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Boehringer Ingelheim
Roxane Laboratories

February 3, 2010

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

Docket No. _____

CITIZEN PETITION

Petitioner Roxane Laboratories, Inc. (Roxane) hereby submits this citizen petition under 21 C.F.R. §10.30. Petitioner requests that the Food and Drug Administration ("FDA") take the actions described below.

I. ACTION REQUESTED

Roxane requests that, in developing a REMS program for brand and generic drugs that are commercialized and being sold prior to approval and implementation of a program, and in particular in developing the REMS program for mycophenolate mofetil, FDA:

1. Ensure that generic drug companies have an appropriate role in developing the REMS program;

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2. Ensure that generic drug companies have an appropriate role in the implementation of the REMS program.[1]
3. Ensure that brand drug companies are not imposing unreasonable financial burdens that may serve to limit full and effective competition from generic companies that are required to participate in a REMS program for a particular generic drug.

If a generic company is not afforded the opportunity to participate in the development and implementation of a REMS, then the company should not be expected to pay any costs associated with developing the program or any costs of implementation that exceed the amount it costs to add the generic company to the program. In addition, if the REMs developed by the brand imposes an unreasonable financial burden on a generic company, then FDA should grant the company a waiver from the requirement to participate in the brand's REMS program.

II. STATEMENT OF GROUNDS

Background

A. Factual Background

Mycophenolate mofetil is an immunosuppressant drug approved for the prophylaxis of organ rejection in patients receiving allogenic renal, cardiac or hepatic transplants. The brand drug, CellCept®, is marketed by Hoffmann-LaRoche (Roche) and was approved on May 3, 1995. Roxane's ANDAs (Nos. 65-410 and 65-413) for generic mycophenolate mofetil were approved on July 29, 2008. In September 2008, FDA, by

[1] Although Roxane's 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.

letter, directed Roche to develop a REMS for CellCept® to ensure that the benefits of the drug outweigh the risk of congenital malformations. FDA also requested a proposed REMS from Novartis Pharmaceuticals Corporation (Novartis), the brand name manufacturer of mycophenolic acid (Myfortic®). On May 1, 2009, Roxane received a letter from FDA stating that its ANDAs for mycophenolate mofetil capsules and tablets required a REMS.

It is Roxane's understanding that, since September 2008, FDA, Roche and Novartis have had a series of discussions regarding the development of a REMS for CellCept® and Myfortic®. Since Roxane's approval on July 29, 2008, it has not been party to any of those discussions and was not made aware of the fact that a REMS program was even under consideration. In fact, the first time Roxane heard about the REMS requirement was in May of 2009 (10 months after approval of its product). When Roxane finally heard from Roche, Roche presented Roxane with the single option of participating in a REMS program that had already been fully developed by Roche and Novartis without the participation of Roxane or, to Roxane's knowledge, any other generic manufacturer.

Despite the fact that Roche and Novartis developed the REMS program without seeking any input whatsoever from Roxane, Roche is now demanding that Roxane pay a portion of the costs of developing and implementing the program. Specifically, Roche's position is that Roxane must pay a share of the development costs[2] determined by the number of companies participating in the program. Roche has also indicated that it

[2] The development costs for which Roche seeks reimbursement originally included the costs of paying Roche's own employees who worked on creating the REMS program; after significant opposition by Roxane, Roche recently agreed to remove those costs from the development totals.

intends to require Roxane to pay a share of the implementation costs based on Roxane's market share.

B. Statutory Background -- FDAAA – Section 505-1

The Food and Drug Administration Amendments Act of 2007 (FDAAA) created new section 505-1 of the FFDCA, which gives FDA the authority to require a REMS if it determines that such a strategy "is necessary to ensure that the benefits of the drug outweigh the risks of the drug." FDA also may require a REMS to a previously approved drug 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 outweighs the risks of the drug."

Pursuant to section 505-1(d), a REMS must have a timetable for submission of assessments of the REMS. In addition, a REMS may include any or all of the other elements listed below if specified criteria are met:

- A Medication Guide (section 505-1(e)(2)(A))
- A patient package insert (section 505-1(e)(2)(B))
- A communication plan to health care providers (section 505-1 (e)(3))
- Elements to assure safe use (ETASU) (section 505-1(f)).

The elements to assure safe use may be required if the drug has been shown to be effective, but is associated with a serious adverse event and can be approved only if such elements are required as part of a strategy to mitigate a specific risk. Elements to assure safe use may include certain restricted distributions, procurement, and dispensing systems. For example, only health care providers with certain training or experience may be permitted to prescribe or dispense a drug to patients, or the drug may be dispensed to patients only in certain health care settings such as hospitals. The elements may also require that the drug be dispensed to patients only with evidence or other documentation

of safe use conditions such as laboratory test results or may require that patients using the drug be subject to certain monitoring.

Subsection (i) provides that drugs subject to section 505(j) are subject to the following elements of a REMS if they are required for the applicable listed drug:

- A Medication Guide or patient package insert and
- Elements to assure safe use (ETASU) (section 505-1(f)).

Subsection (i) further provides that the generic drug and listed drug shall use a single shared ETASU system unless FDA determines (1) 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 (2) that an aspect of the ETASU is claimed by a patent or entitled to trade secret protection and the ANDA applicant certifies that it has sought a license for use of the protected aspect and was unable to obtain one.

C. FDA's Implementation of REMS

To date, FDA has approved approximately 90 REMS for new drugs and has requested REMS for many other products. See http://www.fda/gov/drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm. In addition, pursuant to FDAAA § 909(b)(1), 16 products that were approved prior to enactment of FDAAA and that had in effect elements to assure safe use (typically as part of an approved RiskMAP) have been deemed to have in effect an approved REMS. See 73 Fed. Reg. 16,313 (March 27, 2008).

On September 30, 2009, FDA issued a Draft Guidance for Industry, Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications. The draft document provides

guidance on the format and content of a proposed REMS, the content of assessments and proposed modifications of approved REMS, the appropriate identifiers to use on REMS documents and how to communicate with FDA about REMS. The guidance document specifically states that it does not fully address the provision that applies to ANDAs and that such provision will be the subject of future guidance.

Discussion

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. In fact, although generics only account for 16% of the sales of mycophenolate products, they already account for 57% of the market share based on volume. Thus, the generic manufacturers should have had a role, and arguably the lead role, in the development of the REMS. This is especially true since the brand is insisting that the generics pay a portion of the costs associated with the REMS development and implementation.

A. Generic Drug Companies Should Have an Appropriate Role in the Development of a REMS Required for Their Drug.

Section 505-1(i) requires a generic drug and listed drug to use a single shared ETASU system unless FDA determines 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. One important way that FDA can ensure that the burden of creating a single shared system is

not too great on the ANDA applicant is to permit the applicant to participate in the development of the program.

Roxane understands that there will be many times when a REMS program is developed long before an ANDA application is ever submitted or approved. Obviously, in those cases the ANDA applicant cannot participate in the REMS development. That, however, was not the situation here. Roxane's ANDA was approved several months before FDA decided to impose the REMS requirement on mycophenolate products. 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. It also could have participated in discussions with the agency about the necessity of various requirements. Roxane's contribution of additional ideas during the development of the REMS would have led to a better overall REMS program – one that advances patient safety and assures that the REMS program does not unnecessarily and adversely impact the availability of low-cost generic drugs.

B. Generic Drug Companies Should Have an Appropriate Role in the Implementation of a REMS Required for their Drug.

The ANDA holder should have a role not only in the development of a REMS program, but also in its implementation. While this may not have the same impact on reducing burden as would participation at the development stage, it would give the generic companies an opportunity to positively influence decisions that affect implementation costs and the overall effectiveness of the REMS program. Again, this is

especially important if there is going to be an expectation (as there is from Roche) that the generics pay a share of the implementation costs over and above the cost added by the generic's participation in the program.[3] Absent a significant role in decision-making related to implementation, there should be no expectation that the generics pay anything over the cost they add by participating in the program.

C. REMS Developed by Brand Drug Companies Should Not Impose Unreasonable Economic Burdens on Generic Companies Required to Have a REMS.

As a general matter, Roxane is not opposed to paying whatever amounts would be necessary to cover the additional costs associated with its participation in a REMS program that FDA has determined will advance patient safety. Roxane does not believe, however, that in creating the REMS requirements, Congress intended that generic companies would subsidize brand companies for the costs of marketing branded products and thus be burdened beyond reasonable costs. Roche, however, is proposing that Roxane pay expenses that Roche would have incurred even if there were no generic on the market. Roche is not only expecting generic companies to subsidize development costs of the REMS program and to continue to pay for the program's operational costs, but it is taking the position that the generics companies, which had no input in the development of the program, would effectively have no input in decisions related to its operation both now and in the future. Such an approach disproportionately benefits the incumbent branded products and erects unnecessary barriers for participation by any would-be generics, which in some cases could limit generic competition.

[3] After Roxane objected to Roche's position that generic companies have no decision-making authority regarding implementation of the mycophenolate REMS, Roche proposed to give generics each a vote for decisions relating to the REMS program. If there is not unanimous agreement, however, Roche proposes to retain the right to make all final decisions for issues related to the REMS program, subject to reasonable consultation in advance with Novartis. This proposal does nothing more than pay lip service to the concept of participation by the generic companies. A generic company's vote counts only if it is in agreement with Roche.

Congress did not intend that generic companies be unreasonably burdened by the imposition of REMS requirements nor experience additional barriers to entry into the generic market. In this case, Roche and Novartis developed a REMS program without any input from Roxane, and Roche now expects Roxane and other generic companies to pay a part of costs over which it had no control or input. Roche may have been in the position to develop a program without giving much thought to its cost or considerations relevant to the generic market, but Roxane and other generic companies are not.

If brand companies are free to develop REMS programs without regard to their cost and then generic companies are expected to help pay those costs, it is likely that a good number of generic companies will have to forgo marketing the generic versions of drugs subject to REMS and consumers will have access to fewer lower-cost generics. Under such circumstances, the REMS mechanism could conceivably create economic incentives for brand companies to increase distribution costs in order to protect market position. This is certainly not the result that Congress intended when it passed the REMS provision, and it is bad public policy.

Because Roxane's generic was approved at the time the REMS was developed it was possible for Roxane to be at the table. Roxane understands that FDA has an interest in companies sharing the same REMS program and there could be savings, particularly to health care providers, from such an approach. Nevertheless, FDA should inform the brand companies that they must develop programs that do not impose an unnecessary burden on the generics and where possible allow the generics a role in developing the program and in overseeing the program. Moreover, the FDA should inform the brands that if they do not give the generics an appropriate role and minimize the burden on the generics, the agency will permit the generics to opt out of the brand program and develop

one of their own. Only if FDA takes this approach will the generics be in a position to negotiate a fair agreement with the brand manufacturer.

FDA also should ensure that the brand companies are not making unreasonable demands from the generic to recoup the cost of developing and implementing a REMS. Roxane does not expect that FDA will arbitrate the allocation of costs between the brand and the generic. FDA can, however, provide guidance on appropriate cost allocation. For example, FDA could and should direct the brand to seek only the additional costs associated with including a generic in the REMS program or, if the generic is able to participate in a meaningful way in the development and implementation of a REMS, that the share of costs that is commensurate with the generic's share of the market based on sales. It would be unfair to require a generic to pay on the basis of its share of the market based on the number of tablets or capsules sold when its profits are substantially less than the brand because it charges so much less than the brand. As stated above, in this case, Roxane's market share based on the volume of tables/capsules is approximately 57% and its share based on sales is only 16%. Failure to provide the guidance needed to ensure appropriate cost allocation will inevitably result in many generic firms deciding to forgo the marketing of drugs subject to REMS.

III. CONCLUSION

When FDA determines that a REMS is needed for a drug for which a brand and one or more generics is on the market, FDA should include both the brand and the generic(s) in the development of the REMS. Generic companies also should have a role in the implementation of REMS programs. Generic companies often account for a large part of the market, based on volume of product sold, so excluding them from the

development of a REMS program is unreasonable and not likely to generate a workable process for both brand and generic customers.

Absent such involvement in the development and implementation of a REMS, generics should not be expected to pay any costs associated with developing the program or any costs of implementation that exceed the amount it costs to add the generic to the program. If generics are given a role in the development and implementation of a REMS program, then it could be reasonable to expect them to contribute to the costs, but FDA should ensure that the brands are not imposing an unreasonable financial burden on the generics. Although a generic product may account for a large share of the market based on volume, such products generally account for a much smaller share based on sales. It is the market share based on sales that should dictate how much a generic contributes towards costs. Failure to ensure appropriate cost allocation will inevitably result in generic firms seeking waivers from any requirement that they participate in the brand's REMS program, which would lead to different REMS programs for the same drug, a result which FDA, physicians, pharmacists, and patients have not favored, for sound reasons. If cost sharing is not fair, however, and the generics are unsuccessful in obtaining waivers, then inevitably some generic companies will have no choice but to forgo the marketing of some drugs subject to REMS. As a result patients will lose access to lower cost generic drugs.

IV. ENVIRONMENTAL IMPACT

The action requested in this petition will have no impact on the environment.

V. 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 that are unfavorable to the petition. A certification pursuant to section 505(q)(1)(H) of the FD&C Act is not required for this petition because it does not affect a pending application filed pursuant to section 505(j) or section 505(b)(2).

Respectfully submitted,

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cc: William B. Schultz, Zuckerman Spaeder LLP

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FAX Cover Sheet

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William B. Schultz
FROM

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RE: Citizens Petition filed February 3, 2010 – Boehringer Ingelheim Roxane Laboratories

Comments

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