One hundred twenty-two pregnancies were exposed to isotretinoin during the past year. That rather straightforward statement teems with potential implications for dermatologists, patients, pharmaceutical manufacturers, and, of course, the iPledge program initiated with the apparent goal of zero exposures. In reality, the number of exposures is not necessarily a reliable measure of the “success” or “failure” of iPledge. As a participant in the recent joint meeting on August 1, 2007 of the FDA advisory committees on Dermatologic and Ophthalmic Drugs (DODAC) and Drugs Safety & Risk Management (DSRM), I will review what the data reveal and what changes are coming soon to the program.

Findings About Pregnancies

Certainly 122 pregnancies exposed to isotretinoin—an increase over the last year of SMART, when 120 exposures occurred—is a cause for a concern. Due to the voluntary nature of SMART pregnancy reporting, we cannot know with certainty how many pregnancies actually occurred while it was in effect. iPledge pregnancy reporting is mandatory, therefore it is difficult to make comparisons between the two programs.

A total of 305,366 patients had registered in the iPledge program at the end of the first year. Males comprised a slight majority (50.6 percent), while females of childbearing potential accounted for 45 percent of all patients (137,415 females of childbearing potential were registered; 91,894 of these patients had an isotretinoin prescription authorized through the iPledge system).

The first year’s worth of iPledge reporting provides a baseline count of pregnancies. As the iPledge program matures, prescribers and patients will learn how to reduce the number of pregnancies by reviewing and implementing enhancements based on the data and pregnancy root cause analyses. This adaptability is a benefit of the current program and, in fact, upcoming changes to iPledge (discussed below) will eliminate program features that disrupted continuity of care and thus lengthened patients’ exposure to isotretinoin.

Some features of the identified pregnancies warrant consideration. Eighty percent of the reported pregnancies occurred in patients greater than 20 years old, most of whom have some or all of a four year college education. While the majority of pregnancies occurred while taking isotretinoin, 10 pregnancies occurred before starting isotretinoin, and eight pregnancies occurred within 30 days of stopping isotretinoin therapy.

Oral contraceptives and male condoms were the most common primary and secondary methods of contraception for the women who became pregnant. Oral contraceptives and male condoms were the most common primary and secondary methods of contraception for the women who became pregnant.

According to patient reports, the three top reasons that pregnancy occurred were: 1.) failure to use two forms of contraceptives, 2.) contraceptive failure, 3.) and unsuccessful abstinence.

Of note, nearly all (99.1 percent) of the women who became pregnant reported that they were told to avoid pregnancy and that they received an educational kit (97.3 percent) for females of child-bearing potential. Furthermore, more pregnant women than non-pregnant women reported that they had watched the “Be Aware” video or the “Be Prepared, Be Protected” video.

Among women of child-bearing potential who did not become pregnant, the majority (99.7 percent) reported being told to avoid pregnancy. While 65.7 percent of non-pregnant women of childbearing potential reported receiving contraceptive counseling from their doctor, 13 percent reported not receiving any birth control counseling, and 49.1 percent reported that their prescriber offered to refer them to another healthcare provider for birth control counseling.

The majority of females of childbearing potential (83.4 percent) passed their monthly comprehension test regarding pregnancy risks and the need for contraception the first time they took it (12.4 percent passed on the second try). This compares to 79.4 percent of pregnant patients passing on the first try (18.8 percent on the second attempt).

Other One-Year Findings

A total of 42,362 pharmacies are activated in iPledge, as are 15,742 prescribers. The majority of these are dermatologists.
(9,132 or 58 percent), 3,572 are Family/General Practitioners (23 percent). Two prescribers were deactivated from iPledge. One prescriber was deactivated because he or she entered a woman’s pregnancy test result into the computer before receiving the completed test result. The other prescriber was deactivated after giving a patient Accutane from a previous supply sent by Roche as part of their patient assistance program. Remember that only an iPledge registered pharmacist working at a pharmacy activated in the iPledge system may distribute isotretinoin to a patient. Any practice that has Accutane on hand (even if it hasn’t expired) must properly dispose of it.

We’ve all had patients experience the frustration of the lockout period. The most common reason for women to be locked out was failure to fill out monthly questions within the proper seven-day time frame. The second most common reason was failure of the prescriber to enter the pregnancy test results into the iPledge system within the proper time frame.

The primary reason for lockout among men was failure of the patient to present to the pharmacy within seven days from the date of the prescription. The next most common reason was that the prescriber did not confirm counseling into the iPledge system within the proper time frame.

Program Changes
In light of the pregnancy data released just a day before the FDA committee meeting, some observers wondered whether Phase II changes proposed by Covance (administrator of the iPledge program) would be approved. With some committee members seeming to suggest that the “zero pregnancy” standard simply is not attainable, the committee ultimately voted unanimously to accept the changes. These include:

- Eliminating a 23-day lockout period for female patients of childbearing potential (FNCBP) who do not pick up their medication during the seven-day window following an office visit. This will improve continuity of care and should actually reduce total exposure to isotretinoin for many women.
- Linking the seven-day window for FCBP to the date of specimen collection for a pregnancy test instead of to the office visit, as is now the case.
- Extending the window for filling prescriptions from seven days to 30 days for males and females not of child-bearing potential (FNCBP).
- iPledge will send ‘Dear Prescriber’ and ‘Dear Pharmacist’ letters to all registered prescribers and pharmacists in the program when these changes will take effect.

Several advisors offered suggestions for improving communication with FCBP patients, increasing participation in the pregnancy registry, and meaningfully conducting root cause analyses of isotretinoin pregnancies.

Implications for Practice
Acceptance of the proposed Phase II changes represents the adaptability and responsiveness of the iPledge program. Though many clinicians still find fault with aspects of the program, it is improved since its premier. No matter how much some may deride the system, it is here to stay. Resistance will do no good. Prescribers must learn to navigate the system to ensure continued access for patients.

Representatives from various professional medical societies pointed out that the current system does not allow for off-label use and has no provisions for patient assistance programs. The panel agreed that these are areas of need, and I hope that iPledge will address these issues this year.

One-year findings remind prescribers of the importance of ensuring that female patients know they must avoid pregnancy one month before, during, and one month after therapy.

Make sure iPledge patients have a clear understanding of risks and benefits and what this system requires of them. Be sure to understand the system yourself (as well as the role of staff). Most importantly, don’t bend the rules for anyone. The ramifications for the prescriber and the patient can be significant.

The entire summary document of the iPledge program at year one is available on the FDA website:
http://www.fda.gov/ohrms/dockets/ac/cder07.htm#DermatologicOphthalmicDrugs.