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Can We Ensure the Safe Use of Known Human Teratogens?

Introduction of Generic Isotretinoin in the US as an Example

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Abstract

The prescription of known teratogenic medications requires a careful balance between allowing women access to medications that they might need and avoiding unnecessary exposure to these medications during pregnancy because of their devastating fetal effects. Isotretinoin, a potent human teratogen, is of particular concern because of its widespread use among reproductive-aged women and the dramatic increase in use from 1992 through 2000. A revised risk management system was implemented in 2002 because of concerns about the continued occurrence of isotretinoin-exposed pregnancies. However, the recent approval of three generic versions of isotretinoin in the US has further complicated risk management and raises concerns that use might increase further if the lower cost of generics serves to increase accessibility. There are now four separate isotretinoin risk management systems in the US, each with its own distinct packaging, though the requirements for and substance of each are identical. Some additional concrete steps could be taken to minimise any unnecessary use of isotretinoin and help allow an adequate assessment of the current risk management systems. In addition to being familiar with and following all aspects of the current risk management system, physicians could choose to limit the use of isotretinoin to those who meet the labelled indications in order to reduce the number of exposed pregnancies. All four companies currently marketing isotretinoin in the US could jointly and voluntarily establish a consolidated, mandatory registration and follow-up of all women of reproductive potential who receive an isotretinoin prescription. Mandatory registration has many challenges, but it could allow a clear accounting of the total number of women for whom follow-up information is and is not available. Although the companies cannot be legally compelled to use a consolidated approach, the use of a single registry for the originator's product and all generic brands would allow identification of duplicates and also avoid the confusion that is introduced by providing materials that not only look different, but also have different addresses, contact information and names for participation in follow-up surveys. This is particularly important because women might take more than one version of isotretinoin during a single course of therapy or might receive a different programme's materials from their doctor than from the pharmacy. Though the introduction of generic versions of isotretinoin further complicates

risk management, the companies marketing isotretinoin have an opportunity to work together to demonstrate their commitment to both limit the occurrence of exposed pregnancies and conduct a meaningful evaluation of the occurrence of pregnancies exposed to isotretinoin.

Healthcare providers and public health workers have struggled with the issue of ensuring the safe use of medications during pregnancy since the identification of aminopterin and thalidomide as human teratogens in the 1950s.[1-4] For many medications, the primary concern is one of unknown safety during pregnancy. However, for known human teratogens, the challenge lies in finding the appropriate balance between allowing women access to medications that they might need and avoiding unnecessary exposure to these medications during pregnancy because of their devastating fetal effects.

Prescription drug use is common during pregnancy,[5,6] with women in the US filling an average of about three nonvitamin prescriptions during pregnancy.[7-9] Even higher rates of prescription drug use during pregnancy have been reported in France.[10] Many of the prescriptions filled by pregnant women have possible adverse effects on the fetus.[11-14] While some prescription drugs, such as those used to treat seizure disorders or asthma, are necessary for certain women during pregnancy,[15,16] often the use is inadvertent. The challenge in the use of known human teratogens is exacerbated in the US, which has the highest rate of births to teenage mothers in the developed world and where approximately half of all pregnancies are unintended;[17,18] these factors translate into a greater risk for a time delay before recognition of pregnancy and thus also a delay in modifying any exposures.

A number of prescription medications currently in use are known to have teratogenic effects on the fetus if used during pregnancy.[19] These known human teratogens include isotretinoin, thalidomide, warfarin, valproic acid, phenytoin and ACE inhibitors.[15,20-28] While all are obviously of concern, isotretinoin is particularly concerning because (i) isotretinoin is the teratogenic medication most widely used by reproductive-aged women in the US;[29,30] (ii) use of isotretinoin has increased dramatically in the past decade;[30] (iii) isotretinoin is increasingly being prescribed for uses not indicated on the package label, such as mild to moderate acne (off-label use);[31] (iv) isotretinoin might be used to increase beauty and sexual attractiveness;[32] (v) isotretinoin is widely available under a variety of names and at a wide range of prices via online pharmacies; and (vi) generic versions of isotretinoin are now approved and available in the US. With the recent introduction of generic isotretinoin, it is now even more critical to have a system in place to evaluate the extent to which this known teratogen is being used in an unsafe manner and the effectiveness of the programmes designed to promote safer use. This evaluation must be conducted on an ongoing basis and be capable of providing concrete numbers to assess the success of various components of the programmes being used.

The aim of this review is to evaluate the impact of introducing generic versions of known human teratogens on risk management efforts for these medications. The introduction of generic isotretinoin in the US is presented as an example. We suggest strategies to reduce the occurrence of pregnancies exposed to teratogens as well as methods needed to conduct a meaningful evaluation of pregnancy prevention efforts.

1. Frequency of Use of Known Teratogens

As the number of reproductive-aged women using a teratogenic medication increases, the number of exposed pregnancies will increase, even if the rate of exposed pregnancies remains constant. However, there might also be an increase in the rate of exposed pregnancies with more widespread use because increasing use might reflect less discriminate prescribing both by indication and appropriateness of the

patient. A number of factors can increase the use of teratogenic medications including (i) advertising; (ii) lack of effective (non-teratogenic) alternative therapies; (iii) medication sharing; (iv) lack of perceived risk of pregnancy or adverse outcome or underestimation of risk; (v) ease in obtaining a prescription; and (vi) off-label use.

Direct-to-consumer (DTC) advertising of prescription drugs has increased dramatically over the past decade and there has been a parallel increase in sales of the most heavily advertised prescription medications.[33] DTC advertising increases the number of patients who specifically ask their physicians about a particular medication and/or request a prescription for that medication.[34,35] Roche Laboratories began unbranded DTC advertising for prescription acne medication in 1996, raising concerns of an increase in use among reproductive-aged women and an increase in the occurrence of exposed pregnancies. While a particular spike in use coincident with the introduction of DTC advertising was not noted, from 1992 to 2000 there was a 250% increase in the number of isotretinoin prescriptions.[30] Roche did note a strong relation between DTC advertising and sales of isotretinoin.[36] Of concern, there was a large increase in the proportion of isotretinoin prescribed for mild to moderate acne (off-label use).[30]

The lack of effective alternative, nonteratogenic therapies can lead to increased use of some known teratogens such as isotretinoin.[37] Available information suggests that isotretinoin is widely promoted by former and current users to friends and family.[32] While data are limited, there is also evidence that sharing prescription acne medication is not uncommon among adolescents.[38] In addition, the Internet is now widely used to exchange information on obtaining and using acne medications including isotretinoin.

Another factor that might increase the use of known teratogens such as isotretinoin among reproductive-aged women is a lack of perceived risk on the part of both healthcare providers and their female patients. If the risk is not effectively communicated, patients and healthcare providers may underestimate the true risk. Because the majority of exposed pregnancies result in spontaneous or induced abortions,[39] healthcare providers might not be aware of the magnitude of the problem and might perceive a more limited risk. The perceived severity of having an exposed pregnancy that results in a spontaneous or induced abortion will vary greatly for different women. There is also an assumption among many women that an unintended pregnancy will not happen to them.[40]

The ease or difficulty in obtaining a prescription will also influence the frequency of use of teratogenic medications. Factors that are likely to increase use include access to medical care, availability of all physicians to write prescriptions, low cost and availability from community and online pharmacies. Factors that would be expected to decrease use include lack of access to medical care, restriction of prescription writing to specialists (e.g. allowing only dermatologists to prescribe isotretinoin), restriction of dispensing to certain pharmacies or pharmacists and higher cost. Factors have operated in both directions in recent years. The price of Accutane®[1] in the US increased by 50% from 1997 to 2000 and the cost is two to four times higher in the US than in other countries.[41] The last few years have also witnessed a dramatic increase in the availability of prescription medications online, both with and without prescriptions. As with many prescription medications, the large price differential for isotretinoin between the US and neighbouring countries could encourage its importation.

Off-label use will also increase the number of reproductive-aged women using a known teratogen. The only labelled indication for isotretinoin is for treating severe, recalcitrant nodular acne. However, off-label use of isotretinoin for less severe indications is widespread[42-45] and has even been recommended by a professional consensus meeting.[42] There is a discrepancy in use by sex. While isotretinoin use is approximately equal for men and women, men are more likely to have the severe, recalcitrant, nodular acne that meets the indicated use for

1 The use of trade names is for product identification purposes only and does not imply endorsement.

isotretinoin[46] and women are almost twice as likely as men to visit a physician for acne.[47] This implies either men are under-utilising isotretinoin or women are over-utilising it. There is also evidence that less teratogenic alternative medications are not being utilised prior to prescribing isotretinoin.[48] Use of isotretinoin is estimated to be eight to ten times lower in some European countries than in the US.[49] The relatively high use of isotretinoin in the US is probably due to differences in the healthcare systems and prescribing practices.

2. Risk Management Systems for Known Teratogens

2.1 Experience in the US

The human teratogenicity of most medications is unknown when they are first marketed. However, isotretinoin was labelled as a pregnancy category X drug by the US FDA when it was first marketed in 1982, based on demonstrated animal teratogenicity, indicating the likelihood of human teratogenicity.[50-52] The reporting of isotretinoin embryopathy in humans[20,53,54] made evident the need for a rigorous system in the US to prevent pregnancies exposed to this known teratogen.

The Pregnancy Prevention Programme (PPP) was established in the US by Roche in 1988 in an attempt to address this need. The PPP asked female users of isotretinoin to voluntarily enrol in a survey administered by Boston University's Slone Epidemiology Unit. Women were able to enrol only during their first course of isotretinoin and were paid $US10 upon enrolment. Follow-up was conducted to assess knowledge and behaviours, including use of contraceptives, pregnancy tests prior to prescription, pregnancies and pregnancy outcomes. The PPP enrolled approximately 45% of reproductive-aged women using isotretinoin;[55] no information was available on the 55% of the reproductive-aged women using isotretinoin who did not voluntarily enrol. Among those women enrolled in PPP, 36% did not have any type of pregnancy test prior to beginning treatment with isotretinoin.[39] Of most concern is that, despite the existence of this registration system, pregnancies exposed to isotretinoin continued to occur.[29,55,56]

To address some of these concerns, Hoffman-La Roche Inc. established the System to Manage Accutane® Related Teratogenicity™ (S.M.A.R.T.™) to replace the PPP in 2002.[57] S.M.A.R.T.™ retains the voluntary registration of the PPP but has added a number of elements including (i) a requirement for two negative pregnancy tests prior to the first prescription with the second pregnancy test occurring during menses; (ii) qualification stickers on each prescription to confirm that the patient has agreed to use two forms of contraception and has signed an informed consent about the teratogenic risks of isotretinoin, as well as to verify that the physician has confirmed the negative pregnancy tests and has counselled the patient about participation in the voluntary follow-up survey; (iii) a requirement that prescriptions not be filled without a qualification sticker; (iv) a requirement that prescriptions not be filled more than 7 days beyond the qualification date on the sticker; (v) a restriction of all prescriptions to a 30-day supply; (vi) no automatic refills or phoned-in prescriptions are allowed; and (vii) increased incentives for survey participation ($US20 at enrolment and $US10 more at completion of follow-up). Patients and physicians who use isotretinoin without following all the applicable procedures detailed in the risk management programme are considered to be using the drug in an unsafe manner. The FDA has required assessment of the S.M.A.R.T.™ programme to document that these new procedures are being followed and that voluntary enrolment and compliance with procedures have improved above that observed during the PPP. The FDA requires that Roche conduct this evaluation on the first 12 full months of data from the S.M.A.R.T.™ programme and has indicated to Roche that failure to achieve agreed-upon metrics for success of the programme will result in the need for more significant restrictions. Similar, but distinct, risk management systems have been developed for generic versions of isotretinoin (see section 3.2).

The known teratogen thalidomide has a more rigid registration system than isotretinoin, while oth-

er known teratogens have more lax systems or no system at all. The System for Thalidomide Education and Prescribing Safety™ (S.T.E.P.S.™) was established as a condition of approval when thalidomide was approved by the FDA for the first time ever in 1998. S.T.E.P.S.™ requires mandatory registration of all prescribers, pharmacists and patients.[58] The initial approval of thalidomide was for the treatment of erythema nodosum leprosum, but both the expectation and actual experience is that the majority of thalidomide prescriptions in the US are for off-label uses.[59] While many adverse events have been reported to this programme, only one confirmed pregnancy exposed to thalidomide has been documented to date and that pregnancy outcome was a first trimester spontaneous abortion.[60] Changes to the S.T.E.P.S.™ programme were implemented in 2001 to make the checks between patient registration, prescription and dispensation of the medication at the pharmacy occur in real time allowing enforcement of the programme to occur in a timely manner (Zeldis J, personal communication). However, the differences between isotretinoin and thalidomide are not limited to their risk management systems. Isotretinoin is much more frequently used than thalidomide by healthy, reproductive-aged women. The number of prescriptions for isotretinoin in 3 months exceeds the total number of prescriptions for thalidomide over the past 5 years (Kweder S, personal communication). Only about 4000 women of childbearing potential have used thalidomide in the US in the past 6 years.[60] Thalidomide is used by women with very serious health problems that can limit sexual activity and fertility. In addition, women taking isotretinoin might perceive themselves as more attractive after starting therapy[32] and this change in self-perception could result in an increase in sexual activity, assuming that they have not experienced excessive drying of the mucous membranes that can occur as an adverse effect of isotretinoin. Thus, while the teratogenicity of isotretinoin and thalidomide is similar, the risks of pregnancy are probably much higher for isotretinoin than for thalidomide. Even though the management of the mandatory registration system is complex for thalidomide, it would likely be more challenging for isotretinoin because of its more frequent use and the differences in the patient populations.

Other known or suspected teratogens are monitored by voluntary pregnancy registries. For example, most seizure medications are monitored by the antiepileptic drug registry.[61] The registry is supported by companies marketing certain prescription antiepileptic medications, but scientific decisions are made by an independent scientific advisory committee. This voluntary registry enrols women taking the monitored antiepileptic medications early in pregnancy and follows them prospectively for any adverse outcomes, including major birth defects. Pregnancy registries have the potential to identify important information about any teratogenic effects of medications. However, many pregnancy registries are voluntary efforts by the manufacturers rather than regulatory requirements and they do not directly evaluate or affect how these medications are currently prescribed and used. Nonetheless, these registries can provide preliminary human data that can better inform women who need these medications during pregnancy.

For all of the current risk management systems, the drug companies marketing the drug bear the cost of the programme. However, it would seem reasonable to assume that these costs are ultimately passed along to the consumers.

Some known teratogens (e.g. warfarin) do not currently have any mechanism in place to specifically monitor their possible use during pregnancy. However, the need for such a mechanism is less clear for drugs that are used less frequently by reproductive-aged women. Nonetheless, there might be considerable benefits in creating a comprehensive and consistent approach to preventing pregnancies being exposed to known teratogens.[62]

2.2 Experience in Other Countries

In addition to the differences between drugs, there is tremendous variation between countries in the methods employed to prevent exposure to known teratogens. Using isotretinoin as the example, some countries restrict prescribing to certain

Table I. International variation in the systems to prevent pregnancy exposures to isotretinoin

Country	Prescribers	Formal programme for prevention of exposed pregnancies
US	Any medical doctor	Yes
		PPP (Accutane®), 1988–2001
		S.M.A.R.T.™ (Accutane®), 2002–present
		S.P.I.R.I.T.™ (Amesteem®), 2002–present
		I.M.P.A.R.T.™ (Sotret®), 2003–present
		A.L.E.R.T.™ (Claravis™), 2003–present
Canada	Any medical doctor	Yes
		PPP, 1988–present
Argentina	Any medical doctor	No
Brazil	Any medical doctor	No
France	Any medical doctor	No
Italy	Any medical doctor	No
New Zealand	Any medical doctor, but only prescriptions from dermatologists are fully funded	No
Australia	Dermatologists only	No
Denmark	Dermatologists or hospitals only	No
Ireland	Dermatologists only	No
Sweden	Dermatologists only	Individually licensed patients from 1984–1988; licensed only dermatologists to prescribe after 1988
UK	Dermatologists only	No
Bolivia	OTC purchase possible	No
Mexico	OTC purchase possible	No
Venezuela	OTC purchase possible	No

A.L.E.R.T. = Adverse Event Learning and Education Regarding Teratogenicity™; **I.M.P.A.R.T.** = Isotretinoin Medication Programme Alerting you to the Risks of Teratogenicity™; **OTC** = over-the-counter; **PPP** = Pregnancy Prevention Programme; **S.M.A.R.T.** = System to Manage Accutane Related Teratogenicity™; **S.P.I.R.I.T.** = System to Prevent Isotretinoin-Related Issues of Teratogenicity™.

specialists, others restrict reimbursement, some use formal prevention programmes and some have essentially no restrictions other than labelling (table I).

A retinoid PPP similar to the US programme was implemented in Canada in 1988. However, as with the US experience, pregnancies exposed to isotretinoin have continued to occur.[63,64] Failure to use contraception played a major role in the occurrence of isotretinoin-exposed pregnancies identified in both countries.[29,63] A Canadian report suggested that non-dermatologists were not familiar with the PPP,[65] though there is no clear information on the proportion of all isotretinoin prescriptions in the US or Canada that are written by non-dermatologists.

Other countries restrict the use of isotretinoin by limiting prescription of this drug to specialists. For example, in the UK, only dermatologists may prescribe isotretinoin and there are often delays in gaining access to dermatologists through the National Health Service.[66] Sweden, Australia and Ireland also limit prescribing of isotretinoin to dermatologists.[67-69] While there are no data to suggest that exposed pregnancies are more or less likely to occur with the prescription of isotretinoin by dermatologists versus non-dermatologists in countries where access to dermatologists is difficult or limited, restricting prescribing to dermatologists may result in less use of isotretinoin.

In the US, any medical doctor may legally prescribe any licensed drug with the exception of controlled substances. However, in our opinion, only physicians who are knowledgeable about the teratogenicity of isotretinoin and the programme established for risk management in the use of this drug should prescribe it. One of the goals of the revised risk management systems for isotretinoin is to en-

sure that physicians are knowledgeable about the teratogenicity of isotretinoin and the programme designed to prevent exposed pregnancies; to this end, physicians are required to attest to their knowledge by signing a form prior to receiving the qualification stickers. We believe further education efforts could encourage physicians who have not completed the appropriate continuing education course or reviewed the risk management programme in detail to decline to prescribe isotretinoin.

3. Impact of Introducing Generic Versions of Known Teratogens

3.1 Impact of Generics

Generic brands are less expensive than brand-name products and the lower cost has the potential to increase the number of individuals using a drug. Lower cost can also encourage more prescriptions for a drug earlier in the course of treatment of a given condition. In the case of isotretinoin, availability of generics might lead to greater use as a first-line drug for mild acne. Health insurance plans usually encourage prescribing generics, which might make physicians more likely to write a prescription now that generics for this drug are available[70] and coverage by a health insurance plan will remove a potential barrier to use and make patients more likely to fill a prescription. All generic versions combined usually account for half of the prescriptions dispensed by 1–3 years after they have entered the market,[71,72] with the first generic to enter the market having the greatest share.[73] As discussed earlier, any increase in isotretinoin use would be expected to result in an increased number of pregnancies exposed to isotretinoin.

3.2 Generic Versions of Isotretinoin in the US

The situation in the US for ensuring the safe use of isotretinoin became enormously more complex as the patent for Accutane® expired and generic brands began to enter the market. Three generic versions of isotretinoin have been approved in the US: Amnesteen® (approved November 2002); Sotret® (approved December 2002) and Claravis™ (approved April 2003). Because the features of the S.M.A.R.T.™ programme are part of the product labelling, all generic versions are required to include the same messages and procedures approved for Accutane®. However, the company marketing each generic brand has had to develop its own look and name for the programme. Amnesteen® is monitored by the System to Prevent Isotretinoin-Related Issues of Teratogenicity™ (S.P.I.R.I.T™); Sotret® is monitored by the Isotretinoin Medication Programme Alerting you to the Risks of Teratogenicity™ (I.M.P.A.R.T.™); and Claravis™ is monitored by the Adverse Event Learning and Education Regarding Teratogenicity™ (A.L.E.R.T.™). While each company marketing isotretinoin provides materials that contain the required information, each company's materials also contain clear differences in order to distinguish their product and this could be confusing to women and to their healthcare providers. The healthcare provider might not know which product the patient will receive at her pharmacy, because that will be influenced by the pharmacy she uses and the requirements of her health insurance. Programmes for all versions of isotretinoin provide reimbursement for contraceptive counselling and pregnancy tests. However, any requested counselling will likely be done before the prescription is dispensed and before the woman knows whether she will receive Accutane® or one of the generic brands. Presumably, many women will receive materials and enrolment forms from one programme at their healthcare provider's office and could receive a different unique set of materials and enrolment forms from the pharmacy with their prescription. Women might be unsure whether to enrol in two programmes or neither and duplicate enrolments cannot be identified because of the use of separate vendors for the Accutane® survey and the generic isotretinoin survey. This confusion is unlikely to improve participation in either the voluntary enrolment or the follow-up. Additionally, women might receive a different brand of isotretinoin when they obtain their next 30-day supply. It would be possible for a woman to receive all four versions of isotretinoin currently available in the US during the typical 5-month course of therapy, though how likely that

will be to occur is unknown. There is no mechanism in place to evaluate how often one woman receives multiple versions of isotretinoin during a single course of therapy to determine the magnitude of this potential issue. By the end of the first 12 months that generic isotretinoin was available, the three generic brands combined had approximately 60% of the total market share.[74] Roche's net US sales for Accutane®fell from $US380 million in 2002 to $US144 million in 2003.[75]

Registration and follow-up of women will be nearly impossible if the brand-name product and all generic brands do not use the same registry. Without a combined approach, women could be enrolled in multiple registries or none, or might enrol in the 'wrong' registry. For example, a woman might receive Accutane® information from her dermatologist and enrol in the Accutane®registry, but receive Amnesteem®from her pharmacy when she fills her prescription. This will make it extremely challenging to estimate the percentage of women using isotretinoin who have registered and chosen to participate in the follow-up survey. In the event of pregnancy during treatment, it might not be clear to whom this event should be reported. Dermatologists have been reassured that the "materials are interchangeable".[76] Additionally, dermatologists have been assured by their professional organisation that registration forms and follow-up data from different survey groups will be analysed by the FDA to assess the success of prevention of pregnancies exposed to isotretinoin.[76] However, it is not clear how the data could be combined and duplicates eliminated given that participant confidentiality must be maintained by each registry. Many of these challenges could be overcome if all companies marketing isotretinoin agreed to use a single coordinated registry and follow-up for all versions of isotretinoin.

An additional issue with the introduction of generics is the possibility of women not associating any prior knowledge they might have of the teratogenicity of Accutane® with the new and unfamiliar names of the generic brands. Virtually all of the prior publicity about the teratogenic potential of isotretinoin has been done in reference to the brand-name product Accutane®. Some women using isotretinoin might not realise that the generic brands all have the same teratogenic potential, particularly if they acquire the drug outside the usual doctor-patient relationship.

3.3 Generic Versions of Isotretinoin in Other Countries and Online

There are over 30 names under which isotretinoin is sold worldwide, including at least 25 generics and generic brands (table II). Both the names and prices of isotretinoin vary dramatically between countries. Isotretinoin is widely available from online sources, with prices ranging from less than $US40 for 30 Accuran® 20mg capsules from a European online pharmacy to nearly $US300 for 30 Accutane® 20mg capsules at a US online pharmacy according to currently posted information.[77,78] The use of the Internet for commerce has accelerated rapidly in the US over the past 5 years and presumably an increasing number of prescription drugs will be obtained in this way in the future. While the FDA has warned against purchasing isotretinoin from international sources and importing it for personal use,[79] the availability of isotretinoin at numerous international pharmacies on the Internet and various Web postings on message boards suggest that this practice might be widespread. The Internet also provides a mechanism for facilitating medication sharing, an extremely dangerous practice. Obtaining isotretinoin online essentially guarantees that it will be used without the appropriate restrictions and precautions that are clearly defined in the product label. Certain groups may find it particularly attractive to purchase isotretinoin online, for example (i) body builders purchasing steroids online might find it convenient to purchase isotretinoin from the same site; and (ii) adolescents might be able to obtain a prescription drug in this manner without their parents' knowledge or permission. Other reasons that might motivate women to purchase isotretinoin online include (i) lower cost; (ii) potential to obtain a long-term supply in one purchase; (iii) ability to avoid visiting a doctor and still obtain a prescription; and (iv) ability to obtain a prescription without having to

Table II. Some of the brand-name and generic versions of isotretinoin currently being marketed in selected countries

Name	Countries of distribution	Manufacturer/distributor
Originator's brand		
Accutane®	US, Canada	Roche
Roacutan®	Brazil, Spain	Roche
Roaccutan®	Italy, Switzerland, Argentina, Mexico, Venezuela	Roche
Roaccutane®	Netherlands, New Zealand, Australia, France, Belgium, UK, South Africa, Ireland, Hong Kong	Roche
Roacnetan®	Chile	Roche
Generic brand		
Accuran®	Greece, Spain	Alvia
Accure®	Australia	Alphapharm
Acnotin®	Hong Kong	JDH (Hong Kong)
Amnesteem®	US	Bertek Pharmaceuticals (Mylan Laboratories)
Cecnoin®	Brazil	Ranbaxy (India)
Chem mart isotretinoin®	Australia	Chem mart
Claravis™	US	Barr Laboratories
Curacné®	France	Laboratories Pierre Fabre Dermatologie
GenRx isotretinoin®	Australia	Faulding Healthcare
Healthsense isotretinoin®	Australia	Healthsense
Isoacne®	Brazil	Schering-Plough
Isoface®	Bolivia	Promedical
Isoface®	Colombia	Procaps
Isohexal®	Australia	Hexal Australia
Isotretinoin-BC®	Australia	Biochemie Australia
Lisacne®	Chile	Andromaco Lan
Lurantal®	Austria, Belgium, Colombia, Finland, Germany, Luxembourg, The Netherlands	Schering Health Care Ltd
Nimegen®	Korea, Singapore	Medica Korea
Oratane®	Australia, New Zealand, Singapore, Hong Kong	Douglas Pharmaceuticals; United Italian Corp (Hong Kong)
Procuta®	France	Laboratories Pharmascience
Rexidal®	Italy	Schering Health Care Ltd
Scheritonin®	Argentina, Denmark, France, Greece, Ireland, Portugal	Schering Health Care Ltd
Sotret®	US	Ranbaxy Pharmaceuticals
Terry White Chemists isotretinoin®	Australia	Terry White Chemists
Trivane®	Spain	Schering Health Care Ltd
Unbranded generic		
Retinoic acid cis	Argentina	People's Republic of China
Isotretinoin generic	Brazil	Ranbaxy (India) and Galen Laboratory

encounter the restrictions imposed by risk management systems. This final fact could be especially attractive to teenagers and women who are at risk for pregnancy but are not comfortable acknowledging that risk.

4. Conclusions

While no system is perfect, in our opinion there are some concrete steps that could be taken to help ensure the safe use of isotretinoin by reproductive-aged women now that generic versions are availa-

ble. Physicians who are not knowledgeable about the risk management systems for isotretinoin could choose not to prescribe this teratogenic medication. In addition to following all procedures in the current risk management plans for isotretinoin, physicians could be more discriminate in prescribing and voluntarily limit the use of isotretinoin to those who meet the labelled indications in order to reduce the number of exposed pregnancies.

Most importantly, if all companies marketing isotretinoin chose to work together to establish a consolidated, mandatory registration of all women of reproductive potential who receive an isotretinoin prescription, there could be a clear accounting of the total number of women taking isotretinoin for whom follow-up information is and is not available. This would provide meaningful data that could be used to make timely modifications to the risk management system to improve its effectiveness. There are clearly some practical obstacles to an approach using mandatory registration, including privacy concerns and logistical difficulties given the very frequent use of this drug. There is also reason for concern that this approach could lead more women to obtain the drug via alternative channels such as from Internet sources that do not require prescriptions. Nonetheless, mandatory registration of female, reproductive-aged patients using isotretinoin could allow a clear determination of the denominator for the population at risk. Without knowing this denominator it is, at best, challenging to assess the success or failure of programmes to manage the risk. Use of one consolidated registry for the originator's product and all generic brands would allow identification of duplicates in both the numerator of adverse events and the denominator of women of childbearing potential. It would also avoid the confusion that is introduced by providing different addresses, contact information and names for the registration of follow-up surveys. This is particularly important because women could take more than one version of the drug during a single course of therapy or could receive a different programme's materials from their doctor than from the pharmacy. The companies marketing isotretinoin have an opportunity to work together to demonstrate their commitment to both limit the occurrence of exposed pregnancies and conduct a meaningful evaluation of the occurrence of pregnancies exposed to isotretinoin.

The present manuscript was written prior to the FDA Joint Drug Safety and Risk Management and Dermatologic and Ophthalmic Drugs Advisory Committee Meeting in February 2004.[80] However, many of the same issues raised in this manuscript were voiced by the advisory committee during that meeting. The committee recommended mandatory registration of all patients using isotretinoin with an interactive system that verifies negative pregnancy tests prior to dispensing, mandatory registration of all prescribers and pharmacists, a follow-up survey to more completely ascertain adverse outcomes and the critical need to use one consolidated registry and follow-up system, one set of educational materials and a single enrolment form for all brands of isotretinoin. We hope the companies marketing isotretinoin will work together and in consultation with the FDA to implement these recommendations as soon as possible.

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