The experience of the past two years shows that intensive regulation has not, cannot and will not achieve the Agency's goal of eliminating pregnancy exposure to Accutane. The following describes why I believe Accutane poses an imminent hazard to the public health requiring immediate withdrawal from the market.

The Secretary of Health and the Agency are empowered to do this if the Secretary determines that an imminent hazard to the public health exists (FD&C Act, Section 505(e)). 21 CFR 2.5 describes further that "an imminent hazard to the public health is considered to exist when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held. The imminent hazard may be declared at any point in the chain of events which may ultimately result in harm to the public health. The occurrence of the final anticipated injury is not essential to establish that an imminent hazard of such occurrence exists."

21 CFR continues "(b) In exercising his judgement on whether an imminent hazard exists, the Commissioner will consider the number of injuries anticipated and the nature, severity, and duration of the anticipated injury."
The courts have upheld the following criteria to be considered in evaluating whether an imminent hazard exists:

1. The severity of the harm that could be caused by the drug during the completion of customary administrative proceedings to withdraw the drug from the general market.
2. The likelihood that the drug will cause such harm to users while the administrative process is being completed.
3. The risk to patients currently taking the drug that might be occasioned by the immediate removal of the drug from the market, taking into account the availability of other therapies and the steps necessary for patients to adjust to these other therapies.
4. The likelihood that, after the coustomary administrative process is completed, the drug will be withdrawn from the general market.
5. The availability of other approaches to protect the public health.

A brief discussion of each of these criteria shows that Accutane does pose an imminent hazard.

1. What is the severity of harm that could be caused by Accutane during the completion of customary administrative proceedings to withdraw the drug from the general market?

The severity of harm has been recognized and undisputed from early in Accutane's pre-marketing history. The drug is a potent teratogen capable of causing severe disabling or fatal birth defects in offspring of women who take it in the first trimester of pregnancy, and also of provoking drug-induced spontaneous abortion by injuring the developing pregnancy. In recognition of this, Accutane was one of the first drugs to receive FDA pregnancy category X classification. As our data on drug use and contraceptive failure show, there probably have been between 15,000 and 18,000 pregnancy exposures to Accutane since its appearance

on the market in 1982. The magnitude of injury and death has been great and permanent, with 11,000 to 13,000 Accutane-related abortions and 900 to 1,100 Accutane-related birth defects.

With biologic and mathematical determinism, these exposures have continued relentlessly despite repeated intensive and unprecedented regulatory efforts. During the past year, while the Agency waited for more complete data on the effect of its interventions to accumulate, we have estimated that an additional 1,900 pregnancy exposures occurred with 1,500 abortions and 117 children born with birth defects. Many of these died in infancy.

2. What is the likelihood of harm to users while the administrative process is being completed?

Customary administrative proceedings to withdraw Accutane from the general market would probably take over two years. During this time, many thousands of women would needlessly experience pregnancy exposure to Accutane, with its disastrous consequences. Pregnancy exposure to Accutane occurs in about 3% of women treated with the drug. This is predicted by models incorporating current knowledge of contraceptive practices and pregnancy rates, and details of current use of Accutane in women. In four separate populations, high levels of pregnancy exposure consistent with that predicted by the model have been observed. The likelihood of harm is great.

The wording of this criterion makes reference to "harm to users while the administrative process is being completed." This raises the question of whether the imminent hazard provision can be used to protect developing and full-term children who will be severely injured or killed if Accutane is not removed from the market. Several lines of reasoning show that the imminent hazard provision does protect against in-utero exposure to Accutane.

The pregnancy is directly affected by Accutane. The drug crosses the placenta and enters the child's circulation, which is separate and distinct from that of the mother. The drug exerts a biologic and physiologic effect on the developing child, causing severe injury or death. The extent of this harm has been documented and quantitated, with an estimated 40% of affected pregnancies ending with spontaneous drug-induced abortions and up to 25% of those coming to delivery experiencing birth defects which prove to be fatal in many during infancy. There is also the injury brought about by induced abortion of about 60% of those pregnancies with first trimester exposure who are not spontaneously aborted. This represents a statistically significant two-fold increase in induced abortion over what would be expected in the population and is a direct consequence of exposure to the drug. That abortion is increased substantially over expected shows epidemiologically that were it not for the Accutane exposure in the first trimester, that many of these pregnancies would not have been aborted (both spontaneous and induced).

The mother who takes Accutane by mouth is the proximate user of the drug; the developing pregnancy is an involuntary user of the drug. Of interest in this regard is the fact that the courts have in some instances recently intervened on behalf of the pregnancy in situations where the mother was taking alcohol or drugs which could be injurious to in-utero health.

The manner in which Accutane has been regulated also shows that the pregnancy is clearly recognized as an involuntary user of the drug by the Agency. Pregnancy category X classification (described in FDA Drug Bull 1982; and 21 CFR) accords priority to the health and well-being of the pregnancy by its absolute wording that patient benefit never outweighs risk to the pregnancy. Subsequent actions by FDA to eliminate pregnancy exposure also speaks to the reality that the developing pregnancy and offspring are covered by the imminent hazard provision.

If the Agency refuses to include pregnancy exposure and teratogenic consequences under the rubric of imminent hazard, there may be no legal basis for FDA to refuse to approve a drug such as thalidomide if it is death-dealing to the pregnancy. It might also have no authority to contraindicate a drug for use in situations where pregnancy exposure might occur. It would also relinquish regulatory authority in an area of vital public health importance. The natural question arises of what would FDA have done had the thalidomide disaster occurred in the United States rather than in Europe. Would the Agency have let thalidomide remain on the market? The Kefauver-Harris amendment and the development of postmarketing surveillance were direct responses to thalidomide, intending that such threats to the public health be prevented or curtailed in the future.

The existing criteria for imminent hazard do not make specific reference to in-utero harm resulting from pregnancy exposure because the case law from which the criteria developed did not involve the issue of in-utero health, injury and death and ex-utero disability and death. Accutane presents such a situation. The descriptions of imminent hazard found in FD&C 505 (e) and 21 CFR speak of hazards to the public health and clearly do not exclude issues relating to pregnancy exposure.

3. What risk to patients currently taking Accutane might be occasioned by its immediate removal from the market?

Over 90% of women currently treated with Accutane do not have the disease for which the drug is approved. All of these patients could be treated with other, safer therapies. The product labeling specifies that the drug is only intended for patients with severe cystic acne who have failed to respond to other therapies including systemic antibiotics, and that it is contraindicated in cases with lesser disease.

For the fewer than 10% of women currently taking Accutane, who have severe recalcitrant cystic acne unresponsive to other therapies, there would be no other treatment that is totally effective, although partial improvement would probably be obtained from other existing treatments. However, severe cystic acne is not a fatal or life-threatening disease, and so the actual risk incurred by these patients because of removal of Accutane from the market is non-existent. Also, Accutane carries a pregnancy category X classification which indicates that pregnancy exposure to it is not justifiable or acceptable. The issue of "benefit" in a "risk-benefit" equation is not a consideration. "The use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant." As we have shown by modeling and with data from four different populations, all women of childbearing potential are at risk and "may become pregnant" while on drug.

4. What is the likelihood that after the customary administrative process is completed, that the drug will be withdrawn from the general market?

The likelihood is great because the level of public health risk and harm is extremely high. Over 1% of the nation's women of childbearing age having been treated with Accutane thus far and a woman's reproductive-lifetime risk of exposure to the drug is almost 3%. Of those treated with Accutane, about 3% have pregnancy exposure to the drug. The magnitude of harm which has already occurred, and which will continue to occur in the future is high.

Furthermore, over 90% of the women experiencing pregnancy exposure to Accutane did not have the severity of disease for which Accutane was approved. There was no reason for them to receive this drug based on its labeling, yet 3% of them experienced pregnancy exposure to it. The only way to protect these women, their pregnancies and their offspring is by immediate withdrawal of Accutane from the market.

5. Are there other approaches available to protect the public health?

The answer is no. Accutane cannot safely be administered to women of childbearing potential regardless of the setting in which it is used. This is clearly demonstrated by the occurrence of first trimester pregnancy exposure in 5% of women participating in IND studies, despite intensive counselling, signed informed consent, pregnancy testing and contraception. The use of Accutane cannot be rendered safe for women even by such a controlled setting.

The regulatory history for Accutane is extensive and to quote Dr. Tabor, former Director of the Division of Anti-Infective Drug Products, it has been "truly extraordinary." Multiple advisory committee meetings, "Dear Doctor" letters, FDA Drug Bulletin articles, articles and editorials in professional journals, intensive labeling and relabeling with highlighted warnings, physician seminars and educational programs, and much more have been done. No other drug in recent history has been the subject of such intensive regulatory effort. Despite this, the problem of pregnancy exposure to Accutane has continued virtually unchanged.

The efforts of the most recent two years saw use of signed informed consent forms, and special packaging of the product in an effort to eliminate pregnancy exposure and solve the problem. Signed informed consent did not prevent the 5% of women treated with Accutane during its pre-marketing clinical trials from experiencing pregnancy exposure to it, and it has not worked now.

Restricting Accutane to use only by dermatologists will not eliminate the problem because over 90% of all Accutane currently dispensed is prescribed by dermatologists.

Contraindicating the use of Accutane in women, but leaving Accutane on the market, will not eliminate the problem because physicians will still prescribe the drug for them. This is clearly shown by the experience with the most recent regulatory interventions in which "Accutane is contraindicated in women unless all of the following conditions apply" (May 1988 action letter from FDA to Roche). The letter specified five criteria that must be met in full before the

drug is prescribed. The official lists six exclusionary criteria. As described in recent meetings and written communications, data from both FDA scientists and the sponsor demonstrate that most of the Accutane prescribed to women in 1989 was contraindicated because the five criteria were not met in full. The majority of women did not have severe recalcitrant cystic acne, most did not receive an initial serum pregnancy test and a sizable number did not receive written warnings. Contraindicating the use of the drug has not altered physician behavior very much and has not achieved the Agency's goal. Another problem created by contraindicating the use of Accutane in women but leaving it on the market is that physicians could prescribe the drug for men who do not have severe recalcitrant cystic acne with the understanding that it would be given to women, or other deceptive means could easily be taken to give Accutane to women. In this situation, the Agency would lose all ability to document and quantitate the persistence of the problem.

Restricted distribution, limited to regional university-based centers would also fail to achieve an environment where Accutane could safely be given to women of childbearing age or potential. This message is clear from the substantive body of data showing that if Accutane is given to women, pregnancy exposure to it will occur about 3% of the time, regardless of what is done to avoid it. The only way to eliminate pregnancy exposure to Accutane is to ensure that it is not available for or given to women. Restricting the distribution of Accutane as above and permitting only men to be prescribed the drug would also not be effective at removing the imminent hazard . The reasons are several. First, to design and implement such a system might take two or more years, during which time women would continue to be subject to the public health risks of this drug. Second, the potential for diversion of Accutane to women because of men giving it to them is probably high. It would be difficult or impossible to detect and quantitate this.

There is no alternative to immediate withdrawal of Accutane from the market. To delay only compounds the body count. All previous efforts by FDA to achieve its goal of eliminating pregnancy exposure to Accutane have failed. Only the immediate withdrawal of Accutane from the market will work.

To put things in context, the level of occurrence of most severe and life-threatening adverse reactions to prescription drugs is on the order of 1 per 20,000 to 1 per 100,000 or less. Among drugs approved in the United States and subsequently withdrawn (usually "voluntarily") from the market, the level of risk for serious harm was probably in the range of 1 per 1,000 to 1 per 10,000. With Accutane, the risk is known with biologic certainty to be around 3 per 100, one to two orders of magnitude greater than with these other drugs. The problem is made worse by the fact that cystic acne itself is not a life-threatening disease, and by the fact that more than 90 of every 100 women treated with Accutane don't even have the severity of disease for which the drug was originally approved.

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