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Can We Ensure the Safe Use of Known Human Teratogens?

The iPLEDGE™ Test Case

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Abstract

Minimising the public health burden of isotretinoin-induced teratogenicity has been a challenge for 24 years, the duration of availability of isotretinoin in the US for the treatment of severe, recalcitrant nodular acne. Although the teratogenicity of this drug is well known and risk-management programmes had been implemented, preventable fetal exposures continued to occur, largely as a result of the lack of sufficient controls within the programmes themselves. The manufacturers of isotretinoin implemented a new risk-management programme, iPLEDGE™, in March 2006. iPLEDGE™ is a comprehensive distribution system that includes mandatory registration of patients, healthcare providers, pharmacies, and wholesalers. It allows real-time linkage of pregnancy-test results for verification prior to the dispensing of isotretinoin. Although the challenges of implementing a closed distribution system for a very widely used medication have been extensive, the potential public health benefits from preventing fetal exposure to isotretinoin are substantial.

Isotretinoin has been a risk-management challenge since it was first introduced to the US market. Exposure of the developing fetus to isotretinoin is associated with craniofacial, cardiac, thymic and CNS defects in approximately 30% of infants exposed during the first half of pregnancy.[1,2] Among children without anatomic defects, including those who were exposed through maternal use later in pregnancy, developmental delays and other CNS effects have been described at even higher frequencies.[2] Isotretinoin prescription rates rose rapidly during the 1980s and 1990s, with annual estimates of new isotretinoin prescriptions to females exceeding 200 000 per year by 2003, with most of these women being of childbearing age (15–45 years).[3] The potential public health burden of isotretinoin-related fetal effects is, therefore, substantial. Less quantifiable, but important, is the psychological burden to the mother following her awareness of a fetal exposure, which could be further affected by the pregnancy outcome.

Isotretinoin is highly effective in the treatment of acne vulgaris (particularly severe nodular acne), making its use common in young women of reproductive age.[4] Patients in this population are often sexually active, although they may not perceive themselves to be at risk of an unintended pregnancy. Consequently, despite the preventable nature of iso-

tretinoin-related birth defects, minimising this risk by preventing exposure to isotretinoin during pregnancy has proven extremely difficult in practice.

1. Brief History of Isotretinoin Risk Management

Isotretinoin was first marketed in the US in 1982, and was labelled as being contraindicated in pregnancy, that is, 'Pregnancy: Category X', because of its animal teratogenicity.[5-7] Risk management initially only consisted of professional product labelling; within the first year of marketing there were reports to the US FDA of fetal exposure resulting in birth defects, launching a series of attempts by the FDA and the manufacturer to inform physicians of the drug's risks, including label changes and the issuing of 'Dear Doctor' letters on ten separate occasions from 1983 through to 1988.

The Accutane® Pregnancy Prevention Program (PPP), established in 1988 by Hoffman LaRoche, the drug's manufacturer, was an educational outreach programme, directed at physicians and patients, that attempted to reduce the occurrence of exposure of pregnancies to isotretinoin, which was estimated to occur at a rate of approximately 4 per 1000 new prescriptions.[8] One element of the programme, blister packaging of Accutane®, became well known for its symbol of a cartoon silhouette of a pregnant woman with a red circle and slashed line superimposed upon her (figure 1). Ten years later, reports of exposure to isotretinoin during pregnancy had declined to an estimated rate of 2 per 1000 new prescriptions, but use of the drug was growing rapidly, predominantly in young women of reproductive age, resulting in a public health burden of exposed pregnancies that was unchanged.[8]

Following extensive discussion at an FDA advisory committee meeting, the PPP was strengthened in 2002 with the implementation of the System to Manage Accutane®-Related Teratogenicity (SMART™).[2] SMART bolstered the educational aspects of PPP, but was designed to more actively

Fig. 1. Accutane® Blister Package 1988 used as a component of the risk management for isotretinoin (courtesy of EE Leach).

ensure that prescriptions for women of reproductive age would not be dispensed isotretinoin without having undergone pregnancy testing. Prescribers who enrolled in the programme were provided with yellow stickers to sign and affix to isotretinoin prescriptions as a means of attesting that the patients had undertaken a pregnancy test, that this had been negative and that contraceptive counselling had been provided.[9] Pharmacists were encouraged to only dispense isotretinoin to female patients if the sticker was present and had been filled out.

Shortly after SMART™ was implemented, generic versions of isotretinoin were introduced to the US market. The FDA requested that manufacturers of generic isotretinoin meet the same conditions for risk management as were in place for Accutane®, resulting in each generic product having its own version of SMART™, but under a different name (SPIRIT™, IMPART™, ALERT™).[1] These programmes were often referred to as 'sticker-based programmes'.

Monitoring and assessing the performance of the sticker-based programmes was difficult. For example, low enrolment occurred in a voluntary patient survey.[10] It provided qualitative information about the programme, but not overall rates of participation by physicians or compliance metrics. Studies undertaken by the manufacturers of isotretinoin showed

1 SMART™: System to Manage Accutane-Related Teratogenicity® (Roche); SPIRIT™: System to Prevent Isotretinoin-Related Issues of Teratogenicity (Mylan); IMPART™: Isotretinoin Medication Programme: Alerting you to the Risks of Teratogenicity (Ranbaxy); ALERT™: Adverse Event Learning and Education Regarding Teratogenicity (Barr).

that the compliance of physicians with pregnancy testing was poor, despite the presence of completed stickers on prescriptions.[10] In addition, there was no means, other than through spontaneous adverse event reports and the voluntary survey, to determine whether patients were enrolling in more than one sticker-based programme or whether pregnancy exposures were occurring, and no way to accurately gauge the size of the population of reproductive-aged women using isotretinoin. This made the fundamental goal of the programme, minimisation of exposure during pregnancy, difficult to assess.

Once again, these issues were discussed at an FDA advisory committee meeting in February 2004.[3] That committee, composed of dermatologists and drug safety experts, stressed the importance of tighter controls to minimise exposure to isotretinoin during pregnancy, even with the recognition that such controls could significantly affect the practice of medicine. Specific recommendations included the need for the cooperation of manufacturers to provide a single risk-management programme for all isotretinoin products; a closed system that required the participation of all patients, not just women of childbearing potential; and an intrinsic mechanism to measure programme performance.

2. The iPLEDGE™ Risk-Management System

All major recommendations of the 2004 FDA advisory committee were incorporated into iPLEDGE™, the new isotretinoin risk-management programme, that was approved by FDA in August 2005.[11] The specific details of iPLEDGE™ were announced in November 2005,[12] providing an opportunity for early enrolment in the programme by physicians, pharmacists and wholesalers; the programme was fully implemented on 1 March 2006. iPLEDGE™ employs technology that builds on the content of SMART. The programme is robust in that it includes wholesalers, pharmacies, prescribers and patients, all of whom must agree to the requirements of the programme in order to have access to isotretinoin. All US manufacturers of isotretinoin, including generic manufacturers, participate in the same programme. The stated goals of iPLEDGE are to "prevent pregnancies in females taking isotretinoin and to prevent pregnant females from taking isotretinoin".[12]

The heart of iPLEDGE™ is its performance-linked access system (PLAS), an automated system of checks and balances that links the data provided by all participants in the prescribing loop.[12] Interfaces with the system by each participant occur via telephone or Internet contacts that the participant initiates. The roles and responsibilities of all parties in becoming registered and activated in iPLEDGE™ are outlined in table I.[12]

As in the sticker-based programmes, prescribers are registered in iPLEDGE™.[12] The registration of wholesalers, pharmacies and patients are all new elements in iPLEDGE™. The development of a single system through a partnership between an innovator firm and its generic competitors is unprecedented.

2.1 Wholesalers and Distributors

A novel aspect of iPLEDGE™ is that it includes drug wholesalers (including distributors) who are registered after signing an annual agreement to ship isotretinoin only to registered and activated pharmacies or other registered wholesalers and to provide certain product flow data to the manufacturers of isotretinoin.[12] This tracking is intended to minimise diversion of the product to nonparticipating pharmacies and patients. Violation of the agreement will result in the cessation of isotretinoin sales by the manufacturers to that wholesaler or distributor.

2.2 Pharmacies and Pharmacists

At the retail pharmacy level, additional controls are employed. In contrast to the previous sticker-based programmes, in which any pharmacy could dispense isotretinoin (even without ensuring that a yellow sticker was present and completed), now only pharmacies that are registered (by submitting some basic demographic information) and activated in iPLEDGE™ may purchase isotretinoin from wholesalers.[12] Activation requires that a pharmacist at the registered site provides information to

Table I. Components of registration and activation in the iPLEDGE™ risk-management programme for isotretinoin[12]

Participant	Registration	Activation/qualification	Comment
Isotretinoin manufacturers	N/A	N/A	Co-operatively designed, run and maintain iPLEDGE™[a]
Wholesalers and distributors	Sell and ship to only registered and activated pharmacies or registered wholesalers or distributors[a] Notify manufacturer of any nonregistered/nonactivated pharmacy or unregistered wholesaler attempts to order isotretinoin[a] Provide select product flow data to manufacturers[a]	N/A	Annual renewal required[a]
Retail pharmacies	Sign up and receive educational and other instruction material[a]	Responsible site pharmacist: Attests to relevant knowledge and competencies[a] Agrees to train all site pharmacists on iPLEDGE™ programme requirements[a] Agrees to dispense only to registered and qualified patients[a]	Annual renewal required[a] Pharmacist must obtain authorisation via iPLEDGE™ and write authorisation number on isotretinoin prescriptions[a] Isotretinoin must only be dispensed with no more than a 30-day supply, with the Medication Guide, in response to a new prescription (no refills), after authorisation from the iPLEDGE™ programme and within 7 days of office visit
Prescribers	Sign up and receive educational and other instruction material	Attests to relevant knowledge and competencies Agrees to comply with iPLEDGE™ programme requirements[a] Agrees to report any exposure to isotretinoin during pregnancy to the pregnancy registry[a]	Annual renewal required[a] Staff may be designated to perform data entry[a] To prescribe isotretinoin, prescriber must register patient in iPLEDGE™ and confirm monthly counselling[a] For females of childbearing potential[b], the prescriber must enter the two forms of contraception used by the patient and enter the monthly pregnancy test result[a]
Patients	Registered by physician (ID number assigned; informed consent confirmed; contraceptive counselling reported; demographic data entered in system)[a]	For females of childbearing potential only: Physician entered result of laboratory pregnancy test[a] Physician-entered and separately patient-entered chosen contraceptive methods match[a] Patient demonstrates understanding of risk and its management[a]	Pregnancy test must be performed by a CLIA-certified laboratory[a] Documented contraceptive counselling and pregnancy test occur monthly Patient qualification occurs monthly[a] Prescription dispensed only when a patient is confirmed by pharmacist to be qualified in iPLEDGE™[a]

a Items new to iPLEDGE™ and not a part of previous risk management programme.

b Defined as nonmenopausal women who have not undergone a hysterectomy or bilateral oophorectomy and who do not have medically documented ovarian failure.

CLIA = Clinical Laboratory Improvement Amendment; **ID** = identification; **N/A** = not applicable.

iPLEDGE™ to attest to having the relevant knowledge and competencies to safely dispense the drug, that they agree to dispense it only to patients who are registered and qualified in iPLEDGE™ and that they agree to train other pharmacists at that site about iPLEDGE™ and compliance with its procedures. Once activated, pharmacists at the registered pharmacy may access the relevant components of iPLEDGE™ to confirm that patients qualify to receive isotretinoin, and to order, receive and dispense the drug. Pharmacy activation must be renewed annually.

2.3 Prescribers

Analogous to the previous sticker-based programmes, prescribers first register in iPLEDGE™ by applying, via telephone or the Internet, to receive iPLEDGE™ educational materials.[12] Activation occurs once the prescriber has attested that they have reviewed the materials and are in possession of the relevant competencies, and have agreed to comply with the requirements of iPLEDGE™. Prescriber activation must be renewed annually. Only prescribers who are registered and activated in iPLEDGE™ (or a designated office staff member) may access the system to register patients, confirm that counselling has occurred and enter pregnancy-test results. Each month, for each patient, regardless of gender, the prescriber must interact with iPLEDGE™ at the time of generating another 30-day prescription, in order for the patient to be qualified, within the system, to have isotretinoin dispensed at the pharmacy.

2.4 Patients

All isotretinoin recipients in the US must be registered in iPLEDGE™ and that registration can only be initiated by a prescriber who is also activated within the system.[12] At registration, the patient is provided with an ID number and the prescriber documents informed consent and enters selected identifying data into the iPLEDGE system. These data are closely protected in the iPLEDGE database and used only to prevent duplicate prescriptions and to facilitate physician follow-up of patients. Once these steps occur, the patient, if she is a female of childbearing potential, still must be 'qualified' in iPLEDGE™ in order to be dispensed a prescription for isotretinoin at the pharmacy. She must be qualified each month to receive a new prescription. Although similar to the qualification of female patients of childbearing potential under the sticker-based programmes, iPLEDGE™ patient qualification differs in the following four ways:

1. The confirmatory pregnancy test and each monthly follow-up pregnancy test must be performed at a Clinical Laboratory Improvement Amendment-certified laboratory.[13]

2. Each month, the prescriber must confirm within iPLEDGE™ that contraceptive counselling has occurred at the monthly patient visit. Monthly contraceptive counselling was required in the previous sticker-based programmes, but the requirement for documentation is new.

3. Every month, the prescriber and the patient each must enter into the iPLEDGE system the primary and secondary forms of contraception that the patient has selected. The primary form entered by the prescriber and patient must be an acceptable form and the two entries must match or the patient will not be qualified. As in previous programmes, abstinence is considered an acceptable form of contraception.

4. Each month, the patient must correctly answer questions intended to reinforce key messages about the iPLEDGE™ programme, such as the risk of fetal harm from exposure to isotretinoin and ways to reduce that risk.

Unlike female patients of childbearing potential, male patients and female patients who cannot become pregnant (e.g. postmenopausal women) do not need to access the iPLEDGE™ system each month to be qualified. They must be registered in the iPLEDGE system initially by the prescriber and the prescriber must interact with the iPLEDGE™ system each month to confirm that the patient understands other key safety and risk-management aspects of taking isotretinoin and the iPLEDGE™ programme requirements (e.g. the importance of not sharing medication and not donating blood). This

information essentially serves as qualification and is noted in the system for the pharmacist.

2.5 Pregnancy Registry

iPLEDGE™ includes a pregnancy registry with critical features that were not part of earlier programmes.[12] As was previously noted, a lack of reliable pregnancy data seriously hampered the ability to determine how many episodes of fetal exposure to isotretinoin were occurring, much less the exposure rate. In iPLEDGE™, as part of activation in the system, pharmacies, prescribers and patients all agree to report any exposure to isotretinoin during pregnancy and its outcome (e.g. elective termination of pregnancy, birth defects) to the registry. Previous programmes raised concerns that women who became pregnant were likely to be lost to follow-up because they may well not have returned to the isotretinoin-prescribing provider.[4]

3. Potential Advantages of iPLEDGE Over Previous Risk-Management Systems

A key advantage of iPLEDGE™ is that it is a comprehensive system with real-time verification of pregnancy test results linked to dispensing of the medication. Despite the requirement for pregnancy testing in earlier programmes, several studies and a review of the manufacturers' prior risk-management systems documented low compliance or an inability to adequately assess compliance.[4,10,14,15] Historically, about 12% of fetal exposures to isotretinoin have been in women who were pregnant at the time of isotretinoin therapy initiation.[16] Such exposure should be virtually eliminated (within the bounds of the sensitivity of pregnancy testing) by full compliance with the pregnancy-testing requirement of iPLEDGE™. Monthly, on-treatment testing will also enable early identification of pregnancies that occur during treatment, thereby minimising fetal exposure. Finally, the monthly interface with the PLAS by the patient is expected to serve as an educational reminder to patients about the importance of maintaining use of effective contraception. A second advantage of iPLEDGE™ is that it merges risk-management efforts for all brands of isotretinoin into a single programme. The fragmentation of risk management that occurred under the various sticker programmes increased the potential for confusion among prescribers and patients, and hampered efforts to evaluate the programmes.[3] With iPLEDGE™, all participants interact with a single system that employs one consistent set of educational materials, requirements and procedures, regardless of whether Accutane® or a generic isotretinoin is dispensed.

A third advantage of iPLEDGE™ is its direct interface with the patient population at the highest risk of exposure of pregnancy to isotretinoin. Contraceptive counselling prior to initiation of isotretinoin therapy, and at monthly follow-up, was recommended in the sticker-based programmes; however, in iPLEDGE™, the prescriber and the patient have to independently confirm that the counselling has occurred. Additionally, the fact that the patient's chosen primary contraception method must match what the provider reports (as well as be an acceptable primary method) helps to ensure that sound communication between the prescriber and the patient occurs. Finally, each month the patient must access the iPLEDGE™ system and correctly answer a series of questions related to her contraceptive choice, reinforcing her understanding of the importance of this step in risk mitigation and her own role in ensuring the programme's success.

A further advantage of iPLEDGE™ is its potential to provide timely information about how the system is working. Specifically, the PLAS and pregnancy registry each have features that will allow for the assessment of process and outcome aspects of the programme through root cause analysis. Although originally developed for the manufacturing industry, this technique is now being applied to patient safety issues.[17-19] For example, rates of patients being denied prescription dispensing (i.e. patients who are not qualified within the system) and the reasons why will be tracked by the PLAS. Actual pregnancy events (including both the occurrence of pregnancy and pregnancy outcomes) and the underlying reasons that they might have occurred will be tracked through the pregnancy register. This type of

information is essential to maximising the effectiveness of the system for those patients who are most at risk and minimising the burdens to those who are least at risk. Finally, mandatory registration of all patients receiving isotretinoin in iPLEDGE™ will provide, for the first time, an accurate denominator to enable assessment of the incidence of reported adverse events, including fetal exposure. Evaluation of previous programmes has been severely hampered by the lack of such data. Voluntary surveys had low enrolment, with no way to determine whether those enrolled were at higher or lower risk of an isotretinoin-exposed pregnancy than those who chose not to participate.[20] There could still be under-reporting of pregnancies to the registry, but an accurate denominator will allow for a more robust assessment of how important a problem this is, and iPLEDGE™ will provide information on how often women of reproductive age are lost to follow-up and how they differ from those who stay in the programme.

4. Initial Challenges and Potential Disadvantages of iPLEDGE™

The iPLEDGE™ programme is clearly a departure from how most high-risk drugs are managed within the US healthcare system and its implementation was expected to be a daunting task, despite careful planning and development. It is the largest risk-minimisation programme that has ever been implemented for a drug. Restricted distribution programmes for other medications have typically begun at the time of initial marketing or shortly thereafter and have involved drugs with far less use, such as thalidomide, clozapine and alosetron.[9,21]

First and foremost, the requirement of the programme for changes in clinical practice routines for the treatment of severe acne was obvious to planners of the programme, but still took practitioners by surprise. Media reports, calls to the iPLEDGE™ call centre and calls to the FDA over the first few months of the programme attested to the disruption to usual prescribing processes that followed implementation of iPLEDGE™ (figure 2). Many dermatologists, in particular, described frustration.[22] They cited concerns about the programme's activation process for themselves and office designees, as well as the time it takes to fully counsel, register and qualify patients. For many, another source of frustration was having to enrol all patients, not only those at risk of pregnancy. Many small office practices are not set up to work with a highly detailed risk-management programme for a commonly prescribed medication.

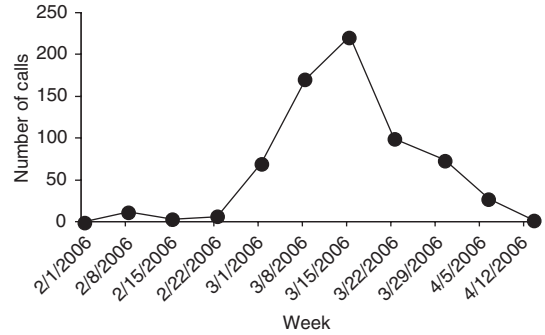

Fig. 2. Volume of calls to the US FDA's Division of Drug Information regarding the iPLEDGE™ risk-management programme for isotretinoin by week (February–April 2006). Dates provided are the midpoint of the week.

Based on FDA testing, data entry by providers to register a female patient of childbearing potential at the initial visit is estimated to take 1–2 minutes, and data entry at follow-up visits is estimated at 30 seconds. However, this does not include the time taken to address initial patient questions about the programme; problems that might arise as part of data entry; or the answering of patients' questions over the telephone, by email or in follow-up should they encounter difficulties with the system. This can be compounded in practices that employ isotretinoin for uses other than the treatment of acne vulgaris, such as for certain paediatric malignancies.

An iPLEDGE™ call centre is available to assist with questions and problems. Call centre wait times were extremely long (with reports of some waits for several hours) during the first month of iPLEDGE™ operation. The time to access a call-centre assistant has since decreased to several minutes as staffing has increased, procedures have been simplified and participants have learned to navigate the system (Isotretinoin Product Group Manufacturers, personal communication).

Other concerns raised about the programme include the time it takes for pharmacies to interface with it, the challenges of using protected passwords to allow patients to become activated in the system (e.g. lost passwords, missing time-limit deadlines for data entry) and the time needed to educate patients about the system and its rationale. In addition, the reality is that, not only is pregnancy prevention very personal for patients, effective pregnancy prevention is something that most nonobstetric providers have limited experience with in clinical practice.

There has been concern that an unintended consequence of iPLEDGE™ might be that isotretinoin will be less accessible to patients who could benefit from it because providers or pharmacies may elect to not participate. Should physicians elect not to participate, patients with limited access to healthcare because of insurance restrictions or geography might have difficulties obtaining isotretinoin. The new programme also enforces the requirement for monthly office visits. The same procedure was recommended under previous risk-management programmes, but the iPLEDGE™ documentation of such interactions specifically seeks to minimise nonadherence. This might be a problem for patients in remote areas or those who have employment or child care responsibilities that make office visits difficult. In the first 6 months after the programme became mandatory, fewer participants than were expected had been registered and activated in iPLEDGE™, although registration and activation of new participants continues (table II).

There is no question that rigorous risk minimisation programmes can decrease the use of a medication, which some might perceive as a disadvantage of iPLEDGE™ and others might contend would be a good way to minimise off-label use. However, decreased use is not a goal of the programme. The programme must balance the need to ensure safe use with the burdens of cost and inconvenience, so that patients who need isotretinoin may access the drug through legitimate means. These considerations were at the forefront of the design of iPLEDGE™. If this balance is not achieved, patients and prescribers might seek the drug through unauthorised sources or outside the usual healthcare provider-patient relationship.

Isotretinoin is widely available via Internet sources, many of which do not require a prescription from a physician,[9] and medication sharing is not uncommon, with approximately 20% of adolescent girls reporting this practice in one survey.[24] Patients who receive isotretinoin from any of these sources are not likely to have adequate, if any, education about the risks associated with the drug and risk mitigation measures or appropriate monitoring for adverse events. They might be less likely to report any adverse event (including fetal exposure) that occurs during isotretinoin therapy. The FDA and the manufacturers of isotretinoin have developed strategies to monitor and shut down Internet sales of isotretinoin and to discourage patients from attempting to purchase it in this manner. However, the availability of the drug from unapproved non-US sources will continue to make this aspect of managing the risks of isotretinoin difficult.

5. Current Operations and Evaluation

The majority of retail pharmacies in the US have registered and activated to participate in the

Table II. Participation in iPLEDGE™ risk-management programme for isotretinoin as of 30 November 2006[a]

Participant	Anticipated potential participation[23]	Registered	Activated
Wholesalers and distributors	298	190	N/A
Retail pharmacies	55 000	51 912	45 868
Physicians	36 000[b]	27 456	16 471
Patients	Unknown	244 283	N/A

a Isotretinoin Product Manufacturers' Group, 18 August 2006, personal communication.

b Based on the number of prescribers enrolled in the sticker riskMAPs during the 3 years preceding the full implementation of iPLEDGE™.

N/A = not applicable; **riskMAP** = risk minimisation action plan.

iPLEDGE™ programme (table II). Over 27 000 prescribers have registered, with about two-thirds of these having been activated. Programme outreach has been targeted to dermatologists, historically the most frequent prescribers of isotretinoin, and other physicians previously registered in the sticker programmes. iPLEDGE™ was modelled after the well established risk-management programme for thalidomide;[25] however, the volume of isotretinoin use in the US far exceeds that of thalidomide, thus amplifying the challenges associated with its implementation. Despite rigorous planning and outreach with measures to minimise disruption to practice, the first few months of the implementation of iPLEDGE™ were difficult. The combination of a widely prescribed, previously unrestricted medication that has its greatest use in patients at the highest risk with minimal participation in the pre-registration programme by potentially participating pharmacies and physicians and an electronic system that did not fully anticipate real-world user needs resulted in a decline in isotretinoin prescriptions being filled in the early weeks of the programme. As users have become more comfortable with the mechanics of iPLEDGE™ and problematic programme elements have been addressed by the manufacturers of isotretinoin, prescribing has stabilised. Also, the rate at which patients' prescriptions are being denied at the pharmacy has declined (Isotretinoin Product Manufacturers' Group, personal communication). The most common reasons for prescriptions being denied involve a lack of compliance on the part of the patient or the prescriber, including no documentation on patient contraception counselling in the system, the patient not answering the monthly questions, the patient not filling the prescription within the allotted time window of the utility of a pregnancy test (7 days), the patient attempting to fill more than one prescription within 1 month and monthly pregnancy test results having not been entered into the system (Isotretinoin Product Group Manufacturers, personal communication).

5.1 Mitigating Risk

Formal metrics for assessing the impact of iPLEDGE™ are under development. As a closed system, it has the potential to capture more complete pregnancy exposure and process-measure data than any previous programme. Listed are the types of data and potential information that will be available from iPLEDGE™, all of which will be essential to understanding whether and how well the risks associated with isotretinoin use are being mitigated.

- The number of patients who are pregnant at the time of their first prescription, including those who were denied qualification and dispensing.
- The number of pregnancies occurring during the course of isotretinoin treatment. Some female patients who discover a pregnancy before their routine monthly pregnancy test might not return to their isotretinoin prescriber, but the programme is designed to allow for active follow-up should this occur.
- Rates of compliance with certain elements of the iPLEDGE™ programme, such as pregnancy testing and prescriber counselling of the patient, as well as patient reports about their own adherence to their chosen contraceptive methods.
- Patient comprehension of educational messages about the risks associated with isotretinoin and how to minimise them.

It will be much more difficult to capture information on the extent to which isotretinoin is accessed outside of the iPLEDGE™ programme through medication sharing or internet sales. Current drug-use data sources capture sales and prescription activity of US sources, including that of retail pharmacies (chain, independent, food stores and mail order), mass merchandisers, pharmacy benefits managers and their data systems and provider groups. Most medication sourcing that occurs over the Internet is not captured by these data, especially if the product is obtained from foreign countries. The pregnancy registry root-cause analysis might provide clues that will assist in understanding the extent of such use and the means to combat it. However, the reality of isotretinoin availability outside of iPLEDGE™ is a reminder that robust data from the programme will

require full participation from all of the parties in the isotretinoin prescribing loop, making it essential to address unnecessary or exceptionally troublesome aspects of the programme.

The greatest challenge when assessing iPLEDGE™ will be determining whether the programme is meetings its objectives. This programme will provide far more, and far more specific, data than its predecessors, which must be taken into account in making temporal comparisons of pregnancy data. For example, it is possible that, with more complete reporting under iPLEDGE™, a higher number or rate of fetal exposures will be reported in comparison to those captured (mostly through spontaneous adverse event reports and voluntary surveys) during earlier programmes.

6. Pragmatism and Public Health

The collaboration of multiple pharmaceutical firms in building and operating a long-term risk-management programme with the rigor of iPLEDGE™ attests to the level of public concern raised by two decades of reports of fetal exposure to a known teratogen as well as the important role isotretinoin has in the treatment of severe acne vulgaris.

Even the most rigorous risk-management programme cannot completely prevent human error or contraceptive failure. Some fetal exposures to isotretinoin are likely to occur even if compliance with iPLEDGE™ processes and testing are optimal. This likelihood cannot and should not be the rationale for the thousands of healthcare providers, manufacturers and regulators to give up on attempts to minimise exposure. Data from the programme should greatly assist in understanding the impact of iPLEDGE™ in moving toward the ideal but perhaps unachievable goal of zero pregnancies exposed to isotretinoin. It will also be useful to identify sources of adverse event reporting outside iPLEDGE™ that might capture events occurring among patients receiving isotretinoin, either those that occur in patients enrolled in iPLEDGE™ that were not reported through the iPLEDGE™ system or those in patients receiving the drug from other sources. For example, in addition to the FDA's Adverse Events Reporting System, the Organisation of Teratology Information Services (OTIS), which has previously conducted research on reasons why pregnancies are exposed to isotretinoin,[14] is a potential source of cases of exposure that are not captured by the iPLEDGE™ system.

Finally, there is no question that substantial effort will be required from every participant in iPLEDGE™, from manufacturers to patients, even as the programme is streamlined over time. Questions will continue to be raised regarding the magnitude of inconvenience that iPLEDGE™ imposes in relation to its effectiveness in mitigating fetal exposure to isotretinoin. These important issues must be raised and vigorously discussed in public forums, employing data from iPLEDGE™ to inform debate, not just by regulators and public health agencies, but by all those potentially affected.

7. Conclusions

Birth defects are a leading cause of infant mortality in the US, and a major contributor to childhood disability.[26,27] It is not currently possible to prevent the majority of major birth defects because their causes are not known. In contrast, the major birth defects and disability caused by isotretinoin exposure during pregnancy are, in theory, completely preventable. Isotretinoin risk management is both extremely challenging and an important public health priority. There are both advantages and disadvantages to the iPLEDGE™ system, which has grown out of ≤24 years of restrictive programmes that resulted in unacceptable rates of preventable fetal exposures. Modifications to the programme are likely to be needed to enhance its operation, make it more readily accessible and facilitate its ease of use by all potential participants. If iPLEDGE™ can prevent fetal exposure to this teratogenic medication, it will have made a positive contribution to public health.

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