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May 10, 2010

Margaret Hamburg, M.D.
Commissioner of Food and Drugs
Division of Dockets Management
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20857

Re: Response to Citizen Petition of Roxane Laboratories
Docket No. FDA-2010-P-0076-0001

Dear Commissioner Hamburg:

Novartis Pharmaceuticals Corporation ("Novartis") submits this response to the above-referenced citizen petition submitted by Roxane Laboratories ("Roxane") on February 10, 2010. For the reasons set forth below, the petition should be denied in its entirety.

Novartis is the sponsor of Myfortic® (mycophenolic acid) Delayed-Release Tablets, intended for use in the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids. In March, 2008, the Food and Drug Administration ("FDA" or "Agency") notified Novartis and Hoffmann-La Roche Inc. ("Roche"), the manufacturer of CellCept® (mycophenolate mofetil) that the Agency had determined that a risk management plan was necessary to ensure that the benefits of the drugs outweigh the risk of congenital malformations associated with their use during pregnancy. Novartis and Roche have worked together since then to develop a shared Risk Evaluation and Mitigation Strategy ("REMS"), and the proposed REMS is currently under review by FDA.

Roxane's petition makes a number of requests – none supported by the facts, the statute, or viable risk management policy. Roxane's petition rests on a factual error, notably that FDA's communications with Roche and Novartis regarding risk management for mycophenolate products followed the approval of Roxane's abbreviated new drug application ("ANDA") for mycophenolate mofetil. Roxane uses this factual inaccuracy to demand that generic mycophenolate manufacturers play a role in the development and implementation of a mycophenolate REMS program. But, as shown below, there is no basis for Roxane's position.

Roxane also requests that FDA assure that Roche and Novartis "are not imposing unreasonable financial burdens" on generic mycophenolate products manufacturers who are required to participate in the single, shared REMS program developed by Roche and Novartis. *See* Roxane Mycophenolate Citizen Petition ("CP") at 2. In the alternative, Roxane requests that FDA grant the company a waiver from the statutory requirement to participate in the single, shared system. In these arguments, Roxane reveals its true purpose. Its petition is little more than a request for bargaining assistance from a federal agency. But, such assistance would be nothing more than an end run around the Food, Drug, and Cosmetic Act ("FDCA") REMS provisions that describe specific procedures for a generic manufacturer seeking a waiver from participating in a single, shared REMS. Moreover, Roxane provides no policy rationale to support its request that patients and providers potentially participate in two different REMS systems. Congress clearly indicated that duplicative REMS within a drug class could have the potential to be unduly burdensome – a logical conclusion that Roxane ignores. Accordingly, FDA should deny Roxane's petition.

I. FACTUAL BACKGROUND

A. CellCept, Myfortic, and Generic Mycophenolate Products

FDA approved Roche's NDA 50-722 on May 3, 1995, for mycophenolate mofetil 250 mg oral capsules. Mycophenolate mofetil is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants, when used concomitantly with cyclosporine and corticosteroids. Subsequent NDAs have been approved for other dosage forms and strengths, including NDA 50-723 for 500 mg oral tablets. FDA has approved numerous ANDAs for generic mycophenolate mofetil: eight for the 250 mg oral capsule form and seven for the 500 mg oral tablet form. In particular, FDA approved Roxane ANDAs 65-410 and 65-413 on July 29, 2008, for the capsule and tablet forms, respectively.

FDA approved Novartis's NDA 50-791 for Myfortic (mycophenolic acid) Delayed-Release Tablets 180 mg and 360 mg on February 27, 2004. There are no currently approved generic mycophenolic acid products.

B. Class-Wide REMS for Mycophenolate Products

FDA has identified potential serious adverse events associated with the use of mycophenolate mofetil and mycophenolic acid in pregnant women. In response to adverse event reports of congenital deformities in children born to mothers exposed to the products, FDA requested revisions to the labeling of both products: 1) to inform healthcare providers that the use of Myfortic or CellCept during pregnancy is associated with an increased risk of first trimester miscarriage and congenital malformations; and, 2) to change the pregnancy category to Category D (positive evidence of fetal risk). FDA approved revised labeling for CellCept on September 21, 2007, and for Myfortic on November 21, 2007.

In March 2008 – before the REMS statute became effective – FDA contacted Roche and Novartis to request that the two companies jointly develop a risk management plan. In May, 2008, the companies were required to disseminate letters to healthcare professionals regarding

these risks.[1] At this time, Roche and Novartis began working together to begin developing the joint risk management plan. On September 4, 2008, FDA formally converted its request for a risk management plan into a request that the companies prepare a joint REMS, to include a Medication Guide, Communication Plan and Elements to Assure Safe Use under the REMS provisions of the FDCA. 21 USC 355-1.

On October 3, 2008, Novartis submitted a proposed Medication Guide for Myfortic. FDA approved this Medication Guide on December 15, 2008, and it has been included in Myfortic's labeling since that time.

Novartis and Roche have developed a REMS program that includes a pregnancy registry, a call center and website (the "REMS Program"), and submitted such program to FDA on December 23, 2008, as part of a comprehensive REMS submission. Negotiations among Novartis, Roche and FDA concerning the REMS Program have been ongoing since that time. Simultaneously, as Roxane alleges, Novartis and Roche have worked with ANDA sponsors on a commercial agreement to govern the allocation of costs and decision-making authority over a single, shared REMS system for all mycophenolate products. *See* CP at 3. In so doing, Novartis's actions have been fully consistent with the REMS provisions of the statute.

II. STATUTORY STRUCTURE

The REMS statute anticipates two scenarios in which the Agency may require a REMS from a drug product applicant. *See* 21 USC 355-1(a). First, the Agency may require a REMS as a condition of the initial approval of a product, if the Agency determines that a REMS is "necessary to ensure that the benefits of the drug outweigh the risks of the drug...." 21 USC 355-1(a)(1). Alternatively, a REMS may be a postapproval requirement. *See* 21 USC 355-1(a)(2). The Agency will require a REMS for an approved drug, as it did for Myfortic, if it "becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug." 21 USC 355-1(a)(2).

Whether FDA requests a REMS post-approval or as a condition of initial approval, the REMS provision applies broadly to all "applicants" and to "covered applications," which may include both NDAs and ANDAs filed under 21 USC 355(b) and 355(j), respectively. *See* 21 USC 355-1(b). The statute places the responsibility for developing and implementing a REMS on "the person submitting a covered application or the holder of the approved application." 21 USC 355-1(b)(7). The statute refers only to one responsible person who must develop, implement, and assess the REMS.

As mentioned, FDA's REMS authority extends to cover generic manufacturers. However, Congress limited the applicability of the REMS provision to generic drugs in certain critical ways. *See* 21 USC 355-1(a)(3), 355-1(i). Although a generic sponsor is defined as a

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[1] *See* Information for Healthcare Professionals: Mycophenolate Mofetil (marketed as CellCept) and Mycophenolic Acid (marketed as Myfortic), *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124776.htm.

responsible person, ANDAs are subject to only two REMS elements: (1) a generic must have a Medication Guide or patient package insert, if first required for the innovator NDA product; and (2) the generic must have "elements to assure safe use" ("ETASU"), if required for the innovator. 21 USC 355-1(i)(1)(A), (B).

Generic applicants need not carry out communication plans, implementation plans, or assessments. *See* 21 USC 355-1(c)-(g). If the REMS includes a communication plan, it is the agency—not the generic manufacturer—that communicates the information to health care providers. 21 USC 355-1(i)(2). Importantly, this subsection also states that the Agency shall inform the generic sponsor "if the risk evaluation and mitigation strategy for the applicable listed drug is modified." *Id.*

The statute strikes a balance not only between the interests of the innovator and generic companies, but also among the other stakeholders, including patients and health care providers. For this reason, the statute requires, with limited exceptions, that generics and innovators "shall use a single, shared system" of elements to assure safe use. 21 USC 355-1(i)(1)(B).[2] The Agency may waive this requirement and "permit the [ANDA] applicant to use a different, comparable aspect of the elements to assure safe use," but only if the Agency makes a determination that one of two conditions exist:

> (i) that the burden of creating a single shared system outweighs the benefit, taking into consideration the impact on heath care providers, patients, the ANDA applicant and the holder of the reference drug product, or
>
> (ii) that an aspect of the ETASU is claimed by a patent or entitled to trade secret protection, and the generic certifies that it has sought a license for use of the protected aspect and was unable to obtain one.

21 USC 355-1(i)(1)(B)(i), (ii). A generic company's certification under clause (ii) "shall include a description of the efforts made by the applicant for the abbreviated new drug application to obtain a license." *Id.*

In a case described in clause (ii), the Agency "may seek to negotiate a voluntary agreement with the owner of the patent, method, or process for a license under which the applicant for such abbreviated new drug application may use an aspect of the elements to assure safe use, if required under subsection (f) for the applicable listed drug, that is claimed by a patent that has not expired or is a method or process that as a trade secret is entitled to protection." *Id.* There are no other waiver provisions in the REMS statute.

III. ROXANE'S PETITION SHOULD BE DENIED

The Roxane petition makes three broad arguments regarding the REMS developed by Novartis and Roche for mycophenolate products. None comport with the carefully designed statutory structure devised by Congress to balance not only the interests of innovator and generic

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[2] This is consistent with other provisions making clear that FDA shall try to minimize the burden REMS present to the healthcare system generally and to certain providers. 21 USC 355-1(f)(2).

drug manufacturers, but also interests of other stakeholders, including patients and healthcare providers.

First, Roxane argues that generic mycophenolate manufacturers should have an "appropriate role" in developing and implementing the REMS program. Second, Roxane argues that Novartis and Roche are seeking to impose "unreasonable economic burdens" on Roxane and other generic manufacturers required to participate in the REMS program. Accordingly, Roxane argues that it should only have to pay the implementation costs associated with adding it to the REMS programs' elements to assure safe use. Finally, Roxane argues that FDA should waive the statutory requirement that Roxane participate in the REMS developed by Novartis and Roche if the costs are an unreasonable burden to Roxane. All are unfounded.

A. FDA has Properly Placed the Responsibility for Developing and Implementing the REMS on Roche and Novartis

1. Neither the Facts Nor the FDCA Envision a Development Role for ANDA Sponsors

There are currently eight generic manufacturers with approved mycophenolate products. Many of the generic mycophenolate products—including Roxane's—were only approved after FDA requested a risk management plan from Roche and Novartis.

As such, Roxane's proposal is based on incorrect factual assumptions. Roxane claims that its petition "addresses only the situation when a REMS is imposed on a brand and generic at the same time." CP at 2 n.1. But, that is not the situation here. FDA contacted Roche and Novartis to jointly develop a risk management plan in March, 2008. FDA then converted that request to a request for a REMS from Novartis in September, 2008. Roxane's ANDAs were approved on July 29, 2008, but the Agency did not inform Roxane of its REMS requirement until May, 2009.[3] *See* CP at 3. Thus, the REMS was not imposed on the brand and the generic at the same time—FDA waited over a year before alerting Roxane to the risk management requirement and over eight months before alerting Roxane that the risk management request had been converted to a REMS requirement. During that time, the Agency corresponded repeatedly with Roche and Novartis, and the companies made multiple submissions to the Agency outlining the proposed joint REMS program.

Critically, FDA's approach in this case has been consistent with the REMS statute. As discussed above, Medication Guides are required for ANDAs, but only if first required of the reference listed drug—indicating that the innovator alone negotiates with FDA the Medication Guide language. 21 USC 355-1(i)(1)(A). Similarly, if the REMS includes a communication plan, the Agency provides that information to health care providers.[4] The ANDA sponsor has no

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[3] Indeed, the patent on mycophenolate mofetil expired on May 4, 2009, at which time Roxane was free to market its generic version.

[4] As a result, there might be an argument that generic manufacturers need not contribute to the development costs of these materials. Roxane does not make this point, and developing a Medication Guide and communication plans account for a very small portion of the development costs associated with any REMS that also includes ETASU.

role in developing or carrying out the communication plan. Finally, by excluding ANDAs from REMS assessments, Congress envisioned that innovators would monitor REMS' effectiveness, suggest modifications to FDA, and negotiate any changes to the REMS. All of these factors indicate that ANDA sponsors have little to no role in ongoing development, implementation, and modification of a REMS – they merely distribute critical labeling and implement elements designed to assure patient safety.

2. *In Most Instances, Innovator Companies Should Develop and Implement the REMSs*

Roxane argues that ANDA sponsors should play a role in developing and implementing a REMS, regardless of when the generic enters the market. Roxane states that "[a]lthough [its] position is that generic drug companies should have a role in the implementation of a REMS program even if it is imposed and developed before a generic is on the market, this petition addresses only the situation when a REMS is imposed on a brand and generic at the same time." CP at 2 n.1. This proposal would, if adopted by the Agency, create an unworkable and confusing system for most REMS.[5] It seems farfetched to presume that FDA could anticipate which ANDAs would be approved and/or ultimately launched and invite the sponsors to the table for REMS development.

Perhaps for that reason, Roxane does not describe how an ANDA sponsor can play a role if its application has not been approved at the time the Agency requests a risk management plan. Nor does it articulate any reasonable standard for determining when an unapproved generic should be included: after submission of the ANDA? After tentative approval?

Critically for REMS policy, however, Roxane fails to address how an ANDA sponsor might reasonably contribute to REMS discussions when it has little or no experience selling the drug. In fact, the innovator has the knowledge, background, and experience with the drug and the marketplace. It has assessed the relevant safety information forming the basis for the REMS request, has familiarity with and understands the drug's distribution and use, and likely has relationships with the physicians who prescribe the drug—who are necessary players in effective risk management programs.

By contrast, an ANDA sponsor has little to no such information, especially prior to the launch of generic competition. The FDCA establishes a drug approval timeline where ANDA applicants necessarily follow innovators to market. Given that there may be many generic firms entering the market at different times, as occurred with the mycophenolate products, Roxane's vision of a collaborative development is simply impractical and contributes nothing in terms of knowledge of the drug or physician prescribing habits to the discussions surrounding creation of the REMS program.

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[5] Novartis acknowledges that for certain classes of products, such as long acting opioids, a class-wide approach is required. 21 USC 355-1(h)(7). And, when the manufacturers of those classes are largely generic companies, it is also logical that they would play a prominent role in developing and negotiating any REMS that might apply. *See* 74 FR 17967 (April 29, 2009) (announcing public process for development of class wide REMS for certain long acting opioid drug products). FDA has not taken the position, nor should it, that the class wide provisions of the REMS statute apply to mycophenolate products.

Roxane itself recognizes this problem:

> In most instances, FDA will be imposing REMS requirements when it is approving a new drug application. In those situations, the approach that FDA adopted in the case of mycophenolate products—*i.e.*, working with only the brand to develop a REMS program—may be the most sensible approach. In this case, however, generic versions of the drug were already on the market when FDA made the determination that a REMS was needed.

CP at 6. Roxane appears to assert that, once an ANDA is approved, FDA should open REMS negotiations to those applicants, even if the REMS negotiations are on-going. This proposal is simply impractical where, as here, the eight generics entered the market over a period of approximately a year.

B. A Single, Shared REMS Program for All Manufacturers Better Serves Patients and Healthcare Professionals

1. A single, shared system assures safe use by patients and practitioners

The carefully designed statutory framework shows Congressional support for a "single, shared system" for implementing ETASU that best effectuates patient safety while reducing provider disruption. As described above, the FDCA contemplates that innovator companies develop the REMS in consultation with FDA, and that generic manufacturers join in a single, shared system.

The benefits of the system for patients and health care providers are obvious. Communications are reduced to the essential information, rather than overlapping and perhaps inconsistent messages from innovators on one hand and generics on the other. One system encompassing all patients also provides greater certainty that patients and health care providers have been reached and allows for more comprehensive assessments of the effectiveness of the REMS program. For these reasons, the statute generally requires that generic and innovators "shall use a single, shared system" of ETASU. 21 USC 355-1(i)(1)(B).

2. Waiver is Available After Enumerated Statutory Procedures that Roxane Has Not Followed

FDA may waive the requirement that the generic participate in a single, shared system for ETASU, but only in very limited circumstances. Recognizing that the innovators would bear the development costs and would likely share trademarked and patented materials with generic competitors in operating a single ETASU system, the statute provides a mechanism to break a stalemate between innovators and generics. In that instance, a generic can seek a waiver or seek the Agency's negotiating help. But these exceptions apply only in limited circumstances, and only after a certification on the part of the generic company seeking a waiver.

As described above, the Agency must determine that either: (1) the burden of creating a single shared system outweighs the benefit, taking into consideration the impact on heath care

providers, patients, the ANDA applicant and the NDA holder of the reference drug product; or (2) that an aspect of the ETASU is claimed by a patent or entitled to trade secret protection, and the generic certifies that it has sought a license for use of the protected aspect and was unable to obtain one. 21 USC 355-1(i)(1)(B)(i),(ii). A generic company's certification under clause (ii) "shall include a description of the efforts made by the applicant for the abbreviated new drug application to obtain a license." *Id.*

When a generic fails to reach an agreement with the innovator regarding licensing of protected material, the statute provides that FDA "may seek to negotiate a voluntary agreement" with the innovator. *Id.* These provisions regarding licensing of protected systems lead to the conclusion that Congress viewed ANDA entry into a REMS program largely as a business transaction – it is a negotiation between the companies designed to minimize the likely burden presented by disparate REMS systems. Although the statute provides some role for FDA in assisting the negotiation of this license agreement, it does not give FDA authority to force an agreement or determine a reasonable licensing fee. This is for good reason -- the Agency lacks the expertise in such matters, and regulating commercial relationships between companies is outside its authority.

Instead, if licensing negotiations are unsuccessful, the generic may seek, and FDA may grant, a waiver of the single, shared elements to assure safe use. However, Roxane has not followed this framework. It has not shown that the burdens of a single, shared system outweigh the benefits, taking into account all stakeholders. Nor has it described an inability to procure a license to the REMS Program. In fact, Roxane admits that it has the ability to join the REMS Program – but at a cost higher than it wants to pay. *See* CP at 3. The Roxane petition is simply an end run around the clear statutory framework.

Importantly, Roxane's reluctance to join the REMS Program does nothing to address the interests of the patients and health care practitioners ("HCPs") who will be required to participate in the system. Patients, HCPs, the Agency and other stakeholders, including the innovator and generic applicants themselves, are all better served by sharing a single system of ETASU. A single system will minimize potential confusion over the contours of the program, allow a unified training and documentation approach, and facilitate the mandated assessments of the REMS Program.

C. It is Not Unreasonable for Generic Manufacturers to Share the Costs of Developing and Implementing a Single, Shared REMS

Much of Roxane's petition is spent arguing that it should pay as little as possible to Roche and Novartis for their work in developing and implementing the REMS Program. But, Roche and Novartis are not seeking unreasonable costs. In fact, Novartis and Roche only seek that all companies using the program share the true costs of developing and implementing it. *See* CP at 3.

Roxane argues that, because Roxane did not participate in developing the program, its costs should be limited to the additional costs accrued by adding Roxane to the program. In other words, all the developmental costs should be borne by Roche and Novartis, even though

the REMS Program assures that patients using Roxane's generic product can do so safely. Roxane also makes a similar argument that its costs should be limited to the "costs to add the [Roxane] generic to the market." CP at 11. Because REMS costs are directly related to the number of units sold, this approach seems to acknowledge that Roxane would be responsible for the REMS Program costs directly attributable to the number of mycophenolate units it sells.

But, Roxane also asserts the contradictory position that costs should be calculated based on dollar sales, rather than based on number of pills dispensed. *See id.* Roxane has a self-serving reason to argue this: collectively, generic products have 16% share of mycophenolate products by sales revenue; 57% by volume of pills dispensed. *See* CP at 6. It makes much more sense to allocate by volume, as the shared system contemplates, because the costs of the program increase in direct proportion to the volume of drug dispensed. The sales price of the tablets or capsules has no effect on the costs of the REMS program, and should not be a factor, as Roxane urges. Innovators should not be required to subsidize generics' costs of assuring patient safety and marketing.

Roxane also argues that any increase in costs would drive generics from the market. This argument is overstated. Roxane seems to acknowledge as much when it later argues that, because generics have a majority of the market share by volume, they "should have had a role, and arguably the lead role, in the development of the REMS." CP at 6. So, on one hand, Roxane argues that it and other generics cannot afford development costs for the REMS program, despite having most of the market share. On the other hand, it contends that generic companies should have been involved in its development. *See* CP at 7 ("Had Roxane been at the table when the REMS was developed, it could have contributed ideas and taken steps to ensure that the program not only meets the paramount interest of ensuring patient safety, but also is feasible from the standpoint of a generic drug company, which generally must pay greater attention to distribution costs due to the highly competitive prices of generic products.") These contradictory claims simply do not add up.

The statute provides that an innovator may not use any ETASU "to block or delay approval of an application under section 355(b)(2) or (j)" or "to prevent application of such element" to a generic drug. 21 USC 355-1(f)(8). Roxane has not alleged that Roche and Novartis have violated this provision, nor does the petition describe any facts that would support such an allegation.

Indeed, Roche and Novartis are not creating a barrier to entry. There are eight generic competitors, who represent over fifty percent of mycophenolate units sold. Roxane simply seems to want a cheaper REMS, (and to pay less than its share), even if that cheaper REMS is less comprehensive. In so stating, Roxane makes clear that it views the profitability of generics as trumping the interests of patient safety.

IV. CONCLUSION

For all the reasons discussed above, Novartis respectfully requests that this petition be denied.

Respectfully submitted,

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