

Background of Isotretinoin Teratogenic Risk Management Plan

Accutane was approved in May, 1982 with a pregnancy category X. Risk management at the time of initial approval was limited to labeling, which described the risk of teratogenicity in the Contraindications, Warnings and Precautions sections of the package insert and in a patient information brochure. Over the years, this risk issue was the subject of multiple advisory committee discussions leading to subsequent additions to the risk management program including Dear Doctor letters, red warning stickers issued to pharmacies, and a pregnancy prevention program (PPP). This PPP (introduced in 1988) consisted of package warning labels, an informed consent form, a PPP kit for prescribers, the Accutane tracking study to assess prescriber use of the PPP kit, and a Patient Enrollment Survey. Despite these additions, there were continued reports of fetal exposures to Accutane.

An Advisory Committee was convened in September, 2000 to address the need for changes to the Accutane risk management program to prevent fetal exposure to isotretinoin. The Advisory Committee recommended augmentation of the program, and these recommendations were accepted by the FDA and communicated to the Sponsor (Hoffman-LaRoche) in a letter from Dr. Janet Woodcock, Director of Center for Drug Evaluation and Research, FDA, on October 6, 2000¹. In brief, the letter stated that the goals of the risk management program (with respect to pregnancy prevention) were that:

1. No one should begin Accutane therapy if pregnant
2. No pregnancies should occur while a patient is on Accutane therapy.

To achieve these goals, the Sponsor was instructed to implement a plan of action containing the following five components:

1. A heightened educational program for each patient that includes verifiable documented written informed consent
2. Complete registration of all patients, both male and female
3. Complete registration and certification of practitioners who prescribe Accutane
4. A comprehensive program to track fetal exposures to Accutane (and outcomes), including a formal mandatory pregnancy registry
5. Linkage of dispensing of Accutane to female patients to verification of adequate pregnancy testing.

On October 30, 2001, following extensive negotiations with the manufacturer, the FDA approved the System to Manage Accutane Related Teratogenicity (S.M.A.R.T.TM) Program, the Sponsor's response to the requested changes in the Accutane risk management program. The S.M.A.R.T.TM program links prescriber qualification of patients to dispensing of Accutane through use of yellow stickers placed on prescriptions, and uses voluntary patient and pharmacy surveys to assess compliance. Components of

¹ Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA, to Russell Ellison, M.D., Chief Medical Officer and VP, Medical Affairs, Hoffmann-LaRoche, Inc, dated October 6, 2000.

the S.M.A.R.T.™ program include patient informed consent forms, a prescriber checklist, Letter of Understanding for prescribers, yellow qualification stickers, Medication Guide dispensed with each prescription, instruction guide for prescribers, instruction guide for pharmacists, FDA Letter to Pharmacy boards, Dear Accutane Prescriber Letter, Dear Pharmacist Letter, separate patient brochures for women and men, carton dispensing instructions, and updated package insert, patient package insert, container and carton labels.

To participate in the S.M.A.R.T.™ program, prescribers sign the Letter of Understanding (LOU) indicating that they are knowledgeable about the diagnosis and treatment of acne, prevention of unplanned pregnancy, risk of teratogenicity with Accutane, and use of the S.M.A.R.T.™ program, and that they agree to use the procedures of the S.M.A.R.T.™ program. Upon receipt of the signed LOU, the Sponsor provides the prescriber with yellow qualification stickers. The prescriber obtains informed consent from the patient, counsels the patient, provides educational materials and encourages enrollment in the voluntary Accutane Survey. Before affixing the qualification sticker to the patient's Accutane prescription, the prescriber "qualifies" the patient by verifying that

- the patient has had two appropriately timed, negative pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription and a repeat pregnancy test monthly thereafter AND
- the patient has committed to use 2 forms of effective contraception simultaneously unless absolute abstinence is practiced or the patient has had a hysterectomy, OR
- the patient is male

Pharmacists are to dispense Accutane only if a valid qualification sticker is in place and only within one week of the qualification date, and refills and dispensing of greater than 30 days supply are not allowed.

Discussion and Assessment of the SMART Program and the Goals of Dr. Woodcock's October 6, 2000 Letter

The S.M.A.R.T.™ program fulfills the first of the five criteria delineated in the October 6, 2000 letter, a heightened educational program including written informed consent, but does not fulfill the remaining four criteria. Nonetheless, due to the compelling need to provide enhanced risk management as well as unresolved issues regarding patient privacy protection with registries, S.M.A.R.T. was agreed to as offering significant improvements over the existing risk management program. The approval letter to the sponsor stated that the Agency would review the adequacy of S.M.A.R.T., and the Sponsor was instructed to develop a back-up program for mandatory registration of patients, prescribers, and pharmacies.

The second criterion in the October 6, 2000 letter, complete registration of all patients receiving Accutane, was intended to provide the denominator (total number of users of Accutane) for ascertainment of the pregnancy rate. The Sponsor submitted an alternative proposal to estimate the denominator from pharmacy databases. Combined with projected increases in survey enrollment, the Sponsor proposed that the alternative

methodology would allow them to provide both an adequate numerator (discussed below) and denominator with better patient confidentiality.

The third criterion specified registration and certification of all prescribers. The Sponsor objected that they did not have the authority to certify prescribers. The FDA and the Sponsor subsequently agreed upon a voluntary prescriber registration for the S.M.A.R.T.TM program based upon the prescriber's self-attestation of relevant competencies. Additionally, S.M.A.R.T.TM provides information for prescribers on each component of the program. The responsibility for obtaining the continuing medical education necessary for achievement of the competencies listed in the LOU rests with the prescriber.

The fourth criterion, a comprehensive program to track fetal exposures to Accutane, including a formal mandatory pregnancy registry, would have provided the numerator for the ascertainment of pregnancy rate. Discussions regarding implementation of a mandatory pregnancy registry raised issues about patient privacy and HIPAA compliance. The Sponsor proposed that by increasing enrollment in the voluntary survey to $\geq 60\%$, they would be able to accurately extrapolate a numerator (and denominator) to ascertain the pregnancy rate among patients treated with Accutane. To achieve the higher enrollment, the Sponsor targeted education to raise prescriber awareness about the survey and increased reimbursement for patient participation three-fold (to \$30).

The fifth criterion required linkage of dispensing of Accutane to female patients to verification of adequate pregnancy testing. The S.M.A.R.T. program asks the pharmacist to verify that the patient has been qualified. By affixing and dating a yellow qualification sticker to the patient's Accutane prescription, the prescriber indicates that a female patient has undergone pregnancy testing of appropriate timing and sensitivity. The participation of pharmacists is voluntary. The report of non pregnant status is not laboratory certified but based solely on the physician attestation on the sticker.

In the October 31, 2001 approval letter for the S.M.A.R.T.TM program, the FDA instructed the Sponsor to, "...submit a comprehensive report on the S.M.A.R.T. Program, including information on the metrics achieved during the first full year of implementation...."² Specific performance benchmarks were not stated in the approval letter; rather, the Sponsor was informed that "...[t]he adequacy of S.M.A.R.T. will be a review issue for re-evaluation on a continuing basis."³ Performance benchmarks were discussed with and communicated to the Sponsor in earlier meetings, however. Specifically, acceptance of the Sponsor's alternatives to the mandatory patient and pregnancy registries was contingent upon achievement of the Sponsor's own threshold of

² Letter from Jonathan K. Wilkin, M.D., Director, Division of Dermatologic & Dental Drug Products, CDER, FDA, to Johanna Waugh, BSc., Hons, Group Director, Drug Regulatory Affairs, Hoffman-La Roche Inc., dated 30 October 2001.

³ Ibid, letter from JKW dated 30 October 2001.

≥ 60% enrollment in the voluntary survey of the of female patients.^{4,5} The Sponsor was informed that use of qualification stickers, "...should be extremely high (near 100%), since it is a surrogate for outcome measures that cannot be reliably assessed without a mandatory patient registry."⁶ Regarding fetal exposures, although elimination of all exposures is the goal of the risk management program, it was understood that achievement of this might not be possible. Hence no threshold for the number of fetal exposures (greater than zero) that would be "acceptable" during the first year of S.M.A.R.T.TM implementation was prespecified.

On November 8, 2002, the first generic version of isotretinoin was approved for marketing. Two additional generic formulations have subsequently been approved, and other applications are pending. The market for isotretinoin has become a multi-source environment. Each of the generic Sponsors have been required to provide an isotretinoin teratogenicity risk management plan identical in all essential elements to the S.M.A.R.T.TM program. Although S.M.A.R.T.TM refers specifically to the isotretinoin teratogenicity risk management plan instituted by Hoffman La-Roche, the risk management plans for each isotretinoin product, the innovator as well as the generics, contain the same essential elements and are considered interchangeable.

⁴ Fascimile from Indira Kumar Hills, Division of Dermatologic & Dental Drug Products, CDER, FDA, to Joanna Waugh, BSc., Hons, Group Director, Drug Regulatory Affairs, Hoffman-La Roche Inc., dated August 14, 2001.

⁵ Submission from Robyn B. Konecne, Pharm.D., Hoffmann-La Roche, to NDA 18-662, dated March 26, 2001 (stamp date March 28, 2001).

⁶ Ibid., fascimile from IKH, dated August 14, 2001.