April 5, 2010

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

Re: Docket No. 2010-P-0076: Hoffmann-La Roche Inc. ("Roche") Comments to Citizen Petition Relating to REMS Submitted by Roxane Laboratories, Inc. ("Roxane")

Dear Sir or Madam:

The Roxane Petition relating, in part, to the mycophenolic acid ("MPA") risk evaluation and mitigation strategy ("REMS"), currently under development by Roche and Novartis Pharmaceuticals Corporation ("Novartis"), threatens to delay implementation of an effective REMS for MPA drugs. In September 2008, Roche and Novartis, at the direction of the Food and Drug Administration ("FDA") began work on the MPA REMS and, in May 2009, when FDA directed them to contact the generic companies, they did so. Roche and Novartis offered to Roxane and the other generic companies the opportunity to participate in decision making for the MPA REMS and have proposed an equitable sharing on the development and operations costs. However, Roxane has refused to participate on this basis, contending, without substantiation, that development of the MPA REMS has been prejudiced by Roxane's failure to participate to date. Roxane should not be permitted to evade its fair share of the costs on the pretext that it was not

involved early enough in development of the MPA REMS. To the extent Roxane raises, at the eleventh hour, legitimate issues as to how FDA should direct NDA and ANDA holders to act in the future as to a REMS that will be implemented after generic entry, those issues should be uncoupled from, and not delay, the MPA REMS that is -- after almost two years -- close to implementation. We urge FDA to continue review and approval of the MPA REMS and ensure that all manufacturers of MPA drugs are required to timely participate in a REMS. Any other response would compromise patient safety and penalize Roche for complying with the law and doing exactly what FDA asked. However, if FDA determines that statutory standards can be met to permit Roxane to develop, implement and operate its own REMS program under a waiver and to do so without delay, Roche has no objection.

I. The Facts

CellCept® (mycophenolate mofetil or "MMF") and Myfortic® (mycophenolic sodium delayed release tablet or "MPS") are immunosuppressant drugs approved for the prophylaxis of organ rejection. CellCept, sold by Roche, was approved on May 3, 1995, and is used for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac, or hepatic transplants.[1] Myfortic, sold by Novartis, was approved on February 27, 2004, and is used for prophylaxis of organ rejection in patients receiving allogeneic renal transplant.

In October 2007, FDA concluded that pregnant women taking CellCept and Myfortic had an increased risk of miscarriage and birth defects. In response, Roche and Novartis revised the

[1] *See* New Drug Application No. 50-722 for CellCept (mycophenolate mofetil) Capsules and 50-723 for CellCept Tablets.

package inserts for CellCept and Myfortic to include a Boxed Warning.[2] Thereafter, in March 2008, FDA asked Roche and Novartis to work together on a Risk Management Program (RiskMAP) for MPA.[3] In May 2008, FDA issued a second alert, focusing on risks when the products are prescribed for unapproved uses, such as treating lupus.[4] At the same time, FDA publicly announced that it was working with the manufacturers of MMF and MPS "to develop and implement means to mitigate the risks of fetal exposure."[5]

Thus, by the time FDA approved Roxane's ANDA for MMF in July 2008, it was clear to all that FDA had safety concerns and was working with Roche and Novartis to mitigate the risks of MPA products. Indeed, the ANDA approval letter reminded Roxane "that if FDA requires a REMS for the listed drug, an ANDA citing that listed drug also will be required to have a REMS. *See* 505-1(i)."[6] Nonetheless, Roxane made no effort to contact Roche or Novartis on a REMS or to discuss these issues with FDA.

Shortly after approving the Roxane ANDA, in September 2008, FDA directed Roche and Novartis each to submit a REMS to ensure that the benefits of MMF and MPS outweighed the risks of congenital malformations. FDA required that the REMS include a Medication Guide, elements to assure safe use (ETASU) -- such as physician training and certification, patient education, a communication plan, a pregnancy registry -- an implementation plan, and a

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[2] http://www.fda.gov/cder/drug/infopage/mycophenolate/default.htm

[3] Before FDAAA was enacted, FDA would require risk management programs ("RiskMAPs").

[4] Such prescribing for unapproved uses makes participation in the MPA REMS by generic companies even more compelling because of the potential for increased use, beyond the transplant community, due to the availability of less expensive generic product.

[5] *Id.*

[6] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm148735.htm

timetable for assessment of the REMS.[7] FDA did not identify MMF ANDA applicants or holders for Roche and Novartis. Nor did FDA ask that they participate in, and share the burdens of developing, the MPA REMS at that time.

Working together, Roche and Novartis developed and, in December 2008, submitted a proposed REMS to FDA. The REMS sought to minimize and limit fetal exposure to mycophenolate containing drugs by informing health care providers and female patients of childbearing potential of the risks associated with use of mycophenolate containing drugs during pregnancy and the appropriate steps to manage the risks. The MPA REMS employs as part of the ETASU: (1) a pregnancy registry; (2) a call center; and (3) a website. The program also includes a comprehensive communication plan targeting both transplant and non-transplant health care providers. In March 2009, FDA provided comments to Roche and Novartis on the REMS seeking additional steps to protect the public health. On April 16, 2009, Roche and Novartis re-submitted the REMS.

On May 4, 2009 the patent covering MMF expired. At that point, seven ANDA holders for generic MMF had been approved, and generic MMF immediately entered the market and promptly garnered the majority of MPA prescriptions. As of the week ending February 21, 2010, the generic companies had a combined market share of 57.2 % (Roxane's market share was 5.1%), Novartis' share was 16% and Roche's share was 26.8%.[8] Roche anticipates that its share will continue to decline.

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[7] *Id.*

[8] Weekly MPA TRx market share for the week ending February 21, 2010 from IMS.

As Roxane notes, it was only after MMF patent expiration that FDA formally notified the ANDA holders that generic MMF required a REMS program and that a single shared REMS would promote patient safety.[9] FDA then provided Roche with the contact information for each generic company and, at FDA's request, Roche contacted each generic company to determine whether each was interested in participating in the MPA REMS as a single, shared program. Each generic company indicated interest in participating in the MPA REMS.

On June 18, 2009, Roche and Novartis provided general information about development of the MPA REMS and status of FDA review to the generic companies via a teleconference. Roche also relayed that development costs were estimated to be $6.5 million (but potentially higher due to additional FDA required program elements)[10] and operating costs were estimated to be approximately $7 million per twelve month period, i.e., about a third of the operating costs of the isotretinoin REMS.[11] Thereafter, Roche and Novartis prepared and sent out a draft Memorandum of Understanding (MOU) to govern participation in the MPA REMS.[12]

Several of the generic companies, including Roxane, have provided comments on the MOU to Roche during the past six months and Roche has responded to each. Roche and Roxane have engaged in several substantive email exchanges and at least two teleconferences to discuss

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[9] In addition to the initial seven generic companies, Roche recently contacted an eighth generic manufacturer at FDA's request.

[10] The development costs for the MPA REMS through December 2009 were $3.0 million. The current estimate of total development costs is $6.9 million.

[11] Roche was involved in developing and is the principal administrator of the isotretinoin REMS that is currently in its fifth year.

[12] Roche can provide the most recent draft of the MOU to FDA upon its request, subject to appropriate confidentiality protections.

the MOU. Roche, after discussions with Novartis, submitted several substantively revised versions of the MOU to the generic companies. The revisions address terms for decision making, definition of development costs,[13] calculation of market share for operations costs, intellectual property rights, and termination from the MPA REMS. The last revised version of the MOU was submitted to the generic companies on February 23, 2010, subsequent to Roxane's filing of this Petition. Although Roche has through its best efforts over the past seven months attempted to resolve all concerns raised, the proposed MOU is still under review by the generic companies.

While discussions with the generic companies were proceeding on the MOU, FDA made further comments on the substance of the MPA REMS. Roche and Novartis anticipate re-submitting the MPA REMS in April 2010. At no point has FDA indicated that the proposed MPA REMS program contained superfluous elements or was in any respect beyond what was required for compliance with FDA requirements. Indeed, in its comments, FDA requested that the program include additional components or resources for prescribers, thereby increasing the cost of the MPA REMS.

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[13] Roxane correctly notes at footnote 2 of its Petition that the original MOU development costs communicated to the generic companies included personnel costs for Novartis and Roche to develop the REMS. These costs are significant, and for Roche, reflected the costs for full time employees dedicated to developing the REMS as a single, shared program. These are costs that each of the generic companies would incur if they developed a REMS on their own. Nonetheless, in an attempt to move the MPA REMS forward, Roche and Novartis agreed to eliminate these costs from the sharing formula. Thus, Roche and Novartis will be solely liable for the substantial personnel costs directly related to development of the MPA REMS.

II. The Statute

Section 505-1 of the Federal Food, Drug, and Cosmetic Act ("FDCA") authorizes FDA to require a REMS if FDA "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." § 505-1(a)(2)(A). A REMS may include:

- A Medication Guide
- A patient package insert
- A communications plan to health care providers
- ETASU, which may also include an implementation system.

The ETASU provision applies to a drug which has been shown to be effective but is associated with one or more serious adverse effects and can be approved or marketed only if such elements are required as part of a strategy to mitigate a specific serious risk found in labeling. § 505-1(f). All REMS include a timetable for assessments. § 505-1(g).

The statute provides that generic and brand drug companies shall use a single, shared REMS system unless the generic company obtains a waiver. §505-1(i)(1)(B). FDA may waive the single, shared system requirement, and permit generic companies to use a different, comparable aspect of the ETASU, if: (1) the "burden of creating a single, shared system outweighs the benefit of a single system, taking into consideration the impact on health care providers, patients, the applicant for the [ANDA], and the holder of the reference drug product"; or (2) subject to a certification process, an aspect of the ETASU is subject to patent or trade secret protections and the ANDA is unable to secure a license to the use of the protected aspect. § 505-1(i)(1)(B)(i) and (ii). FDAAA specifies that generic companies are responsible for

complying with the Medication Guide and/or package insert requirements and any required ETASU. § 505-1(i)(1)(A)-(B).

For the MPA REMS, FDA has determined that a Medication Guide is necessary for safe and effective use and that ETASU shall include physician training and certification, patient education, and a pregnancy registry.

III. Roxane's Petition Should Not Delay the MPA REMS

Roxane is correct that Roche and Novartis began to develop the MPA REMS before generic entry, but after approval of the Roxane ANDA.[14] FDA did not ask Roxane to participate in this effort. And, despite knowledge that a REMS was being considered, Roxane did not ask FDA, Roche or Novartis to let it participate. Roche and Novartis contacted the generic companies when FDA asked them to, in May 2009, after significant work had been done and a proposed REMS and revised REMS had been submitted to FDA. The MPA REMS is close to implementation and Roche and Novartis have received feedback from FDA on the proposed REMS.

Roxane suggests without any supporting facts that, had it "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." Roxane Pet. at 7. Importantly, Roxane does not identify any changes that would reduce

[14] Roxane's statement that "generic versions of the drug were already on the market when FDA made the determination that a REMS was needed" is wrong. Roxane Pet. at 6. However, as noted, at the time Roche and Novartis were directed to develop a REMS, Roxane's ANDA had been approved.

costs or aspects that are not feasible for a generic company or point to ways in which Roche has unnecessarily increased costs. In fact, FDA's comments to Roche and Novartis on the proposed REMS have sought greater efforts (with corresponding higher costs), not less. Nor are sources of Roxane's purported cost savings readily apparent. Roche has used competitive bidding for MPA REMS service providers and has taken extensive measures to ensure that the MPA REMS is a cost-effective and efficient program while meeting all statutory requirements. Given its declining market share, Roche has every incentive to consider costs in developing an effective MPA REMS program.

Roxane also asserts that its "contribution of additional ideas during development of the REMS would have led to a better overall program." Roxane Pet. at 7. However, given Roxane had no experience with marketing its mycophenolate drug, whereas Roche and Novartis have approximately 20 years combined in the MPA market, as well as extensive experience in the development and implementation of REMS and pre-FDAAA risk management programs for other drugs, it is speculative that Roxane's input would have "led to a better overall REMS program." Roxane Pet. at 7. In fact, given that at no point in the seven months that Roche has been negotiating the MOU with Roxane and the other generic companies, has Roxane even asked for information about the structure or details of the proposed REMS program, Roxane's assertion that it could have developed a better or more "feasible" program at lower cost is without foundation.

Roche has no objection to FDA considering a change in the timing of generic company involvement should a similar situation arise in the future. But, Roche submits, the MPA REMS

should not be delayed by that broader consideration. In light of the significant public health interest, this Petition should not be used by Roxane to restart the process or permit a delay in Roxane's or any other generic company's participation in a MPA REMS.

IV. The MOU Gives Roxane and the Other Generic Companies an Appropriate and Significant Role in Implementation and Operation of the MPA REMS

Roxane states that the MOU does not offer generic manufacturers a significant decision making role in implementation and ongoing operations of the MPA REMS. Roxane Pet. at 7-8. This is not correct. The original draft MOU provided for one vote for each participant and required unanimity among the participants for changes in the REMS. If unanimity was not reached, a final decision would be made by Roche, as the NDA holder (upon prior consultation with Novartis), subject to FDA review and approval. This was not arbitrary or an attempt to "pay lip service to the concept of participation by the generic companies." Roxane Pet. at footnote 3. Rather, based on Roche's experience administering the isotretinoin program for five years, it has learned that, as to most issues, unanimity is desirable and should not only be attempted but can also be achieved. However, there can be impasses as to program decisions, and where such an impasse involves patient safety issues, a quick resolution may be necessary. Roche, as NDA holder and principal architect of the MPA REMS, has an obligation as to patient safety, including the proper operation of the REMS.

In response to concerns raised by several generic companies regarding decision making, Roche did revise the MOU. Under the current draft, which Roxane received subsequent to filing this Petition, if unanimity is not possible, the decision is elevated to the Chief Executive Officers ("CEOs") of the participating companies to resolve the deadlock. In the event unanimity among

the CEOs is not reached, and a decision is necessary to promote patient safety as determined by Roche's Chief Medical Officer, then Roche may make the final decision. To ensure rapid implementation, Roche and Novartis will also make all up-front payments for such a decision if the other participants are not in agreement, subject to reimbursement. Thus, except for decisions necessary to promote patient safety, lack of unanimity results in deadlock.[15] Given there is potentially no additional economic burden placed on Roxane beyond what would be required to protect patients, it is unclear why Roxane would object to this decision making process.

Roche, as the NDA holder, believes it has primary responsibility to ensure continuing compliance with regulatory requirements including REMS. As such, Roche has also assumed a greater role, at considerable expense, than the other participants in the administration and operation of the REMS. While it is willing to give up its rights as final arbiter for all operational decisions in the event of impasse, it is not willing to forego its final decision making rights with regard to patient safety and does not believe FDA would want decisions regarding patient safety to be delayed because of a voting impasse. This is in the best interests of patients and regulatory compliance regardless of how costs are allocated for the REMS.

V. If Roxane Chooses to Participate in the MPA REMS, Roxane Should Pay Its Fair Share of the Costs to Develop and Operate the REMS

Consistent with their statutory responsibilities, all participants in the MPA REMS should pay an equitable share of the REMS development costs and operations costs, and each

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[15] This may result in more FDA involvement for deadlocked decisions. But Roche believes that under a shared system in which the brand and generic participants may have different interests, attempting to achieve consensus, even at the risk of rare deadlocks, is superior to having polarization that may result from requiring only a majority for decision making.

participant should be solely responsible for its "independent costs."[16] Accordingly, the MOU provides that development costs be shared equally by all participants in the REMS.[17] As each new participant joins the program, the costs will be re-apportioned so each participant's share of the costs continues to be proportionate to the total number of program participants (e.g., 25% if 4 participants; 50% if 2 participants). Ongoing operations costs are also shared by all participants and allocated by market share as measured by amount of drug sold (i.e. grams), not dollar sales. Such an allocation is consistent with the actual financial burden associated with development and implementation of the MPA REMS. Any other basis for sharing costs would not be equitable to all participants and would permit Roxane and the other generic companies to avoid paying a reasonable and fair share of the development and operations costs necessary to develop and maintain the FDA mandated REMS.

Roxane argues that this allocation of costs "disproportionately benefits the incumbent branded products" and that being asked to share in the costs to develop and implement a single, shared REMS amounts to "subsidizing brand companies for the costs of marketing branded products." Roxane Pet. at 8. Thus, Roxane argues it should only have to pay the additional costs associated with its participation in the REMS. Roxane Pet. at 8. Roxane is incorrect.

First, the costs involved in developing and implementing the MPA REMS relate to fulfilling an important regulatory requirement relating to MPA and patient safety, not "the costs

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[16] Independent Costs include those costs to include the manufacturer as a participant in the REMS and costs incurred by a manufacturer for preparing and/or updating its medication guide and educational materials relating solely and specifically to its drug.

[17] Development Costs are those costs incurred by Roche to develop the REMS prior to launch of the REMS program including, but not limited to payments to the REMS program service providers (i.e. the vendors assisting in the development of the Pregnancy Registry, REMS program website, etc.)

of marketing branded products."[18] As the FDCA recognizes, the costs of the REMS are part of the cost of selling MPA, no less necessary than packaging or distribution costs that should and must be borne by each market participant, whether branded or generic. Nevertheless, Roxane is attempting to exempt itself from paying the development and operations costs for the MPA REMS on the theory that the brand companies would have incurred these costs regardless of whether there were generic companies on the market. Roxane Pet. at 8. Given that the MPA REMS will be implemented after generic entry, one could just as easily argue the reverse: that generic companies, who sell the majority of MPA products, would incur these costs regardless, and that the NDA holders should pay only incremental costs of participating in the REMS.

In fact, absent a shared program (which Congress has determined is presumptively in the public interest), each generic company would have to develop and operate an independent REMS that meets all FDA requirements, including a pregnancy registry, call center and website. The costs to develop a REMS would be incurred regardless of the number of patients served. And, the generic company would incur the total costs to operate the REMS program, such as inputting data into the pregnancy registry and responding to calls from patients. Although Roche cannot state a figure definitively, based on its extensive experience developing and operating REMS programs, Roche believes it is likely that the costs incurred by any single generic company would be far greater than that which the generic company would incur by participating in a shared MPA REMS under the cost sharing method proposed by Roche and Novartis. If,

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[18] Roche believes anything other than an equitable sharing of costs by the generic companies will result in the brand companies subsidizing the generic companies for the costs of fulfilling their regulatory requirements.

however, Roxane believes, as this Petition seems to indicate, that it can develop a more effective, less costly REMS program for its generic MMF, Roche has no objection to FDA granting Roxane a waiver so long as Roxane can implement its REMS on the same timetable as other sellers of MPA products.

Second, Roxane's speculation that "if brand companies are free to develop REMS programs without regard to their cost and generic companies are expected to help pay for their cost, it is likely that a good number of generic companies will have to forego marketing the generic versions of drugs subject to REMS and consumers will have access to fewer lower-cost generics," is entitled to no weight. Roxane Pet. at 9. There is no basis for assuming that Roche developed the MPA REMS without regard to cost. Moreover, as noted above, nothing in the FDCA exempts generic companies from paying the costs associated with complying with regulatory requirements in the sale of their products even if such costs have an effect on generic competition. Any other result would have the brand companies subsidizing generic participation in REMS.

Third, there is no basis for Roxane's argument that sharing the development and operations costs of the MPA REMS would impose an undue burden on Roxane or any other generic company. Assuming the estimated development costs of $6.9 million for the MPA REMS are shared amongst the ten companies manufacturing a MPA product, Roxane's share of the development costs is less than $700,000. It simply strains credulity to argue that a generic manufacturer, even Roxane, would have forgone entering a billion dollar a year market because

it was required to incur development costs of $700,000 (or .07% of the market opportunity) to participate in an effective REMS.[19]

Similarly, there is no evidence that calculating Roxane's share of ongoing operations costs based on market share and commensurate with the number of patients that take its drug imposes an undue hardship. Roche estimates that operations costs will be approximately $7 million per year or $70,000 for every one percent of the prescriptions written for the product.[20] Roxane offers no evidence that with 5% share of the market it cannot bear the financial burden of the ongoing operations costs.[21]

Finally, the fact that Roche and Novartis were required by FDA to submit a REMS before FDA notified Roxane it needed a REMS is irrelevant to the basis for determining how costs should be shared. The proper result here, as with the isotretinoin REMS, is equal sharing of development costs and proportional sharing of operations costs. This cost sharing principle is also reflected in FDA's views on cost sharing for the class REMS under consideration for certain opioid products.[22] Given the costs to participate in the MPA REMS versus the potential costs for

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[19] Even at post-entry generic MMF prices (estimated to be 10% of pre-entry brand prices) there is no reason to assume that a cost of $700,000 or less than .15% of the market opportunity will impair the ability of generic companies to compete. The $6.9 million in development costs for the MPA REMS is significantly less than the $35.3 million in development costs for the isotretinoin REMS.

[20] The estimated operations costs of $7 million per year compare quite favorably with the annual cost of over $18 million for the isotretinoin REMS.

[21] Roxane's Petition asserts at page 10 that it has 57% of the sales of MMF products. That is in fact the share of all generic companies, not the share held by Roxane, which is 5%. Indeed, Roxane's failure to gain market share may explain its lack of interest in making constructive comments to the MOU and instead engage in an effort to delay bearing its share of costs for a MPA REMS.

[22] **"2. Industry Question/Comment:** Who is responsible for the cost of developing and implementing the proposed REMS program?

a generic company to create its own REMS program (as well as the significant time and effort to create a REMS program), Roche has in fact reduced the burden on each generic company by developing a cost effective REMS program that can be shared with generic companies as contemplated under FDCA.

VI. Conclusion

Roxane has known for at least ten months that generic MMF requires a REMS. And for approximately seven months, Roxane has objected to virtually every aspect of the proposed MOU for participation in the MPA REMS. Although Roxane is clearly dissatisfied with the MOU developed by Roche and Novartis, Roxane took no steps to propose alternative approaches or to seek a waiver from any aspect of a single, shared REMS system. And even at this date, as the MPA REMS nears completion of development, Roxane has filed a petition rather than propose to create its own REMS.

Agency Response: Companies are expected to assume the cost of developing and implementing the proposed REMS program. A joint effort by all companies to develop and implement the REMS program will distribute the costs across companies. The cost to the healthcare system of opioid abuse is enormous. A successful REMS will lower healthcare costs related to prescription opioid drug abuse. "

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"16. **Industry Question/Comment:** What if the cost to participate in a central system is prohibitive for some companies?

Agency Response: The Agency's expectation is that the companies will work together to develop a shared system. Companies will need to work together to set up the program and share the costs of its implementation. The costs will be spread among many companies, thereby decreasing the burden on each individual company."

Meeting Minutes, Industry Meeting to Discuss Opioid REMS, February 24, 2009, at 4, 7. (http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM170568.pdf) Roxane is one of a number of generic and brand companies that are part of the effort to develop a class wide REMS for these opioids.

Anything other than a prompt denial of the Petition as it relates to the MPA REMS will cause delay and risk injury to patients and reward Roxane for its dilatory actions. Roche has gone as far as it can in addressing Roxane's concerns and revising the MOU for participation in the MPA REMS, including modifying the MOU terms to assume substantial personnel costs associated with REMS development and broaden generic companies' role in decision making. It is only fair that each MPA REMS participant pay its reasonable and fair share of the development and operations costs of the MPA REMS. FDA should promptly approve the MPA REMS and ensure that all manufacturers of MPA products participate in the MPA REMS or, pursuant to a waiver, put in place their own REMS on the same time schedule in order to continue marketing their generic MMF.

Hoffmann-La Roche Inc.

By: _____

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