Appendix II.

Overview of Accutane and Pregnancy Exposure

Performance of the Current Pregnancy Prevention Program

A pregnancy prevention program has been in place since 1988. There has been suboptimal participation in the program by female Accutane users. Although more than 500,000 women are enrolled in the program, this represents 40% or less of all female Accutane users. Furthermore, substantial non-compliance with critical elements of the program has been documented in the sponsor's most recent periodic report dated June 2000. Whereas 99% of women were told to avoid pregnancy, 25% did not have a pregnancy test before treatment and 33% did not postpone treatment until after receiving their pregnancy test results. According to a 1999 report by the sponsor, approximately 11% of pregnant women identified by Slone were pregnant at the beginning of therapy and another 14% became pregnant during the first 3 weeks of treatment. These statistics indicated that the sponsor's current pregnancy prevention program has not been completely effective in minimizing pregnancy exposure during Accutane treatment and that better alternatives are urgently needed.

An Improved Pregnancy Prevention Program is Needed Because Pregnancy and Fetal Exposures Are Continuing

The sponsor has documented a total of 1,995 Accutane-exposed pregnancies since marketing approval in 1982. Of these, 958 were identified in the Slone Epidemiology Unit's Accutane Survey since institution of the Pregnancy Prevention Program. The remaining 1,037 were identified through spontaneous reporting. The outcomes of these pregnancy exposures were as follows: 72% (or 1,446) were terminated, 19% (or 383) resulted in live births. The outcome was unknown in 8% (or 166).

Based on data submitted by the sponsor, there is about a three-year lag in reporting of pregnancy exposure events. Thus, it is not possible to reliably estimate changes in the occurrence of particular events in recent years. Nonetheless, it can be concluded that pregnancy exposures are still occurring.

Both the sponsor and the FDA agree there is a need to improve the most recent version of the PPP to further reduce the numbers of pregnancy and fetal exposures to Accutane.

Sponsor's Proposed Targeted Pregnancy Prevention Program for Women on Accutane

The sponsor is proposing to revise the current Pregnancy Prevention Program (PPP) and rename it the Targeted Pregnancy Prevention Program for Women on Accutane (TPPPWA). Modifications target the areas of education, participation,

compliance (including pregnancy testing), and monitoring. The TPPPW seeks to increase voluntary participation from the current level of 40% to 60%.

Specific educational components will include a more extensive and convenient PPP Kit containing expanded prescriber information, patient information, a patient video, and urine pregnancy tests. Provisions for continuing medical education will be added to encourage physician education as well as participation. Product labeling will reinforce the existence of the PPP kit.

To encourage still-optional participation, the sponsor will increase the current $10 financial incentive that is offered to patients for participation. The program's existence will be described in product labeling and in the PPP kit materials for physicians and patients, and will be promoted by regular publications of data from the program's survey.

Measures to increase voluntary compliance with pregnancy prevention practices in the TPPPWA will include previously described education efforts to patients and prescribers, encouragement of PPP Kit use by prescribers, and the provision of all urine pregnancy test kits for patients. In addition, the sponsor proposes that no written prescriptions for Accutane be given to female patients. Instead, they recommend that all prescriptions for women be phoned into the pharmacy after the physician determines all pregnancy tests are negative.

Monitoring of the impact of the program will be improved if efforts to increase voluntary participation are successful. More information will be collected on each patient who chooses to participate. In addition, non-participants who voluntarily contact the sponsor or Slone on their own will be asked a set of standardized questions to enhance understanding of the nonparticipating population.

<u>FDA Assessment of TPPPWA and Recommended Characteristics of an Optimal Pregnancy Risk Management Program</u>

FDA acknowledges that the TPPPWA improves upon the previous PPP insofar as that is possible within a voluntary program. The TPPPWA education program reemphasizes the importance of pregnancy testing and adequate contraception. If a larger group of physicians and patients in fact take advantage of increased education and patient urine pregnancy tests kits, pregnancy testing before and during therapy could increase and potentially result in earlier identification of pregnancies and reduced duration of in-utero exposure to Accutane.

Notwithstanding the potential improvements proposed by the sponsor, FDA notes the TPPPWA still has 3 principal shortcomings:

- Participation in the program by patients and physicians is still voluntary
- Compliance with program components is voluntary and unmonitored

- Measurement of pregnancy exposures and outcomes remains limited

Based upon its experience in drug risk management, the FDA believes the following elements are critical to the optimal performance of a pregnancy risk management program for a known human teratogen:

- High quality education
- Universal informed consent
- Universal participation of patients
- Engineering of program components to maximize compliance
- Representative monitoring of program performance and impact on pregnancy and fetal exposures.

Inclusion of all these elements is felt to be necessary to assure that no one starts Accutane if pregnant, no one becomes pregnant while taking Accutane, and that adequate data are available to determine whether these conditions are being met.

FDA Proposed Options for Accutane Pregnancy Risk Management Options

The following series of options for an Accutane Risk Management Program are presented here for further consideration by the Advisory Committee. The critical elements of each are briefly described.

Option 1

- Education and informed consent as proposed by the sponsor for the TPPPWA
- Complete participation via *mandatory* registration of *all* female patients
- Monitoring of impact by the program as well as external data sources. This would include continuing the Accutane pregnancy registry for all identified exposures and surveying a sample of program participants to monitor compliance with pregnancy prevention activities. In addition to this programmatic monitoring, the sponsor would also be required to employ independent surveillance systems to capture of drug use and pregnancy exposures that are not represented in the sample. An example would be surveillance of data reported to the Organization of Teratogen Information Services, a toll-free service organization that advises women on the risks of pregnancy exposures.
- All Accutane prescriptions be limited to a 30 day supply, as in the current program.

Option 2

This option would encompass all elements of Option 1 and optimize compliance so that no prescriptions could be dispensed to pregnant patients. This option establishes a real-time linkage between pregnancy test results and dispensing. This linkage would require that:

- pharmacists confirm that a negative pregnancy test has been documented before dispensing an Accutane prescription.

Logistically, both male and female patients would have to be registered for such a program to be implemented without loopholes.

Option 3
This option would encompass all elements of Option 2 and increase the linkage requirements. In addition to confirmation of a negative pregnancy test before dispensing Accutane, the pharmacist would confirm that appropriate patient compliance with contraceptive practices, drug sharing, and blood donation guidelines was documented.

Option 4
This option would encompass all elements of Option 3 and impose further restrictions on pharmacists in order to assure compliance with linked dispensing constraints. Pharmacists would have to be trained, registered, and authorized before they would be allowed to dispense prescriptions for Accutane.