Department of Health and Human Services

Food and Drug Administration
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Silver Spring, MD 20993

JUL 19 2013

Jennifer L. Bragg
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1440 New York Avenue, NW
Washington, DC 20005

Re: Docket No. FDA-2013-P-0509

Dear Ms. Bragg:

This letter responds to your citizen petition dated April 29, 2013 (Petition). In the Petition, you request that the Food and Drug Administration (FDA or Agency) take certain actions with respect to any new drug application (NDA) for a new, modified, or reformulated immunosuppressant product indicated for maintenance therapy[1] following renal transplantation. Specifically, you request that sponsors of all primary and adjunctive drugs in this class[2] be required to successfully complete at least one 12-month, double-blind clinical trial, except in certain limited circumstances where a double-blind clinical trial may not be technically feasible.[3]

As explained below, the Petition is granted in part and denied in part. The Petition is granted in part insofar as your request for 12-month, double-blind clinical trial design is, with some exceptions, consistent with our general recommendations for approval of immunosuppressant products indicated for prophylaxis of organ rejection in kidney transplant recipients (hereinafter referred to as maintenance immunosuppressants). The

[1] We note that the FDA-approved labeling for these immunosuppressant products does not list "maintenance therapy" as part of the approved indication for the product. Instead, the labeling for these products states that they are indicated for the prophylaxis of organ rejection in various transplant patients (see section I.A of this document).

[2] You state that primary immunosuppressants are usually calcineurin inhibitors and that adjunctive immunosuppressants are agents used to enhance the potency of the primary immunosuppressant and significantly improve transplant outcomes (Petition at 2). For the immunosuppressant products discussed in the Petition, we note that we do not specify in the indication whether these are primary or adjunctive immunosuppressants. Although the immunosuppressant products that are the subject of this Petition are not indicated for "maintenance therapy," we adopt that terminology for purposes of brevity in this response, and refer to them indistinguishably as "maintenance immunosuppressants."

[3] You specify that these "limited circumstances" are when (i) a novel primary immunosuppressant is compared directly to a standard primary immunosuppressant that requires close therapeutic drug monitoring (TDM) 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 (Petition at 7).

Petition is denied in part because, on a case-by-case basis, we will accept NDAs for these products that rely on data from alternative clinical trial designs.[4] We will make decisions about the acceptability of alternative clinical trial designs for these products in the normal course of NDA review.[5] Each decision will be based on our scientific experience and expertise regarding maintenance immunosuppressants and applicable legal standards, and take into consideration the risks and benefits of the proposed product in the NDA, as well as our evaluation of current relevant scientific data and information. This response should not be construed as addressing specific issues raised by any pending or future NDAs, nor does it purport to make any final decisions with respect to any such NDAs.

I. BACKGROUND

A. Immunosuppressant Products Following Renal Transplantation

Immunosuppressant products are administered to recipients of kidney transplants to prevent rejection of the kidney. In the past three decades, FDA has approved the following immunosuppressants for kidney transplantation based on outcomes in adequate and well-controlled clinical trials[6]:

- Sandimmune (cyclosporine, USP), for prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants
- Neoral (cyclosporine, USP) MODIFIED, for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants
- CellCept (mycophenolate mofetil), for prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants
- Prograf (tacrolimus), for the prophylaxis of organ rejection in patients receiving allogeneic kidney transplants

[4] For instance, exceptions to the use of double-blinding of trials for these products may go beyond the limited circumstances that you describe in your petition or the duration of the trials for these products may be shorter than 12 months.

[5] We note that in some circumstances, relative bioavailability studies may constitute the primary basis for approval (e.g., the demonstration of equivalent bioavailability for an oral suspension compared to an approved oral capsule), provided applicable scientific and legal standards are met.

[6] All the immunosuppressants in this list are drugs that are approved under an NDA, except Nulojix (belatacept), which is a biologic that is licensed under a Biologics License Application (BLA). We also note that FDA approved Imuran (azathioprine) in 1968 "as an adjunct for the prevention of rejection in renal homotransplantations" based on experience in over 16,000 transplants that showed a five-year patient survival of 35 percent to 55 percent. See the Renal Homotransplantation subsection of the INDICATIONS AND USAGE section of Imuran's labeling.

- Rapamune (sirolimus), for the prophylaxis of organ rejection in patients 13 years and older receiving renal transplants

- Myfortic (mycophenolic acid), for the prophylaxis of organ rejection in adult patients receiving a kidney transplant

- Zortress (everolimus), for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant

- Nulojix (belatacept), for the prophylaxis of organ rejection in adult patients receiving a kidney transplant

Today, we have approved Astagraf XL (tacrolimus extended-release capsules, NDA 204096), for the prophylaxis of organ rejection in adult patients receiving kidney transplants. The sponsor of Astagraf XL is Astellas Pharma US, Inc.

B. Statutory and Regulatory Framework

The Federal Food, Drug, and Cosmetic Act (the FD&C Act) and FDA regulations require that a sponsor seeking to market a new drug submit an NDA. NDAs are submitted under section 505(b)(1) or (b)(2) of the FD&C Act (21 U.S.C. 355(b)(1) and (2)) and approved under section 505(c) of the FD&C Act.[7] NDAs generally contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought.

Sponsors of NDAs must provide "substantial evidence" of effectiveness for claimed indications in their applications. As stated in section 505(d) of the FD&C Act, *substantial evidence* means:

> . . . evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the

[7] A 505(b)(2) application is an NDA that relies for approval, at least in part, on data and information that are not owned by the applicant and to which the applicant does not have a right of reference. For example, the Agency may approve a 505(b)(2) application that relies on published literature or on the Agency's finding of safety and effectiveness for another listed drug product, provided that such reliance is scientifically justified. A 505(b)(2) applicant must submit data necessary to support the safety and effectiveness of any aspects of the proposed drug product that represent modifications to or changes from the listed drug on which it relies.

> Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.

The Agency generally requires at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness for the approval of an NDA. The Agency's guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* outlines our current thinking on acceptable approaches.[8]

The characteristics of adequate and well-controlled clinical investigations are described in FDA's regulation at 21 CFR 314.126. First, there must be a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results. The protocol for the study and report of results should describe the study design precisely (21 CFR 314.126(b)(1)-(2)). Additionally, a clinical investigation that is adequate and well-controlled generally must, for example, have at least one control group to permit a valid comparison to provide a quantitative assessment of drug effect; use an appropriate method of selection to enroll a sufficient number of adequately characterized study participants; minimize bias (usually through random assignments of study participants to control and treatment groups and through the blinding of participants and investigators to those assignments); include well-defined and reliable methods to analyze subjects' responses; and analyze the results of the study adequately to assess the effects of the treatment (21 CFR 314.126(b)(2)-(7)). One of the purposes of requiring rigorously controlled investigations is to ensure that the drug products taken by patients have been shown to be safe and effective based on accepted scientific methods (21 CFR 314.126). Well-controlled clinical investigations help distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation (Id.).

Sponsors must also describe, in addition to other information, the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling (21 CFR 314.50(d)(5)(viii)).

II. DISCUSSION

You request in the Petition that FDA require that any NDA for a maintenance immunosuppressant contain at least one 12-month, double-blind clinical trial, except in certain limited circumstances. We discuss your request below.

A. 12-Month Minimum Duration

You request that FDA require at least one clinical trial with a minimum duration of 12 months for all NDAs for a maintenance immunosuppressant (Petition at 1 – 6). You

[8] Available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

claim that FDA has consistently adhered to this standard in the past. You state that FDA has approved eight maintenance immunosuppressants in the last three decades and that only one, CellCept (mycophenolate mofetil) ("MMF"), was approved based on clinical trials with durations shorter than 12 months (Petition at 2 and 4). You state that MMF is an outlier because: (1) MMF demonstrated superiority against standard of care (a statistically significant reduction in treatment failure compared with both placebo and azathioprine) in each of three trials at 6 months, (2) MMF's development preceded a 1994 FDA advisory committee meeting in which FDA stated that clinical trials should be designed to assess biopsy-proven acute rejection at 12-months, and (3) MMF was approved approximately 18 years ago (Petition at 4).

You further state that the Agency should continue to consistently require a 12-month minimum duration for clinical trials of maintenance immunosuppressants[9] (Petition at 2). You claim that with graft and patient survival rates reaching 94 percent, most modern-era NDA approvals for maintenance immunosuppressants are evaluated in non-inferiority trials (Petition at 5). You claim that given the lower discriminatory ability of non-inferiority trials to detect an improvement in therapeutic benefit, FDA would "compromise product safety" if the agency does not require a 12-month trial for approval of maintenance immunosuppressants (Petition at 5 – 6).

You state that the difficulty inherent in predicting long-term patient and graft survival also supports a 12-month clinical trial standard for approval of maintenance immunosuppressants (Petition at 6). You allege that, at present, there is no established endpoint for predicting long-term patient and graft survival and that there is a growing body of academic research that underscores the difficulty of determining long-term patient and graft survival using short-term data (Petition at 6). You assert that scholars who advocate the adoption of a surrogate endpoint, such as serum creatinine, recommend that the surrogate be measured at 12 months (Petition at 6).

The agency generally recommends that clinical trials intended to support approval of maintenance immunosuppressants evaluate safety and efficacy for 12-months or longer. Seven of the eight maintenance immunosuppressants approved by FDA in the last three decades were approved on the basis of at least one clinical trial of 12 months' duration or longer.[10] We note that our approval of Astagraf XL (tacrolimus extended-release

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[9] You state that FDA's Dr. Marc Cavaille-Coll stated in a September 2012 public workshop that the "most important" recommendation from the 1994 FDA advisory committee meeting was that biopsy-proven acute rejection should be a primary endpoint "assessed, ideally, at one-year after transplantation" (Petition at 5). You claim that this statement indicates FDA's intent to continue to follow established precedent (Petition at 5). We note that, in accordance with 21 CFR 10.85(k), an oral statement by an FDA employee does not represent the formal position of FDA, and does not bind or otherwise obligate or commit the Agency to the views expressed.

[10] As described in the Petition, FDA approved MMF in 1995 based on three double-blind add-on trials, each of which demonstrated superiority against standard of care (a statistically significant reduction in treatment failure compared with both placebo and azathioprine) at 6 months (Petition at 2 and 4). Treatment failure at 6 months was defined as biopsy-proven acute rejection, death, graft loss, and loss-to follow-up (see the Renal Transplant subsection of the Clinical Studies section of MMF's labeling). We agree with the petitioner that the primary efficacy endpoint of biopsy-proven acute rejection in the three

capsules) today was based on two non-inferiority trials, both of which assessed efficacy, as well as safety, at 12 months.[11]

Any decisions about the acceptability of clinical trials lasting less than 12 months to support safety and efficacy for these products will be made during the NDA review process. Our decisions will be based on our scientific experience and expertise regarding maintenance immunosuppressants and applicable legal standards, and take into consideration the risks and benefits of the proposed product, as described in the NDA, as well as our evaluation of current relevant scientific data and information.

C. Double-Blind Design

You request that FDA require at least one double-blind clinical trial for approval of a new maintenance immunosuppressant (Petition at 1 and 7). You claim that a double-blind design is necessary because open-label clinical trials are inherently more susceptible to bias (Petition at 6 – 7). As an example, you allege that in an open-label trial, knowledge of the 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 (Petition at 6 – 7).

You cite to a guidance developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) on the technical requirements for clinical trials to support your request[12] (Petition at 9 – 10). You contend that this guidance recognizes the following: (1) the double-blind trial is the optimal approach, and (2) extensive efforts should be made to address challenges to the creation of a double-blind clinical trial (Petition at 10).

MMF studies was assessed at 6 months; however, we also note that these three trials were prospectively designed to collect safety information, including patient and graft survival, for 12 months or longer. At the time of NDA submission the application contained 12-month safety data, including patient and graft survival, in each of the three studies. You provide a 1995 article by the European Mycophenolate Mofetil Cooperative Study Group entitled *Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection* that was published in Lancet (volume 345: pages 1321-25) in which the authors state that "[t]his European, multicentre, double-blind, and placebo-controlled study of 1 year's duration was carried out to establish the efficacy of MMF as an immunosuppressive agent, when given with cyclosporin and corticosteroids" (Petition at Exhibit 9). At the time of initial approval of MMF, the Clinical Studies section of its labeling included tables of the incidence of treatment failure at 6 months, as well as a separate table titled "Cumulative Incidence of Combined Graft Loss and Patient Death at 12 Months" (see MMF's labeling of June 1995 in the 1996 Physicians' Desk Reference). Therefore, in FDA's view, the initial approval of MMF was based on three 12-month studies which assessed biopsy-proven acute rejection at 6-months and safety, including patient and graft survival at 12-months (see the Renal Transplant subsection of the Clinical Studies section of MMF's labeling).

[11] See the CLINICAL STUDIES section of Astragraf XL's labeling.

[12] See ICH guidance for industry *E9 Guidance on Statistical Principles for Clinical Trials*, 63 FR 49583 at 49587, September 16, 1998.

You claim that FDA has consistently required double blinding for maintenance immunosuppressant clinical trials, and that 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 (TDM) 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 (Petition at 7).

You provide examples of maintenance immunosuppressants that were approved following a double-blind clinical trial that did not meet the exception criteria you specified (Petition at 7 – 9). In these cases, you allege that either the same primary immunosuppressant, cyclosporine, was used in both arms of the trial or the standard dose of cyclosporine was present in both arms (Petition at 7 – 9). You also provide an example in which you claim that a concentration-controlled, open label trial was needed to establish a safe and effective dosing regimen for everolimus, because safety issues (i.e., increased renal toxicity) occurred with this product during a double-blind study (Petition at 8 - 9).

Of the eight maintenance immunosuppressants approved by FDA in the past three decades, four were approved based on double-blind studies and four were approved based on open-label studies. Although we recommend that double-blind trials be conducted to evaluate the safety and efficacy of these products, we recognize that there are situations where double-blind studies are not feasible. For example, we agree with the two exceptions identified in the Petition. However, those are not the only circumstances in which a double-blind design might not be feasible. For example, FDA has accepted open-label trials when: (1) matched active drug and placebo products were not available and over-encapsulation was not feasible (cyclosporine versus tacrolimus) or (2) an increased safety risk was possible (placebo infusions in immunocompromised patients may increase the risk of infection).

As noted above, today's approval of Astagraf XL was based on two 12-month non-inferiority trials.[13] One was a three arm open-label trial. This trial was open-label because either immediate-release or extended-release tacrolimus was used in two of the arms and cyclosporine was used in the third arm and both tacrolimus and cyclosporine required TDM and different target trough concentrations. The second trial compared immediate-release tacrolimus to extended-release tacrolimus. Because both arms targeted the same tacrolimus trough concentrations, the trial was double-blind until the last subject had completed 6 months of the study. After the last patient completed 6 months of the double-blind phase of the study, patients were followed in an open-label phase until all patients completed 12 months of the study. The patient treatment assignments remained blinded for 12 months for 96 percent of the patients participating in the trial.

We encourage sponsors to use double-blind trials for maintenance immunosuppressants. However, if a sponsor believes such a trial is not feasible and/or ethical, the sponsor

[13] See the CLINICAL STUDIES section of Astragraf XL's labeling.

should provide a justification for why such a design is not possible. We will consider each of these situations on a case-by-case basis to determine whether a non-double-blind trial design would be acceptable for demonstration of the safety and effectiveness of these products.

III. CONCLUSION

In general, we agree with your requests related to the duration and design of clinical trials for approval of maintenance immunosuppressants, including the exceptions you specify. Consequently, we grant your Petition insofar as your requests are consistent with our general recommendations for approval of these products. However, we deny your Petition in part because, on a case-by-case basis, as previously described in this response, we will also accept NDAs for maintenance immunosuppressants that rely on clinical trial(s) of alternative design or shorter duration (or both).

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research