DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
Rockville MD 20857

Ellen J. Flannery, Esq.
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1201 Pennsylvania Ave., N.W.
Washington, DC 20004

Re: Docket No. 02P-0059/CP1

Dear Ms. Flannery:

This letter responds to your citizen petition (Petition) dated February 5, 2002, submitted on behalf of Hoffmann-LaRoche Inc. (Roche). You request that the Food and Drug Administration (FDA) refrain from approving abbreviated new drug applications (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 Roche's SMART (System to Manage Accutane Related Teratogenicity) 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. For the reasons that follow, your petition is granted in part and denied in part.

I. BACKGROUND

In 1982, FDA approved Roche's new drug application (NDA) for isotretinoin, marketed under the trade name Accutane, for the treatment of severe recalcitrant nodular acne. The drug, however, is a potent teratogen with the potential to cause severe birth defects in the event of fetal exposure through maternal use during pregnancy. After Accutane's approval, Roche sought to educate prescribers, pharmacists, and patients about the risk of birth defects associated with the use of isotretinoin in pregnant women. This education effort included several initiatives, including labeling and packaging notifications. However, incidents of fetal exposure to isotretinoin continued to be reported. Therefore, Roche worked with FDA to develop the SMART risk management program.

When FDA approved Roche's supplemental NDA for labeling revisions to reflect the SMART program on October 30, 2001, the Agency identified the family of documents that is the basis of the SMART program. These documents include new package insert language, informed consent forms and educational booklets for males and females, a Medication Guide, and qualification stickers. In addition, FDA posted extensive labeling and safety information regarding isotretinoin on the Agency's website.

Several companies have submitted ANDAs for generic isotretinoin. Based on the SMART program, the generic isotretinoin applicants have developed risk management programs with, among other things, the following components and tools:

- Placement of Medication Guide into unit packaging;
- Pharmacist Isotretinoin Dispensing Guide;
- Bulk carton dispensing instructions for pharmacists;
- Patient educational video;
- Same informed consent/patient agreements as that of the SMART program;
- Same educational brochures, including a phone number for patients to call;
- Same methods of conducting the prescription compliance survey;
- Same methods of conducting the isotretinoin survey;
- Report on teratogenicity risk management program.

On November 5, 2001, Roche sent FDA a letter and a memorandum (Attachment 2 of the Petition) detailing certain concerns that the company believed would arise when ANDAs were approved and multiple isotretinoin products with other SMART-like risk management programs were available on the market. On December 5, 2001, FDA met with Roche to discuss some of the company's concerns.

On January 31, 2002, Roche sent a letter to FDA (Attachment 3 of the Petition) listing the company's understanding of FDA's position on issues discussed at the December 5, 2001, meeting. Roche also requested a meeting to further discuss issues and concerns relating to the requirements for the approval of isotretinoin ANDAs.

FDA, Roche, and generic isotretinoin manufacturers met on February 6, 2002. At the meeting, Roche presented FDA with several issues relating to the SMART program and the potential requirements for sponsors of ANDAs for isotretinoin. FDA provided answers to several questions but withheld final decisions on certain complex issues requiring further internal FDA discussion and review.

We have placed copies of the official minutes of the December 5, 2001, and February 6, 2002, meetings referenced above in the public docket for this petition.

II. DISCUSSION

You request that before FDA approves any ANDA for isotretinoin, ANDA sponsors establish proper risk management programs that comply with any statutory requirements regarding same labeling and conditions of use, and that are coordinated with Roche's SMART program (Petition at 2). You also request that each sponsor's risk management program be linked to the specific drug product actually dispensed by the pharmacy. As discussed below, generic isotretinoin risk management programs will have the same essential elements as the SMART program. However, we do not agree that each ANDA sponsor's risk management program must be linked to the specific isotretinoin product dispensed.

A. Relevant Law on Generic Drug Labeling

Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)) permits a duplicate version of a previously approved innovator drug to be approved without submission of a full NDA. Under section 505(j)(4) of the Act, an ANDA must refer to a previously approved drug product (defined below) and rely on the Agency's prior finding of safety and effectiveness for that drug product.

Under section 505(j)(2)(A)(i) of the Act, a generic drug applicant must include in an ANDA information showing that the proposed conditions of use for the drug have previously been approved for a drug that is listed by FDA as approved for safety and efficacy (the listed drug) (*see also* 21 CFR 314.94(a)(4)). In addition, an ANDA must contain information showing that the proposed labeling is the same as the labeling approved for the listed drug, except for differences related to an approved suitability petition or because the proposed drug product and the reference listed drug are produced by different manufacturers (section 505(j)(2)(A)(v) of the Act; § 314.94(a)(8)). This required labeling includes the container label, package insert and, if applicable, Medication Guide (§ 314.94(a)(8)(iv)). Under section 505(j)(4)(B) of the Act, FDA will not approve an ANDA with insufficient information to show that each of the proposed conditions of use has been previously approved for the listed drug referred to in the application. Similarly, under section 505(j)(4)(G) of the Act, the Agency will not approve an ANDA with insufficient information to show that the labeling proposed for the drug is the same as the labeling for the listed drug referred to in the application, except for changes approved under a suitability petition or because different manufacturers are involved.

B. Isotretinoin Risk Management Program Requirements

You maintain (Petition at 4) that for the "same labeling" requirement to have any real meaning in this context, FDA must ensure that ANDA applicants implement risk management programs that (1) are as effective as SMART and (2) match each program and data collection to a specific product.

We agree that manufacturers of generic isotretinoin should have risk management programs that contain the same essential elements as SMART. However, we do not agree that the risk management program for each generic isotretinoin product, as well as each data collection system, must be limited to the specific drug product that is the subject of the ANDA. Limiting the risk management program for each isotretinoin product strictly to that particular product would not be practical in a marketplace where substitution can occur freely. Neither would such a limitation be necessary to meet the public health concern of ensuring that each party involved in the prescribing, dispensing, and use of isotretinoin will have adequate information regarding risk management. In addition, the suggested limitation would not be necessary for FDA to assess the effectiveness of the risk management programs.

FDA considered the possibility of a multiple isotretinoin product environment in the development of SMART. As noted in the FDA approval letter of October 30, 2001, for the Accutane labeling supplement, the documents in the SMART program are part of product labeling. In compliance with the "same labeling" requirements of the Act, all generic isotretinoin manufacturers, as part of their labeling for ANDA approval, will have the same educational materials as those designated in the October 2001 approval letter for the SMART program (as modified in the labeling supplement approved in June 2002). In addition, all generic isotretinoin manufacturers will have all educational materials available and approved by FDA prior to launch. The SMART program is specific to the Accutane brand name for Roche's isotretinoin drug product, but each of the essential elements of the risk management program in the approved labeling will also be followed by all generic isotretinoin manufacturers.

Also in compliance with the "same labeling" requirement of the Act, generic isotretinoin manufacturers will be required to include a Medication Guide in their packaging, and they will be required to use the same text on their package as described in the October 2001 approval letter (as modified in June 2002). In addition, all generic isotretinoin manufacturers will provide physicians with qualification stickers to inform pharmacists that particular isotretinoin users have fulfilled the four essential components of pregnancy prevention.

C. Physician Database

All isotretinoin manufacturers will develop and distribute a Letter of Understanding for Prescribers and will maintain a physician database. To receive the materials needed for qualification to prescribe isotretinoin and be included in the physician database, each physician must attest to having read the educational material from *any* isotretinoin manufacturer. Because the educational materials will not vary in content, the physician need only read the materials from any one manufacturer. The physician database will help manufacturers ensure that certified physicians receive adequate supplies of stickers and will provide a means for pharmacists to verify a physician's isotretinoin certification status.

D. Isotretinoin Survey

FDA's October 2001 approval letter describes an Accutane Survey that is to be conducted by Roche. The approval letter details the objectives and elements of the survey. Although the letter refers to the isotretinoin drug product with the trade name Accutane, because the makers of generic isotretinoin products for which Accutane is the reference listed drug will perform the same survey, all references to "Accutane" with respect to the survey will apply equally to them.

All generic isotretinoin manufacturers will have an isotretinoin survey protocol and questionnaire in place before marketing the drug product. All isotretinoin manufacturers will use survey instruments that are the same with respect to methodology (including

participation incentives), design, content, questions, analytic techniques, format, and order of questions. As part of the survey, respondents may be asked what isotretinoin product they received and the name of the educational materials used. Photographs or other means of product identification may be used in the survey to identify the brand of isotretinoin that a respondent used.

All isotretinoin manufacturers will use the same enrollment form for all respondents. All manufacturers will enroll respondents using the same three enrollment modes: blister pack, physician's office, and telephone. The aim of using these modes is to increase overall enrollment. Manufacturers will make reasonable efforts to minimize or eliminate the possibility of a patient enrolling in the survey more than once per treatment course.

Each isotretinoin manufacturer will submit to FDA a comprehensive report on the results of its isotretinoin survey. FDA will consider these reports in assessing the performance of the manufacturers' risk management programs.

E. Prescription Compliance Survey

The prescription compliance survey (pharmacy survey) was designed to ensure that the risk management program and the distribution system lead to the safe use of isotretinoin in patients by minimizing the risk of fetal exposure to this drug.

All generic isotretinoin manufacturers will perform the same essential elements of the innovator's pharmacy survey. These essential elements include the following:

1. **Methods**: The survey protocol will provide a detailed description of the population to be surveyed and the sampling process, including an assessment of the representativeness of the pharmacies surveyed compared with all U.S. retail pharmacies. Pharmacy characteristics that are anticipated to affect compliance with the use of qualification stickers will be critically evaluated in terms of representativeness. These include store type, geographical region, density of population served, and total prescription volume. The survey protocol will describe methods (such as incentives and follow-up phone calls) to achieve a survey response rate of at least 60 percent.

2. **Survey endpoints:** The primary objective of the survey will be to measure compliance with use of the qualification stickers. Therefore, the primary survey endpoint will be the total number of stickered isotretinoin (all brands) prescriptions divided by the total number of isotretinoin (all brands) prescriptions filled. The secondary objective will be to measure the completeness of the stickers used. A correctly completed qualification sticker will provide the patient's gender and, if the patient is female, the qualification date. The secondary survey endpoint will be the total number of correctly completed isotretinoin (all brands) stickered prescriptions divided by the total number of isotretinoin (all brands) stickered prescriptions filled.

3. **Data collection:** Data will be collected retrospectively to prevent pharmacists from modifying their behavior toward dispensing isotretinoin. That is, pharmacists will be responding about isotretinoin prescriptions written prior to their initial recruitment in the survey. Pharmacies that refuse to participate in the survey will be removed from the sampling frame and not recontacted. A description of the plan to ensure that data are not collected from pharmacies that have already participated or that have refused to participate in any isotretinoin survey will be provided. Data elements collected in the survey will include:

   - The presence of a qualification sticker;
   - If a qualification sticker was used, whether the qualification date blank was appropriately completed;
   - The product name on the prescription, manufacturer, strength, number of authorized refills, and mode of receipt (original in person, phoned, faxed, or emailed);
   - Whether a Medication Guide was dispensed with the drug;
   - Patient characteristics, including gender and age;
   - The prescriber's postal zip code;
   - An estimate of the number of isotretinoin prescriptions presented but not filled by the pharmacy during the time period under study due to inaccurate or incomplete information.

4. **Data validation:** A validation step is essential to ensure the completeness and accuracy of the self-reported data collected in the survey. A proposal to validate some portion of the data collected will be included in the survey protocol. The proposal will provide for validation of a random sample of at least 15 percent of survey responses. The following information provided on the qualification stickers will be validated: prescription type (original, phoned, faxed, or emailed), whether a qualification sticker was attached, patient gender, and whether the date was recorded on the qualification sticker.

5. **Analysis plan:** Based on projected prescription volume and the anticipated response rate, the projected numbers of pharmacies and prescriptions to be surveyed will be provided. Preliminary analyses will be performed to inspect the distributions and correlations of all key variables. A descriptive analysis, including means, standard deviations, and the frequency distribution of outcome measures, will be performed. Rates and basic summary statistics will be calculated.

6. **Nonretail sales:** Generic isotretinoin manufacturers will track sales volume of their products through nonretail pharmacies (e.g., mail order, Internet sales by valid U.S. pharmacies, closed staff HMOs) on a periodic basis and submit this information to FDA on a quarterly basis.

7. **Reporting expectation:** Each generic isotretinoin manufacturer will submit to FDA a comprehensive report on its risk management program, including information on the metrics achieved during the first full year of implementation following marketing approval.

All generic isotretinoin manufacturers will include the following elements as part of their prescription compliance surveys:

1. **Data collection:** Consideration will be given to collection of pharmacy characteristics, including geographic region, urban vs. rural location, and pharmacy type (i.e., independent, grocery, small chain, large chain).

2. **Data validation:** The process proposed for validating survey responses will take into consideration each pharmacy stratum surveyed, as characterized by store type, geographical region, population density served, and total prescription volume.

3. **Reporting expectation:** Generic drug manufacturers marketing isotretinoin will submit available data on the effectiveness of their risk management programs to FDA on or before June 30, 2003, in support of a meeting that will be convened with the Dermatologic and Ophthalmic Drugs Advisory Committee.

All generic isotretinoin manufacturers will have a pharmacy survey protocol in place prior to launch. All protocols will contain the same design, random samples, analysis, and minimum percentage audit of pharmacies. All isotretinoin manufacturers will evaluate prescriber compliance with the use of prescription qualification stickers and the dispensing recommendations for the qualification stickers, as well as the completeness of the information recorded in the qualification stickers. In addition, all such manufacturers will compare prescription compliance rates for male and female patients. Further, all isotretinoin manufacturers' qualification stickers will be the same yellow color and contain the same statement as detailed in the October 2001 approval letter. Each manufacturer will place its name or other identification mark on its yellow stickers.

The pharmacy survey will be designed to measure compliance with use of qualification stickers. FDA will not request assessment of compliance with the risk management program by brand of isotretinoin because our primary safety concern is with isotretinoin in general. If a prescription is filled without a qualifying sticker, it would be difficult to ascertain which sponsor's risk management program "failed" without obtaining additional information from the prescriber. The current risk management program does not provide for obtaining this additional information from the prescriber.

F. Assessment of Performance of Risk Management Programs

We understand that two major issues associated with isotretinoin products in a multisource environment are adequately managing the risk to patients posed by isotretinoin products and ensuring that the Agency can assess the effectiveness of all

manufacturers' risk management programs. We believe that we are adequately addressing these concerns in the review of ANDAs for generic isotretinoin products.

FDA will advise each manufacturer of generic isotretinoin that the Agency will reevaluate the adequacy of the company's risk management program on a continuing basis. Each manufacturer will propose benchmarks against which compliance with stickered prescription requirements can be measured. For example, a proposal could state the percentage of isotretinoin prescriptions filled by pharmacists expected to have stickers at the end of the first year of the risk management program and at the end of the second year. In addition, a proposal could state the percentage of prescriptions filled by pharmacists expected to have correctly completed stickers at one year and two years after implementation.

You state (Petition at 5) that Roche cannot take responsibility for the risk management systems or drug products of generic isotretinoin manufacturers, and you maintain that it would be unfair and illegal for FDA to take action against Roche based on those systems and products.

Neither Roche nor any generic isotretinoin manufacturer is responsible for the risk management programs or drug products of any other manufacturer. However, all manufacturers, both innovator and generic, share responsibility for managing the risks associated with the use of isotretinoin products. Each manufacturer's risk management materials will convey essentially the same important information to prescribers, pharmacists, and patients. Effective risk management may, in turn, preserve access to isotretinoin for patients for whom isotretinoin is uniquely effective.

Compliance by generic manufacturers with the essential elements of the risk management program is an issue distinct from approval of generic versions of isotretinoin. In any situation in which multisource production of a particular drug exists, adverse reactions could result from manufacturer-specific causes, rather than from the active ingredient common to all manufacturers' drug products. Action can be taken to address these issues should they materialize, but their potential occurrence does not block the ability of duplicate producers to enter the marketplace. Thus, the possibility that one or more manufacturers of isotretinoin will fail to fully meet their risk management obligations is not an impediment to approval of their applications conditioned on full performance.

All isotretinoin manufacturers will be included in FDA's assessment of the overall risk management program to determine its effectiveness. We will make a weight of evidence assessment based on analysis of internal FDA data as well as data supplied by the manufacturers. This assessment will also permit the evaluation of the SMART program—notwithstanding the existence of generic isotretinoin manufacturers' risk management programs—by assessing Roche's compliance with the essential elements of the SMART program. If evidence shows that the risk management program of a particular manufacturer is inadequate with respect to the essential elements or is

performing significantly worse than the programs of other manufacturers, we will address the particular manufacturer's deficiency.

III. CONCLUSION

We have carefully considered the arguments raised in your petition. To the extent that you request that the Agency require generic isotretinoin manufacturers to have risk management programs that contain the essential elements of the SMART program, your petition is granted. Your petition also is granted to the extent that you request that generic manufacturers have the same product labeling as Accutane, including the family of documents listed in the Agency's October 30, 2001, letter to Roche. Such action is required to comply with the statutory requirements for approval of duplicate isotretinoin products. However, to the extent that you ask us to require that each isotretinoin risk management program, including performance metrics, be linked to the specific drug product dispensed, and that generic manufacturers coordinate with Roche's SMART program, your petition is denied.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research