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

CITIZEN PETITION

The undersigned submits this petition on behalf of Wyeth Pharmaceuticals ("Wyeth") pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the "Act" or "FDCA") and in accordance with 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs refrain from approving any Abbreviated New Drug Application ("ANDA") for sirolimus with Rapamune® (sirolimus) as the reference listed drug before the expiration of the statutory exclusivity that applies to Rapamune. Wyeth is the manufacturer of Rapamune.

A. Action Requested

Wyeth requests that FDA refrain from approving any ANDA for sirolimus with Rapamune as the reference listed drug before April 11, 2006, the expiration date of the statutory exclusivity for information in the Rapamune labeling that is integral to the safe use of the product.

B. Statement of Grounds

I. Background

Rapamune (sirolimus) is an immunosuppressive agent indicated for the prophylaxis of organ rejection in patients receiving renal transplants. An oral solution formulation was approved on September 15, 1999 (NDA 02-1083), and a tablet on August 25, 2000 (NDA 02-1110). Both formulations are protected by new chemical entity ("NCE") exclusivity until September 15, 2004. There is a formulation patent listed in the Orange Book for the oral solution formulation with an expiration date of September 30, 2013 (Patent No. 5,536,729), and a formulation patent listed in the Orange Book for the tablet with an expiration date of March 11, 2018 (Patent No. 5,989,591). The same four use patents are listed in the

Orange Book for both the oral solution and the tablet (Patent Nos. 5,100,899; 5,212,155; 5,308,847; and 5,403,833).

Rapamune was originally approved only for use in a regimen with cyclosporine and corticosteroids. Over time, however, the use of cyclosporine can cause damage to the patient's liver and kidneys. For this reason, it is advantageous to limit the duration of cyclosporine use when possible.

On April 11, 2003, based on clinical studies that Wyeth performed, FDA approved labeling supplements for both the oral and tablet formulations of Rapamune to provide for the withdrawal of cyclosporine from the Rapamune immunosuppressive regimen two to four months after renal transplantation in patients considered at low to moderate immunologic risk for renal transplant rejection. The approved withdrawal procedure significantly reduces the incidence of cyclosporine toxicity. The Rapamune labeling states that cyclosporine withdrawal has not been adequately studied in high-risk patients, and that therefore it is not recommended for those patients.

The new cyclosporine withdrawal labeling received three years of marketing exclusivity, extending until April 11, 2006. This exclusivity applies to both the oral and tablet formulations.

II. Argument

The FDCA provides that an ANDA must contain the same labeling as the labeling approved for the reference innovator drug, except for labeling differences based on a suitability petition or due to the fact that the generic drug is manufactured by a different entity.[1] FDA's regulations permit an ANDA applicant to omit "an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act,"[2] *provided that* the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."[3]

Under this regulatory standard, no ANDA for sirolimus that contains incomplete labeling -- without full cyclosporine withdrawal information -- may be approved. The cyclosporine withdrawal labeling is essential to the safe and effective use of sirolimus. FDA's regulations do not permit FDA to approve an ANDA without the protected cyclosporine withdrawal labeling, because omitting that labeling would render the generic drug less safe than the listed drug. This conclusion is directly supported by the principles FDA set forth in its response to citizen petitions regarding Ultram® (tramadol).

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1 FDCA §§ 505(j)(2)(A)(v) & 505(j)(4)(G).

2 21 C.F.R. § 314.94(a)(8)(iv).

3 21 C.F.R. § 314.127(a)(7). FDA justifies this position under the statute on the grounds that omitting protected labeling is a difference due to the fact that the generic drug is manufactured by a different entity. *See Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996).

A. The Cyclosporine Withdrawal Labeling is Integral to the Safe and Effective Use of Sirolimus.

Wyeth conducted a randomized, multicenter, controlled trial at 57 centers in Australia, Canada, and Europe, with 525 patients enrolled. The study compared patients who were administered Rapamune, cyclosporine, and corticosteroids continuously with patients who received the same standardized therapy for the first three months after transplantation followed by the withdrawal of cyclosporine. At three months, 430 patients were equally randomized to either Rapamune with cyclosporine therapy or Rapamune as a maintenance regimen following cyclosporine withdrawal. The trial excluded high-risk patients.[4]

The benefits of cyclosporine withdrawal were substantial. In the clinical study, the incidence of hypertension, cyclosporine toxicity, increased creatinine, abnormal kidney function, toxic nephropathy, edema, hyperkalemia, hyperuricemia, and gum hyperplasia was significantly higher in patients who remained on cyclosporine than in patients in the cyclosporine withdrawal group. Mean systolic and diastolic blood pressure improved significantly following cyclosporine withdrawal, and incidence of *Herpes zoster* infection was significantly lower. The overall incidence of malignancy was higher in patients receiving Rapamune plus cyclosporine.

Conversely, cyclosporine withdrawal increased only certain adverse reactions. These included a higher incidence of abnormal liver function tests, hypokalemia, thrombocytopenia, abnormal healing, ileus, and rectal disorder.

Based on this clinical study, FDA approved a change in the Rapamune labeling to indicate cyclosporine withdrawal in patients at low to moderate risk of immune system reactions. The approved labeling warns that in low- to moderate-risk patients, combination therapy beyond four months following transplantation should only be considered when the benefits outweigh the risks of the combination for individual patients. Thus, for those patients, the cyclosporine withdrawal labeling is integral to the safe use of Rapamune.

B. FDA's Regulations Do Not Permit Approval of an ANDA Without the Protected Cyclosporine Withdrawal Labeling.

FDA's regulations do not permit an ANDA applicant to omit protected labeling information where the omission would render the proposed drug product less safe or effective than the listed drug for the remaining conditions of use.[5] This criterion cannot be met here.

Extensive information from the cyclosporine withdrawal clinical study has been included in the Rapamune labeling, including in the pharmacokinetics, clinical studies,

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[4] High risk patients included those with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal; dialysis-dependent patients; patients with serum creatinine > 4.5 mg/dL; black patients; re-transplants; multi-organ transplants; and patients with a high panel of reactive antibodies.

[5] 21 C.F.R. § 314.127(a)(7).

indications and usage, warnings, precautions, and adverse reactions sections of the labeling. As explained above, the data from the clinical study show that withdrawal of cyclosporine can have a significant impact on the adverse event profile of patients on Rapamune therapy. This is important information that *all* prescribers should have before making treatment decisions for their patients.

The only patient population not covered by Wyeth's cyclosporine withdrawal labeling is a narrowly defined "high-risk" subset of patients.[6] Information from the cyclosporine withdrawal study could benefit even a prescriber treating such high-risk patients. The study results provide important safety data about the degree of patient tolerance for cyclosporine and may help to raise physicians' awareness of the serious risks faced by patients who remain on cyclosporine, including high-risk patients who must do so. Conversely, the protected labeling also includes data on adverse reactions suffered by patients from whom cyclosporine was withdrawn; in a given case, such data may be important for determining the appropriate treatment protocol for a particular high-risk patient.

In addition, incomplete labeling may endanger the low- to moderate-risk patients who would clearly benefit from physician-supervised withdrawal from cyclosporine. If FDA permits two sets of labeling for otherwise identical sirolimus products, doctors may unwittingly read and follow the incomplete generic labeling. In those cases, some patients may unnecessarily continue to receive cyclosporine beyond the initial post-transplant period and may suffer serious adverse consequences.

In short, the distribution of Rapamune with incomplete labeling would create potentially dangerous prescriber confusion, may undermine the quality of care provided to high-risk patients, and pose real safety risks to low- to moderate-risk patients, the bulk of patients who receive Rapamune. The cyclosporine withdrawal labeling is critical prescribing information that any physician should receive in order to be informed about appropriate use of this therapy.

The extent of important labeling information that would have to be omitted, and the narrowness of the remaining use, indicate that generics should not be approved until they are able to incorporate all of the Rapamune labeling. In a case like this, where the generic label would require extensive omissions and contain only narrow remaining indications, FDA should not approve an ANDA. The extensive prescribing information that would have to be omitted from the labeling is simply too important and too integral to the prescribing drug. FDA applied this basic test in the case of Ultram (tramadol), and FDA's actions in that case directly support the actions Wyeth requests here, as discussed next.

C. FDA's Policies from the Ultram (tramadol) Case Support this Citizen Petition.

Ultram (tramadol) is indicated for the management of moderate to moderately severe pain. The product labeling originally provided for dosing of 50 to 100 mg every four to

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6 *See supra* note 4.

six hours, not to exceed 400 mg per day. Johnson & Johnson ("J&J") then obtained two labeling changes with new dosing information. First, J&J obtained new labeling with a 50 mg, 10-day titration schedule, which yielded fewer discontinuations due to adverse events for patients who do not require rapid onset of relief. Next, J&J obtained labeling for a 25 mg, 16-day titration schedule, which produced fewer adverse events for patients previously shown to be intolerant to the drug. FDA granted three years of exclusivity for these labeling changes.[7]

The Ultram labeling retained the original, non-titrated dosing instructions for patients who require rapid onset of relief. Thus, the product ultimately contained labeling for three basic groups of patients: (1) patients requiring rapid onset of relief (no titration), (2) general patients not requiring rapid onset of relief (50 mg, 10-day titration), and (3) tramadol-intolerant patients not requiring rapid onset of relief (25 mg, 16-day titration).

Three generic applicants filed citizen petitions seeking to exclude the protected portions of the Ultram labeling. When FDA responded to the citizen petitions, exclusivity had expired for the 50 mg, 10-day titration dosing. The issue remaining was whether the generics could exclude the 25 mg, 16-day titration dosing. FDA decided that they could, concluding that the product would be safe and effective with the remaining labeling (after omission of the 25 mg, 16-day titration information) for patients who require rapid relief and for "the general population of patients who do not require rapid relief."[8]

Importantly, FDA stated that a proposal from one of the generic companies (Teva) to omit *all* of the titration information (50 mg, 10-day *and* 25 mg, 16-day), leaving only labeling for rapid onset of relief, "poses difficult questions that would require resolution before a product with the labeling proposed could be approved."[9] However, FDA went on to state that such a result was not required in that case, because the exclusivity for the 50 mg, 10-day titration had already expired.

FDA's response to the tramadol citizen petitions shows that the key factor in considering the omission of labeling information is how broad or narrow the remaining uses are following omission of the protected labeling. Thus, FDA indicated that omitting all of the dose titration information for tramadol -- resulting in labeling for the generic product that would cover only patients requiring rapid onset of relief -- would raise serious and difficult questions. In contrast, FDA permitted the generics to omit only the 25 mg, 16-day dose titration labeling, because the remaining labeling would cover all patients except tramadol-intolerant patients not requiring rapid onset of relief.

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7 J&J also obtained pediatric exclusivity for Ultram.

8 Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Marcy Macdonald, Associate Director, Regulatory Affairs, Apotex Corp., *et al.* (June 11, 2002) (Docket No. 02P-0191).

9 *Id.* at 8.

FDA should apply the same policy in this case. Omitting the cyclosporine withdrawal information is directly analogous to omitting all of the dose titration labeling for tramadol. As in the tramadol case, where omission of all dose titration resulted in a drug properly labeled only for a small subset of patients, here the remaining labeling would likewise apply only to a narrow subset of patients -- i.e., high-risk transplant recipients.

Just as FDA suggested in the case of tramadol, an ANDA should not be permitted to omit extensive labeling from the reference listed drug and retain only a narrow use. Doing so would raise safety concerns, and is not acceptable under the agency's regulations.

III. Conclusion

For the foregoing reasons, FDA should not permit any ANDA for sirolimus to omit the cyclosporine withdrawal information in the Rapamune labeling. No such ANDA may be approved until the statutory exclusivity for the cyclosporine withdrawal labeling expires on April 11, 2006.

C. Environmental Impact

This petition is categorically exempt from the requirement for an environmental assessment or an environmental impact statement pursuant to 21 C.F.R. §§ 25.30 and 25.31.

D. Economic Impact

Information on the economic impact of the petition will be provided upon request.

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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