because graft survival rates reached approximately 80 percent.[7] Cyclosporine was soon combined with azathioprine, corticosteroids and antibody preparations to achieve 1-year graft and patient survival rates of over 90 percent.[8] To date, cyclosporine has been the only primary immunosuppressant present in the control arms of maintenance immunosuppressant clinical trials supporting successful NDAs.[9]

In 1995, FDA approved a new formulation of cyclosporine (Neoral®) following a 12-month study in which this new formulation was shown to be non-inferior to Sandimmune®.[10]

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[7] *See* Sundaram Hariharan, Maureen A.McBride & Eric P. Cohen, *Evolution of Endpoints for Renal Transplant Outcome*, 3 Am. J. of Transplantation 933, 934-35, tbl 2 (2003) (Exhibit 6) ("[S]ubstantial short-term survival benefit with CsA therapy was detected in a small cohort of patients."); *see also* FDA Transcript, at 33:18-22 ("The Canadian multicenter study, which also used a randomized concurrent control of azathioprine and steroids, showed a graft survival of 80 percent; statistically significantly greater than that of 64 percent of the actual control.").

[8] *See* Danovitch, *supra* note 3, at 390 ("With these medications – cyclosporine, azathioprine, corticosteroids, and the antibody preparations – the transplant community entered the 1990s achieving . . . success rates of up to 90% and minimal mortality in many centers.").

[9] All three subsequent primary immunosuppressants (Neoral®, tacrolimus and belatacept) were approved following successful clinical trials with cyclosporine in the control arm. *See* D. Niese, *A Double-Blind Randomized Study of Sandimmun Neoral Versus Sandimmun in New Renal Transplant Recipients: Results After 12 Months*, 27 Transplantation Proceedings 1849, 1849 (1995) (Exhibit 7) ("Patients were . . . randomized in equal proportions at the time of starting oral cyclosporin therapy to receive either SIM [Sandimmune®] or Neoral as part of the usual local immunosuppressive regimen."); Prograf® (tacrolimus) Prescribing Information, §14.1 (Aug. 2012) ("Prograf-based immunosuppression in conjunction with azathioprine and corticosteroids following kidney transplantation was assessed in a randomized, multicenter, non-blinded, prospective trial. . . . There were 205 patients randomized to Prograf-based immunosuppression and 207 patients were randomized to cyclosporine-based immunosuppression."); Nulojix® (belatacept) Prescribing Information, §14.1 (Apr. 2013) ("The efficacy and safety of NULOJIX in *de novo* kidney transplantation were assessed in two . . . trials (Study 1 and Study 2). These trials evaluated two dose regimens of NULOJIX . . . compared to a cyclosporine control regimen."). Additionally, all adjunctive agents have used cyclosporine (either Sandimmune® or Neoral®) in both the control and the treatment arms of clinical trials used to support successful NDAs. *See* CellCept® (mycophenolate mofetil) Prescribing Information, at 10 (June 2012) ("The three renal studies compared two dose levels of oral CellCept [] with azathioprine (2 studies) or placebo (1 study) when administered in combination with cyclosporine (Sandimmune®) and corticosteroids"); Rapamune® (sirolimus) Full Prescribing Information, § 14.1 (Dec. 2012) ("The safety and efficacy of Rapamune Oral Solution for the prevention of organ rejection following renal transplantation were assessed in two . . . trials. These studies compared two dose levels of Rapamune Oral Solution [] with azathioprine (Study 1) or placebo (Study 2) when administered in combination with cyclosporine and corticosteroids."); Myfortic® (mycophenolic acid) Prescribing Information, Clinical Studies (June 2012) ("The safety and efficacy of Myfortic® . . . in combination with cyclosporine, USP (MODIFIED) and corticosteroids for the prevention of organ rejection was assessed in two multicenter, randomized, double-blind trials in de novo and maintenance renal transplant patients compared to mycophenolate mofetil."); Zortress® (everolimus) Full Prescribing Information, §14.1 (Feb. 2013) ("A 24-month, multi-national, open-label, randomized (1:1:1) trial was conducted comparing two concentration-controlled Zortress regimens . . . with reduced exposure cyclosporine and corticosteroids, to 1.44 g per day of mycophenolic acid with standard exposure cyclosporine and corticosteroids.").

[10] Niese, *supra* note 9, at 1855 ("Over the whole 12-month period, the number of patients presenting with acute rejection episodes was lower in the Neoral group and the rejection-free time following transplantation was longer, although this difference was not statistically significant.")

In 1997, following two 12-month clinical trials, FDA approved tacrolimus (Prograf®), a CNI, for use as an alternative to cyclosporine.[11] Most recently, in 2011, FDA approved belatacept (Nulojix®), a recombinant soluble fusion protein, following a 36-month trial in which the drug was shown to be non-inferior to cyclosporine at 12-months.[12]

With the sole exception of MMF, the first drug approved for use as an adjunctive to cyclosporine, all adjunctive immunosuppressants have been approved following 12-month clinical trials. MMF, approved on the basis of three 6-month superiority trials, is an outlier for several reasons. First, MMF was approved following three separate clinical trials, each of which demonstrated superiority against standard care: a "statistically significant reduction in treatment failure" over both placebo and azathioprine.[13] Second, most of its development preceded a 1994 FDA advisory committee meeting in which FDA stated that clinical trials should be designed to assess biopsy-proven acute rejection ("BPAR") at 12-months.[14] Third, MMF was approved approximately 18 years ago. In the modern transplant era, "as new immunosuppressive drugs and protocols are introduced and the incident of acute rejection falls, it has become increasingly difficult to prove the statistically significant benefit of even newer agents."[15]

All subsequent adjunctive agents have been approved following 12-month clinical trials. In 1999, FDA approved sirolimus (Rapamune®), a mammalian target of rapamycin (mTOR) inhibitor, for use with cyclosporine and steroids.[16] Sirolimus was approved following two clinical trials that showed superiority to standard of care at 6-months with respect to a reduction in the incidence of efficacy failure, and non-inferiority to standard of care at 12-

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[11] *See* Meier-Kriesche & Lodhi, *supra* note 6, at tbl 2.; *see also* Prograf® (tacrolimus) Prescribing Information, § 14.1 (Aug. 2012) ("Overall 1 year patient and graft survival was 96.1% [for patients randomized to Prograf-based immunosuppression] and 89.6% [for patients randomized to cyclosporine-based immunosuppression].").

[12] Nulojix® (belatacept) Prescribing Information, § 14.1 (Apr. 2013) (stating that the efficacy of belatacept was assessed in two trials and in both trials "[e]fficacy failure at one year was defined as the occurrence of biopsy proven acute rejection (BPAR), graft loss, death, or lost to follow-up").

[13] FDA Transcript, at 36:2-9 ("The basis of approval was a statistically significant reduction in treatment failure for MMF, cyclosporine, plus steroids in three double-blind, randomized, controlled trials, compared to azathioprine, cyclosporine, and steroids in two studies, the USA and the Tricontinental Study[, and] were compared to placebo, and cyclosporine plus steroids in the European study."); *see also Mycophenolate Mofetil for the Prevention of Acute Rejection in Primary Cadaveric Renal Allograft Recipients*, 60 Transplantation 225, 227 (1995) (Exhibit 8) ("Treatment with MMF resulted in a reduction in the incidence of a first biopsy-proven acute rejection episode or treatment failure during 6 months after transplant from 47.6% in the azathioprine group to 31.1% in the MMF 2 g group and 31.3% in the MMF 3 g group."); *Placebo-Controlled Study of Mycophenolate Mofetil Combined with Cyclosporine and Corticosteroids*, 345 Lancet, 1321, 1321 (1995) (Exhibit 9) ("Significantly fewer ($p \leq 0.001$) patients had biopsy-proven rejection or withdrew early from the trial (for any reason) during the first 6 months after transplantation with MMF 2 g (30.3%) or 3 g (38.8%) than with placebo (56.0%).").

[14] FDA Transcript, at 35:20-36:1 ("Mycophenolate mofetil was approved in 1995 for the prevention of rejection in kidney transplantation. Most of its development preceded the advisory committee meeting of 1994.").

[15] Danovitch, *supra* note 3, at 391.

[16] *See* CDER Approval Package for Application No. 21-083, Medical Officer's Review, Sept. 15, 1999, at 13, tbl 3, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21083A_Rapamune_medr_P1.pdf.

months with respect to patient and graft survival.[17] In 2004, FDA approved mycophenolic acid, the sodium salt form of MMF (Myfortic®), following two 12-month trials in which mycophenolic acid was shown to be non-inferior to MMF.[18] In 2010, FDA approved everolimus (Zortress®), a mTOR inhibitor, for adjunctive use with reduced doses of cyclosporine, an induction agent, and corticosteroids.[19] Everolimus was approved following a 24-month clinical trial in which everolimus was shown to be comparable to mycophenolic acid in preventing efficacy failure at 12-months.[20]

FDA recently indicated its intent to continue to follow established precedent. In a September 2012 public workshop, FDA reiterated that the "most important" recommendation from the 1994 FDA advisory committee meeting was that BPAR should be a primary endpoint "assessed, ideally, at one-year interval after transplantation."[21]

B. *Non-Inferiority Trials Should be Supported by 12-Month Efficacy Data.*

During the same September 2012 workshop, FDA also highlighted the challenges inherent in obtaining clinically meaningful results from short-term clinical studies that assess treatment failure.[22] With graft and patient survival rates reaching 94 percent, most modern-era maintenance immunosuppression NDAs are supported by non-inferiority trials.[23] In non-inferiority trials, efficacy is established by demonstrating that the new drug is comparable to the active drug in the control arm.[24] Given the lower discriminatory ability of non-inferiority trials

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17 *See* Rapamune® (sirolimus) Full Prescribing Information, § 14.1 (Dec. 2012) ("In both studies, the primary efficacy endpoint was the rate of efficacy failure in the first 6 months after transplantation. . . . Patient and graft survival at 1 year were co-primary endpoints.").

18 *See* Myfortic® (mycophenolic acid) Prescribing Information, Clinical Studies (June 2012) (noting that both clinical trials assessed incidents of treatment failure, defined as BPAR, graft loss, death or lost to follow-up, at 6 and 12 months); CDER Approval Package for Application No. 50-791, Medical Officer's Review, Feb 20, 2004, at 17, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/50-791_Myfortic_medr.PDF ("A face to face, Phase III meeting/Type C with the Applicant was held at the Division . . . The Agency also noted that review of the NDA application *would be incomplete* if the submitted efficacy safety data lacked the co-primary endpoints analysis at 12 months to include acute rejection at 6 months, rates of death at 12 months, and graft loss at 12 months.") (emphasis added).

19 Zortress® (everolimus) Full Prescribing Information, § 1.1 (Feb. 2013) ("Zortress is to be administered in combination with basiliximab induction and concurrently with reduced doses of cyclosporine and corticosteroids."); *see also* FDA Transcript, at 39.

20 Zortress® (everolimus) Full Prescribing Information, § 14.1 (Feb. 2013) ("Results at 12 months indicated that everolimus 1.5 mg per day is comparable to Myfortic with respect to efficacy failure, defined as treated biopsy-proven acute rejection, graft loss, death or loss to follow-up.").

21 FDA Transcript, at 34:17-18.

22 *See id.* at 49:2-21 ("[E]arly superiority trials were possible because a new drug greatly improved the overall patient and graft survival . . . . Superiority trials are now quite a bit more difficult . . . because with the current four-drug regimen, one year patient and graft survival is high. . . . So it's almost just unfeasible . . . to do a superiority trial.").

23 As outlined in section B.II.A, Neoral®, belatacept, sirolimus (with respect to patient and graft survival), mycophenolic acid, and everolimus were all approved following findings of non-inferiority.

to detect an improvement (as opposed to a worsening) in therapeutic benefit, FDA should not compromise product safety by reducing the current 12-month standard required for maintenance immunosuppressant product approval.

C. *The Difficulty Inherent in Predicting Long-Term Patient and Graft Survival Supports a 12-Month Standard.*

At present, there is no established endpoint for predicting long-term patient and graft survival. Moreover, there is a growing body of academic research that underscores the difficulty of determining long-term patient and graft survival using short-term data.[25] In an effort to reduce trial durations and make early efficacy determinations, researchers are looking for a diagnostic marker that can serve as an early predictive surrogate for eventual graft loss.[26] Researchers, however, have yet to find a surrogate that will allow for shorter but equally predictive trials. Notably, even scholars who advocate the adoption of a surrogate endpoint, such as serum creatinine, still recommend that the surrogate be measured at 12-months.[27]

Thus, in light of FDA precedent, the predominant use of non-inferiority trials, and the difficulty of predicting long-term efficacy, petitioner respectfully asks FDA to require that all NDAs for renal transplant maintenance immunosuppressive therapies include at least one successful 12-month clinical trial as evidence of efficacy.

III. Open-Label Studies Undermine the Scientific Integrity of the Clinical Trial Process and Produce Less Persuasive Results.

The progressive improvements achieved in BPAR and patient and graft survival make open-label clinical trials for new maintenance immunosuppression drug therapies inherently more susceptible to bias.[28] In an open-label trial, knowledge of the

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(cont'd from previous page)

[24] FDA Transcript, at 43-44.

[25] *See* Herwig-Ulf Meier-Kriesche, et al., *Lack of Improvement in Renal Allograft Survival Despite a Marked Decrease in Acute Rejection Rates Over the Most Recent Era*, 4 Am. J. of Transplantation 378, 378 (2004) (Exhibit 10) ("Our data suggest that decreasing acute rejection rates between 1995 and 2000 have not led to an increase in long-term graft survival."); Bruce Kaplan, Jesse Schold & Herwig-Ulf Meier-Kriesche, *Poor Predictive Value of Serum Creatinine for Renal Allograft Loss*, 3 Am. J. of Transplantation 1560, 1560 (2003) (Exhibit 11) ("[T]here has been a concerted effort among the transplant community to attain a diagnostic that may serve as a surrogate for eventual graft loss.").

[26] *See, e.g.*, Kaplan, Schold & Meier-Kriesche, *supra* note 25, at 1560 ("A surrogate endpoint for graft loss could allow for more rapid evaluation of drug therapies, transplant techniques, and patient care protocols.").

[27] *See, e.g.*, Hariharan, McBride & Cohen, *supra* note 7, at 933-34 (2003); Sundaram Hariharan et al., *Post-Transplant Renal Function in the First Year Predicts Long-Term Kidney Transplant Survival*, 62 Kidney Int'l 311, 317 (2002) (Exhibit 12) (arguing that "one year creatinine and Δ creatinine values are the variables that correlate best with long-term graft survival.").

[28] As used in this petition, bias means "the systematic tendency of any aspects of the design, conduct, analysis, and interpretation of the results of clinical trials to make the estimate of a treatment effect deviate from its true value." Guidance for Industry: *E 10 Choices of Control Group and Related Issues in Clinical Trials*, May 2001, at 3.

immunosuppressant treatment regimen may unconsciously influence the investigator's decision to biopsy a patient suspected of an acute rejection, use induction or a concomitant immunosuppressant or otherwise modify the treatment practice.[29] Even well-defined, objective endpoints are susceptible to bias because the clinical course that precedes such endpoints cannot be objectively measured in an open-label trial.[30] Further, the well-documented, short-term success of the conventional four-drug regimen may impact the reporting of patient prognoses and outcomes. Given this risk of bias, FDA should continue to require at least one successful double-blind trial for new maintenance immunosuppression drug therapies as the minimum standard necessary to meet the requirements of an adequate and well-controlled study.

As a rule, FDA has consistently required double-blinding in maintenance immunosuppression clinical trials. The only exceptions to this rule arise in the limited circumstances in which (i) a novel primary immunosuppressant is compared directly to a standard primary immunosuppressant that requires close therapeutic drug monitoring and rapid dose adjustments or (ii) a novel adjunctive immunosuppressant requires researchers to alter the standard dose of the primary immunosuppressant and its resulting blood-level target range.[31] New maintenance immunosuppressant drug applications that seek approval of drugs that either add to the current drug regimen, replace an adjunctive agent or reflect a modification or reformulation of a current primary immunosuppressant do not raise similar patient health and safety concerns.

A. A Successful Double-Blind Clinical Trial Should be Required to Support an NDA for a Reformulation or Modification of a Maintenance Immunosuppressant.

FDA has required double-blind clinical testing for all NDAs that propose a reformulation or modification of a maintenance immunosuppressant. In 1995, FDA approved Neoral®, a new formulation of cyclosporine, following a double-blind clinical trial.[32] Neoral® was appropriately assessed through a double-blind, active-control clinical trial because the presence of cyclosporine in both arms made it possible to mask the treatment group. *See* C.F.R § 314.126(b)(2)(iv) ("Active treatment trials usually include randomization and blinding of

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[29] *Id.* at 4 ("Blinding is intended to minimize the potential biases resulting from differences in management, treatment, or assessment of patients, or interpretation of results that could arise as a result of subject or investigator knowledge of the assigned treatment.").

[30] *Id.* (noting that "[o]bservers might be less likely to identify and report treatment responses in a no-treatment group or might be more sensitive to a favorable outcome or adverse event in patients receiving active drug" and that "[k]nowledge of treatment assignment could affect decisions as to whether a given subject's results should be included in an analysis.").

[31] As noted above, to date, cyclosporine has been the only primary immunosuppressant present in the control arm of a clinical trial used to support an NDA for a maintenance immunosuppressant. *See supra* note 9. The same considerations would, however, also apply to a future NDA comparing a novel primary immunosuppressant to tacrolimus in the control arm.

[32] *See* Meier-Kriesche & Lodhi, *supra* note 6, at tbl 2 ("Neoral® was approved by the FDA for transplant immunosuppression in 1995 on the basis of a double-blind randomized study of Neoral® vs Sandimmune® in new renal transplant recipients.").

patients or investigators, or both."). Similarly, in 2004, FDA approved mycophenolic acid (Myfortic®), the sodium salt form of MMF, following two 12-month, double-blind clinical trials.[33] Although the new drug application for mycophenolic acid proposed to modify the form of the underlying reference drug (MMF), a double-blind trial was feasible, and therefore required, because the standard dose of cyclosporine was present in both arms of the clinical trial.

B. A Successful Double-Blind Clinical Trial is Needed to Substantiate the Efficacy of New Adjunctive Agents.

Starting with the approval of MMF, the first drug approved for use as an adjunctive to cyclosporine, NDAs for adjunctive immunosuppressants have consistently relied on data derived from double-blind trials to establish efficacy.[34] In the MMF trials, all patients received cyclosporine and steroids. Although MMF was added to only one arm of the clinical trial, both groups received the underlying primary immunosuppressant, cyclosporine, which made it possible to mask the treatment arm. *See* 21 C.F.R § 314.126(b)(2)(i) ("A placebo-controlled study . . . usually includes randomization and blinding of patients or investigators, or both."). Likewise, sirolimus was approved as an adjunctive agent in 1999 following two, double-blind clinical trials.[35] And, as discussed above, the adjunctive agent Myfortic, was approved in 2004 following two 12-month, double-blind clinical trials.

In 2010, FDA approved everolimus, a second mTOR inhibitor, as an adjunctive immunosuppressant.[36] The initial everolimus trials, which compared the efficacy of everolimus to MMF in patients treated with cyclosporine and steroids, were double-blind for the first 12

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[33] Myfortic® (mycophenolic acid) Prescribing Information, Clinical Studies (June 2012) ("The safety and efficacy of Myfortic® (mycophenolic acid) . . . was assessed in two multicenter, randomized, double-blind trials in de novo and maintenance renal transplant patients compared to mycophenolate mofetil.") *see also* CDER Approval Package for Application No. 50-791, Medical Officer's Review, Feb 20, 2004, at 5, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/50-791_Myfortic_medr.PDF (noting that "the Applicant submitted the reports for two adequate and well controlled clinical studies (B301 & B302) in renal transplant patients" and that both studies were double-blind).

[34] FDA Transcript, at 36:2-9 ("The basis of approval [of MMF] was a statistically significant reduction in treatment failure for MMF, cyclosporine, plus steroids in three double-blind, randomized, controlled trials, compared to azathioprine, cyclosporine, and steroids in two studies, the USA and the Tricontinental Study[,and] were compared to placebo, and cyclosporine plus steroids in the European study.").

[35] *See* Rapamune® (sirolimus) Prescribing Information, § 14.1 (Dec. 2012) ("The safety and efficacy of Rapamune Oral Solution for the prevention of organ rejection following renal transplantation were assessed in two randomized, double-blind, multicenter, controlled trials."); CDER Approval Package for Application No. 21-083, Medical Review Officer's Review, Sept. 15, 1999, at 12, table 1, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21083A.cfm (describing both double-blind clinical trials as "Adequate and Well-Controlled").

[36] Zortress® (everolimus) Prescribing Information, § 1.1 (Feb. 2013), ("Zortress is indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. . . . Zortress is to be administered in combination with basiliximab induction and concurrently with reduced doses of cyclosporine and corticosteroids.").

months following kidney transplantation.[37] At year 1, preliminary data indicated that everolimus, when paired with standard doses of cyclosporine, increased renal toxicity. As a result, the cyclosporine dose was reduced in the treatment arms and the studies were un-blinded to achieve target blood trough concentration levels.[38] Although the initial trials demonstrated that everolimus was non-inferior to MMF, an additional, concentration-controlled, open-label trial was needed to establish a safe and effective dosing regimen.[39]

C. *Double-Blind Clinical Trials Reflect A Well-Established, Cross-Border Standard.*

As early as 1994, FDA indicated that double-blind trials are needed to minimize bias.[40] Similarly, in response to open-label studies submitted in support of a proposed change to the sirolimus label, FDA representative Marc Cavaillé-Coll, M.D., Ph.D., Medical Team Leader in the Division of Special Pathogen and Immunologic Drug Products, advised members of the Antiviral Drugs Advisory Committee that "open-label design creates a potential for bias in the assessment and comparison of rates of acute rejection, because the investigator who is informed of the treatment assignment may make treatment or diagnostic decisions that ultimately influence the rate of rejection."[41]

The importance of double-blind trials is also reflected in guidance developed by the U.S., Japan and the European Union in 1998 in connection with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human

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[37] *See id.* at § 14.1 ("Two earlier studies compared fixed doses of Zortress . . . combined with standard doses of cyclosporine and corticosteroids to mycophenolate mofetil . . . and corticosteroids. . . . Both were multicenter, double-blind (for first 12 months). . . .").

[38] *See id.* ("Therefore, reduced doses of cyclosporine should be used in combination with everolimus in order to avoid renal dysfunction and everolimus trough concentrations should be adjusted using therapeutic drug monitoring to maintain trough concentrations between 3 to 8 ng/mL."); *see also* CDER Approval Package for Application No. 21-560, Medical Review(s), Clinical Review by Ergun Velidedeoglu, MD, Apr. 18, 2010, at 59, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021560s000medr.pdf ("Due to these observed renal toxicities, the NDA was not approved and the applicant was asked to establish a safe and effective dosing regimen for everolimus and CsA that minimizes renal function impairment while maintaining efficacy, such as concentration controlled regimens of everolimus and cyclosporine using therapeutic dose monitoring (TDM).").

[39] *See* CDER Approval Package for Application No. 21-560, *supra* note 38, at 20 (" Efficacy of everolimus was demonstrated in Studies B201 and B251; however, interpretation of the results was complicated by the premature treatment discontinuations due to reduced graft function and higher serum creatinine concentrations seen in the everolimus groups compared to the MMF control groups. The 12 month analysis of GFR showed increased rate of renal impairment in both of the everolimus groups compared to the MMF control group in both studies.").

[40] *See* FDA Transcript, at 34:5-35:5 (referencing the December 1994 Advisory Committee meeting on Biological and Response Modifiers during which the committee recommended "using double-blind designs").

[41] Memorandum from Marc Cavaillé-Coll, M.D., Ph.D. to Antiviral Drugs Advisory Committee on Clinical/Statistical Background Information for January 24, 2002 Advisory Committee Meeting, at 3 (Dec. 28, 2001), *available at* http://www.fda.gov/ohrms/dockets/ac/02/briefing/3832b1_04_FDA-Rapamune-Backgrounder.pdf.

Use.[42] The three countries developed written guidance on the technical requirements for clinical trials that recognizes that "the double-blinded trial is the optimal approach" and that "extensive efforts" should be made to address challenges to the creation of a double-blind clinical trial.[43]

D. *The Only Exceptions FDA Should Recognize are NDAs in which the Comparison of Primary Immunosuppressants Necessitates Constant Therapeutic Blood-Level Monitoring or NDAs that Require Researchers to Alter the Standard Dose and Consequent Blood-Level Target Range of the Standard Primary Immunosuppressant.*

The nephrotoxicity associated with CNIs is well-documented.[44] As a result, therapeutic dose monitoring is required for CNI-treated patients, which inevitably reveals the presence or absence of the CNI. Given these restrictions, the time-lag required to utilize an independent central dose titration committee might jeopardize patient safety.[45] Likewise, if preliminary blinded results reveal that the interaction between the CNI and a novel adjunctive agent creates unsafe levels of renal toxicity, blinding may not ultimately be possible.[46]

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[42] *See* International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials, 63 Fed. Reg. 49,583, 49,587 (Sept. 16, 1998); *see also* European Medicines Agency, *E9 Statistical Principles for Clinical Trials*, at 11 (Sept. 1998) (Exhibit 13).

[43] Even the extra pill burden of a double-blind, double-dummy trial is not insurmountable. *See, e.g.*, Klemens Budde et al,. *Enteric-Coated Mycophenolate Sodium can be Safely Administered in Maintenance Renal Transplant Patients: Results of a 1-Year Study*, 4 Am. J. of Transplantation 237, 238 (2003) (Exhibit 14) (outlining the double-blind, double-dummy approach that was used by researchers in one of the clinical trials that supported Novartis's successful Myfortic® NDA).

[44] *See, e.g.*, Yabu & Vincenti, *supra* note 4, at 229 ("To avoid the various metabolic and cosmetic side effects in addition to the known nephrotoxic effects that can generate profibrotic factors that contribute to chronic graft injury and survival, there has been considerable interest in developing protocols that minimize the use of CNIs while maintain adequate immune-suppression."); Meier-Kriesche & Lodhi, *supra* note 6, at Nephrotoxicity: The Achilles' Heel of Cyclosporine ("Although the nephrotoxic side effects of CsA were known relatively early on, they were not fully appreciated until data from multicenter trials showed that CsA-treated groups had worse renal function than [azathioprine]-treated control groups. Despite its nephrotoxic effects, CsA (combined with steroids) became the dominant primary immunosuppressant . . . ."); Danovitch, *supra* note 3, at 390 ("Although the benefits of cyclosporine were clear cut, its capacity to produce both acute and chronic nephrotoxicity was soon recognized to be a major 'thorn in its side.'") (internal quotation marks and citations omitted).

[45] The infeasibility of double-blind trials in these circumstances is reflected in the fact that the two primary immunosuppressants approved since the introduction of cyclosporine have been based on open-label clinical trials. *See* Meier-Kriesche & Lodhi, *supra* note 6, at tbl 2 ("Prograf® was approved by FDA . . . on the basis of 2 randomized, open-label, multicenter trials comparing TAC with Sandimmune"); F. Vincenti et al., *A Phase III Study of Belatacept-based Immunosuppression Regimens versus Cyclosporine in Rena Transplant Recipients (BENEFIT Study)*, 10 Am. J. of Transplantation 535, 536 (Exhibit 15) ("The [belatacept] study was . . . open-label with respect to allocation of belatacept or cyclosporine, primarily due to the need for therapeutic dose monitoring in cyclosporine-treated patients.").

[46] For example, the clinical trials for everolimus, an adjunctive agent, were only un-blinded upon the discovery that everolimus, when used in combination with cyclosporine, created unsafe levels of renal toxicity. *See* CDER Approval Package for Application No. 21-560, *supra* note 38, at 59 ("Due to these observed renal toxicities, the NDA [supported by double-blinded studies] was not approved and the applicant was asked to establish a safe and effective dosing regimen for everolimus and CsA that minimizes renal function impairment while

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Thus, for the reasons set forth above, 12-month, double-blind clinical trial data represent the standard that should be applied to all new maintenance immunosuppressant drug applications that seek approval of drugs that either add to the current drug regimen, replace an adjunctive agent or reflect a modification or reformulation of a current primary immunosuppressant.

C. ENVIRONMENTAL IMPACT

An environmental assessment report on the action requested in this Petition is not required because petitioner claims a categorical exclusion pursuant to 21 C.F.R. §§ 25.30 and 25.31.

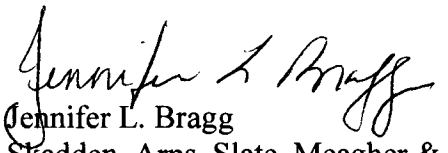
D. ECONOMIC IMPACT

An economic impact statement will be submitted if requested by the Commissioner, pursuant to 21 C.F.R. § 10.30(b).

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



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maintaining efficacy, such as concentration controlled regimens of everolimus and cyclosporine using therapeutic dose monitoring (TDM).").

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