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

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CITIZEN PETITION

The undersigned, on behalf of Hoffmann-La Roche Inc. (Roche), submits this petition under sections 502 and 505 of the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs to ensure the proper design and implementation of risk management programs for isotretinoin drug products approved through the abbreviated new drug application (ANDA) process in reliance on Accutane as the reference listed drug. This is essential to protect the public health in view of the potent teratogenicity of isotretinoin.

The risk management program developed by Roche and approved by FDA for Accutane – the System to Manage Accutane Related Teratogenicity (S.M.A.R.T.) – is an innovative and highly complex system involving the company, the agency, prescribers, pharmacists, patients, and third-party epidemiologists. Roche developed the program with FDA in the context of a single-product environment. Numerous questions arise when ANDA applicants copy that program in a multiple-product environment. These questions must be resolved before, not after, ANDAs are approved in order to assure that women of childbearing potential will be adequately protected against the risk of pregnancy and birth defects and to assure that the data being collected are accurate, meaningful, and assignable to specific products.

FDA apparently is moving toward approval of one or more isotretinoin ANDAs without first addressing these concerns in a manner that complies with the Act. The labeling and conditions of use of the ANDA products must be identical to that of Accutane, meaning in this context that the ANDA applicants must implement their own risk management programs that are identical to the S.M.A.R.T. program in all required respects. Among other things, the S.M.A.R.T. program is specific to Accutane. The ANDA programs therefore must be specific to their products. Rather than requiring that each ANDA applicant adopt a program design that conforms to the S.M.A.R.T. design, FDA appears to be moving in

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precisely the opposite direction, namely, changing the S.M.A.R.T. program from one that is product-specific to one that relates to all isotretinoin products. This would turn the Hatch-Waxman provisions on their head. FDA must require generics to copy the innovator, not change the innovator to conform to the generics. In addition, FDA's actions would make it impossible for Roche accurately to track and measure the performance of its specific program, which is a required condition of approval of the S.M.A.R.T. program. FDA cannot legally require conditions of Roche and then change the ground rules in a way that will prevent Roche from fulfilling those conditions.

Roche has attempted to address these issues with FDA in a timely and cooperative fashion, beginning immediately after FDA approved the S.M.A.R.T. program last fall. Only over the past few days, however, has Roche learned from FDA that the agency has moved forward without obtaining further input from the company regarding the complex questions presented. Roche believes that, in doing so, FDA is disregarding the public health, violating Roche's legal rights, and violating the basic requirements of the Act for ANDA approvals. Accordingly, the company is filing this citizen petition.

A. Action Requested

Roche requests that the Food and Drug Administration (FDA) refrain from approving ANDAs for isotretinoin drug products until adequate procedures and standards have been developed to ensure that (1) the risk management programs for those products will comply with statutory requirements and be properly coordinated with the S.M.A.R.T. program to protect the public health; (2) each program can be properly linked to the specific drug product actually dispensed by the pharmacy; and (3) each data collection system has been developed to ensure that performance metrics can be accurately measured for the specific drug product. There are currently no approvable letters posted on FDA's website for any isotretinoin ANDAs. However, pediatric exclusivity for Accutane expires on February 7, 2002. As stated above, Roche urges that the actions described in this petition be taken before the agency approves any ANDAs.

B. Statement of Grounds

Accutane (isotretinoin) is intended for the treatment of severe recalcitrant nodular acne. It is a highly effective drug for this serious, painful, and disfiguring condition. However, the drug also is a potent teratogen with the potential to cause severe birth defects in the event of fetal exposure through maternal use during pregnancy. Over the years since Accutane was approved in 1982, Roche has undertaken extensive efforts to educate prescribers and patients about the risk of birth defects and to reduce the incidence of fetal exposures to the greatest possible extent. Roche's efforts have included labeling and packaging initiatives, informed consent procedures, free pregnancy counseling services, follow-up with physicians and women who have become pregnant, and pregnancy test kits.

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These efforts have been extremely successful. Nonetheless, both Roche and FDA have been concerned that a small number of fetal exposures have continued to be reported. Following an advisory committee meeting in the fall of 2000, Roche undertook the development of an enhanced risk management program in full cooperation with FDA. The purpose of the new program is to ensure that no woman who is pregnant begins Accutane therapy and that no woman becomes pregnant while on Accutane therapy.

FDA approved the new S.M.A.R.T. program on October 30, 2001. The program includes required labeling providing for new package insert language; patient informed consent forms and educational booklets for both females and males; a Medication Guide; a "best practices" booklet and checklist for prescribers; a letter of understanding that prescribers must sign before prescribing Accutane; a special "qualification sticker" that must be used on all prescriptions for Accutane; a pharmacist dispensing guide; carton dispensing instructions; immediate container and carton labels; a pharmacy prescription audit; and an enhanced epidemiological study designed to measure the efficacy of the components of the S.M.A.R.T. program and to track fetal exposures. The new program includes the following elements based on this mandatory labeling:

- The new yellow self-adhesive Accutane Qualification Sticker must be attached to the prescriber's regular prescription form to indicate that the patient (both females and males) has been qualified to receive Accutane.
- All female patients must have two negative pregnancy tests and education about pregnancy before their first Accutane prescription, and one negative pregnancy test each month thereafter.
- All Accutane prescriptions must be limited to no more than a one-month supply, and every female patient must have a new negative pregnancy test before each new prescription.
- All female patients who are, or might become, sexually active with a male partner must use two safe and effective forms of contraception simultaneously for at least one month before starting Accutane, while on therapy, and for one month following therapy.
- Prescribers must encourage women to join the voluntary Accutane Survey.

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- Pharmacists must dispense Accutane only based on a prescription with the Accutane Qualification Sticker. Requests for refills without a new prescription and phone prescriptions must not be filled.

See Attachment 1. Recognizing the importance of the new program, FDA has posted extensive information regarding it on the agency's website. *See* <http://www.fda.gov/cder/drug/infopage/accutane/default.htm>. Since FDA's approval of the S.M.A.R.T. program, Roche has devoted extensive efforts to educating physicians and pharmacists about its requirements and to related roll-out activities.

Roche developed the S.M.A.R.T. program, and FDA approved it, in the context of a single approved isotretinoin product, Accutane. The law requires that any isotretinoin products approved through the ANDA process duplicate all of the required labeling for Accutane, including the mandatory labeling describing and implementing the S.M.A.R.T. program. *See* 21 U.S.C. § 355(j)(2)(A)(v) and (j)(4)(G). But that is only the beginning of the inquiry from both a legal and a public health perspective. In order for the "same labeling" requirement to have any real meaning in this context, FDA must ensure that ANDA applicants actually implement risk management programs that are equally effective to the S.M.A.R.T. program, and it must ensure that the multiple programs are implemented in a fashion that protects against fetal exposures and matches each program and data collection to a specific product. In addition, the Act requires that ANDA applicants demonstrate that their products will be subject to the same "conditions of use" as the innovator drug. *See* 21 U.S.C. § 355(j)(2)(A)(i) and (j)(4)(B). This provision also requires that the ANDA applicants' risk management programs be as effective as and properly coordinated with the S.M.A.R.T. program. Roche raised the public health issues with FDA through the submission of a white paper to the agency on November 5, 2001, and at a meeting on December 5, 2001. *See* Attachment 2.

A product approved through an ANDA would be misbranded under section 502 unless the assurances and coordination measures described above have been undertaken. *See* 21 U.S.C. § 352(a) (drug is misbranded if its labeling is false or misleading). The labeling that must be used by an ANDA product will need to state that the product can only be prescribed under its own manufacturer's version of the S.M.A.R.T. program, that the prescriber must obtain a supply of that manufacturer's qualification stickers and return a letter of understanding to the manufacturer, and so forth. Yet with an uncoordinated system, that labeling will not reflect the reality of how the programs will work.

As a legal matter, moreover, the ANDA programs must be implemented consistently with the fundamental proposition that each program will be specific to the manufacturer's product. The S.M.A.R.T. program is specific to Accutane. Any program approved through an ANDA therefore must be specific to its product. FDA cannot lawfully convert S.M.A.R.T. from an Accutane program to an isotretinoin program by fiat: Roche has a legal right to sell

Accutane under the conditions of approval embodied in its current NDA. ANDAs must duplicate those conditions. FDA would violate Roche's rights under section 505(e) and the restraints on approval of ANDAs under section 505(j) by moving forward with ANDA approvals based on the notion of a non-product-specific single isotretinoin survey.

An additional legal objection to FDA's action arises out of the conditions FDA placed on approval of the S.M.A.R.T. program. FDA is requiring Roche to track detailed metrics for compliance with the S.M.A.R.T. program and made clear in the approval letter that, unless these quantitative objectives are achieved, the agency will move to a mandatory registration and restricted distribution system. *See* Attachment 1. Roche appreciates this condition and is confident that the company can meet the metrics based on the S.M.A.R.T. system as applied to Accutane. However, Roche cannot take any responsibility for the risk management systems or drug products of any other manufacturers. It would be both unfair and unlawful for FDA to take action against Accutane based on those other systems and products, which are beyond Roche's control. It is therefore essential that the issues be worked out before ANDAs are approved and not afterwards.

As a practical matter, the complexities that can arise in the context of multiple products are enormous. For example, a woman may be provided the materials of one manufacturer in her physician's office, and the prescriber may use that manufacturer's qualification sticker, only to have another manufacturer's product dispensed by the pharmacy. She may enroll in the epidemiologic survey conducted for the first manufacturer while in the doctor's office, or the other manufacturer's survey at the pharmacy, or both. A third manufacturer's drug – or the first manufacturer's – might be dispensed for the second month's prescription. Other issues involve the prescriber letter of understanding. A prescriber might sign the letter for one manufacturer and use that manufacturer's qualification stickers, but a different manufacturer's drug might be dispensed. If there is a failure to comply with each element of the program, it is unclear how the system will ensure that this is accurately allocated to the responsible manufacturer. This uncertainty will not only add to confusion on the part of providers and patients, but also with regard to the measurement of program success. FDA's failure to address these issues will lead to unreliable measurements of numerators and denominators, thereby preventing accurate assessment of the program. This violates basic public health and epidemiological principles.

These complexities cannot be addressed casually or informally. Hundreds of thousands of women are prescribed Accutane every year, far more than use any of the small number of other drugs subject to stringent postmarket risk management programs. The logistical difficulties are staggering. The consequences of getting it wrong would be tragic. FDA has pointed to the S.M.A.R.T. program as the way forward toward further reductions in fetal exposures to Accutane, but the agency is now fundamentally changing the risk management program in the context of ANDA approvals to something that will not work as well and that, in any event, cannot be measured in the scientific manner contemplated when

S.M.A.R.T. was approved. By failing to address these issues and to coordinate the programs, FDA is setting the stage for the development of inaccurate data and for the failure of this important risk management initiative.

In short, unless there is some assurance that the isotretinoin risk management programs will be equally effective to the S.M.A.R.T. program, women will be put at risk depending on which one is used. And unless there is some way to link the program used to the drug dispensed, there will be no way to know which programs are working and which are not. FDA has ample authority under sections 502 and 505 to protect the public health before moving headlong toward ANDA approvals, apparently based on a wooden reading of the "same labeling" requirement, without adequate attention to the unprecedented and complex real-world environment presented in this particular case, and it would violate both those provisions by approving ANDAs without addressing the issues presented in this petition.

Roche has consistently offered to work closely with FDA and with the ANDA applicants to resolve these issues. That was the company's purpose in submitting the white paper on November 5 and in meeting with the agency on December 5. In fact, during that meeting, Roche understood that the agency recognized the complexity of the issues and was committed to working together with all parties to address them appropriately. Recent communications, however, suggest that FDA is moving forward on a different path without having involved Roche. This has denied the company a meaningful opportunity to be heard and raises serious threats to the public health and to the integrity of the data that will be used to track compliance with the S.M.A.R.T. program. *See Attachment 3.*

Accordingly, the company is filing this citizen petition in order to protect the public health, to safeguard its procedural and substantive rights, and to ensure that the issues are addressed in a timely fashion. Roche remains ready, willing, and able to work cooperatively with FDA and with the ANDA applicants to resolve the issues, so that ANDAs can be approved in a manner that complies with the law and protects the public health.

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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