FDA Joint Advisory Committee Hearing on the Risk Management of Accutane
February 27, 2004

Statement of Bart Stupak, Member of Congress

Thank you for allowing me this opportunity to address this Accutane Advisory Committee.

This is the second FDA Advisory Committee hearing on Accutane in three and a half years. Since that time, three generic equivalents of Accutane have been approved and possibly eleven more generics may be pending. The FDA has documented 366 pregnancy exposures during this time frame.[1] Because the reporting of pregnancy exposures to Isotretinoin is voluntary, there is no way of knowing how many pregnancy exposures have actually occurred. And according to the FDA's own Dr. David Graham, the yearly exposure rate may be as high as 2000,[2] and this does not include abortions.[3]

Now, the FDA's own analysis of the current SMART voluntary registry launched three years ago has led, at a minimum, to no improvement in pregnancy exposure rates of those taking this drug.

It seems clear that the only way to dramatically reduce the rate of pregnancy exposures in Accutane patients is to regulate it like the FDA regulates Thalidomide.

A toothless, voluntary registry doesn't work, and we all know it. The registry should be mandatory for all female and male patients, for all prescribers and dispensers of Accutane. And there should be real consequences for those who refuse to participate.

And I plan to introduce legislation in the coming weeks to do just that.

For 22 years, we have seen the harm Accutane can do to pregnant women and to our children. How many more babies have to be born with serious defects, how many

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[1] FDA Briefing Memo.

[2] December 11, 2002 hearing of Oversight and Investigations subcommittee of the Energy and Commerce Committee statement of Dr. Graham, page 38.

[3] December 11, 2002 hearing of Oversight and Investigations subcommittee of the Energy and Commerce Committee, Exhibit 20: Clinical Review, Accutane Quarterly Report – Last Quarter 1999.

more women need to have miscarriages, and how many more children have to die before the FDA implements meaningful protections and restrictions on the use of Accutane?

Now, I'd like to give a little history on how the FDA and Roche have managed this drug since 1982, when Accutane was first put on the market.

Background:

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The risk of severe birth defects caused by Accutane is undisputed. When Accutane was first approved by the FDA in 1982, it was given a Category X pregnancy designation. This means that the drug should be avoided under all circumstances during pregnancy.

After the first reports of birth defects, bold print warnings were introduced in 1983, but those warnings were given only to the prescriber. A year later, a black box warning was instituted at the top of the package insert. But it was only given to the prescriber.[4] Patients, their parents and families never directly notified of the birth defects risk caused by Accutane.

1980's Advisory Committees:

During the Accutane Advisory Committee hearings in 1988, 1989 and 1990, Roche assured the Advisory Committees that Accutane would be prescribed only to those women with "severe recalcitrant cystic acne" and pregnancy exposure rates would dramatically decrease as the average dermatologist would "see less than one [female] patient per year" that would require Accutane therapy. The manufacturer of Accutane, Hoffman-LaRoche, promised that new female Accutane patients would be limited to about "5,000 cases per year" and their advertising would not focus on Accutane usage but future ads would "dramatically" focus on "contraindication and proper use of pregnancy prevention".[5]

The 1988 Advisory Committee by "consensus" considered limiting the use, prescription and distribution of Accutane in four ways. The committee felt it may be necessary to restrict "....the actual distribution of the drug, restriction of two special physicians for distributing the drug, restriction of special patients who get the drug, and the necessity of having a second opinion in those high risk females."[6] But, this "consensus" was never acted upon, and committee concerns were largely forgotten as Roche went on to make Accutane their second highest selling drug.

Ten years later, the FDA and Roche implemented the Pregnancy Prevention Program (PPP), after continued pregnancy exposures. The PPP sought to include

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[4] Roche SMART Briefing Package. Advisory Committee Briefing Book.
[5] Dermatologic Drugs Advisory Committee, FDA 1989, Dr. William Cunningham, page 86.

[6] Dermatologic Drugs Advisory Committee, FDA 1988, Dr. Bergfeld, page 272.

pharmacists, patients and physicians to decrease the pregnancy exposures to Accutane. Despite the PPP, the red stickers, the voluntary Consent Form, and the NO pregnancy symbol with the red line through it, Accutane pregnancy exposures continued at unacceptable levels. Some patients even thought the NO pregnancy symbol meant Accutane was a form of birth control.

Meanwhile, Accutane use shot up in the 1990s as a result of Roche's successful marketing through direct to consumer advertising, television ads, magazine and other advertisements targeting young people, mothers and certain minority populations.

Not only did the number of female patients receiving Accutane dramatically increase, so did "off-label" use of Accutane. It is estimated that 90% of Accutane is for "off-label" use and the FDA is of the opinion that many of the prescribing physicians do not understand the teratogenic effects of Accutane.[7]

2000 Advisory Committee

Finding the number of pregnancy exposures under PPP "unacceptable," the FDA called for another Advisory Committee hearing in September, 2000. At the end of the September 2000 hearing, the Advisory Committee recommended a risk management plan that met five conditions:

1) A heightened educational program for each patient that includes verifiable documented written informed consent;
2) Complete registration of all patients, both male and female;
3) Complete registration and certification of practitioners who prescribe Accutane;
4) A comprehensive program to track fetal exposures to Accutane (and outcomes), including a formal mandatory pregnancy registry; and
5) Linkage of dispensing of Accutane to female patients to verification of adequate pregnancy testing.

The FDA agreed with the Advisory Committee's recommendations. On October 6, 2000, FDA wrote Roche informing them of its decision to implement all five recommendations. The FDA and Roche then began discussions on how to implement those recommendations.

While the focus of these negotiations centered on a pregnancy risk management program, the U.S. House of Representatives became involved in Accutane after the suicide of my son. In October of 2000, my family and I went public with our concerns that Accutane was associated with suicides in some patients. While Roche and the FDA claimed that there were only 37 suicides, I believed there were at least 54 suicides associated with Accutane therapy.

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[7] December 11, 2002 hearing of Oversight and Investigations subcommittee of the Energy and Commerce Committee, statement of Dr. Graham, page 39.

Congressional hearings were held in December of 2000 and again, on December 11, 2002, on the issues relating to the safety of Accutane. By the 2002 hearing, suicides associated with Accutane had grown to approximately 200.

The December 11, 2002 congressional Oversight and Investigation subcommittee hearing was attended by 12 members of the Energy and Commerce Committee. The Members of Congress sought answers to numerous issues relating to Accutane including the continued pregnancy exposures and psychiatric effects of Accutane. Committee members were appalled when they learned that the FDA had reversed its position and decided it was not necessary to implement the September 2000 Advisory Committee recommendations. The FDA excuses of privacy concerns and HIPPA for not implementing the 2000 Advisory Committee recommendations rang hollow with the Congressional committee members.

In the meantime, Roche continued to aggressively market Accutane with the number of prescriptions growing to 1.51 million in 2001 and approximately one-half of the prescriptions to high-risk young women.[8]

The FDA negotiations with Roche produced an agreement on a new pregnancy exposure risk management plan called System to Manage Accutane Related Teratogenicity (SMART). SMART did not fulfill the recommendations made by the Advisory Committee.

The SMART program began approximately 5 months prior to the December 11, 2002, committee hearing. Witnesses from the March of Dimes and the Organization of Teratology Information Services (OTIS), testified that the SMART program would not achieve its objectives, as the SMART program did not go "far enough":

> "....although Physicians are required to registered with Roche, no consequences have been specified for those who fail to register. Also, patients are strongly encouraged to enroll in the Accutane survey, but patient enrollment is not mandatory. No safeguards are in place to ensure that pharmacists only fill prescriptions that bear a yellow sticker."[9]

The OTIS representative further testified that a partial survey of their organization found that "...17 cases of pregnancy exposure to Accutane" had already been reported since the start of the SMART program and that there is "a lot of slippage in the system."[10]

At the hearing, the Chairman asked what "....is the FDA's fallback position if the voluntary [SMART] program" doesn't improve things [Accutane's pregnancy exposures]? Dr. Janet Woodcock of the FDA responded that they have "....run scenarios on fallback positions, and we have relayed this to Roche, and they are aware of our

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[8] FDA Background Memo: Overview of the First Year of the Isotretinoin Risk Management Program
[9] December 11, 2002 hearing of Oversight and Investigations subcommittee of the Energy and Commerce Committee, statement of Liz Martinez, page 88.
[10] Ibid.

position [of a mandatory program]." With respect to the FDA's authority to implement a mandatory registry mirroring the STEPS program for Thalidomide, the FDA provided testimony from its Chief Council and a letter from its Associate Counsel for Legislation stating that it "would first try to get the sponsors to agree to such a registry. The Agency has found that working together with the sponsor results in the most success in managing the risks of a particular drug. For a variety of reasons, FDA would invoke its authority under the Federal Food, Drug, and Cosmetic (FD&C) Act only as a last resort."[11]

What Subcommittee members learned from this hearing was that Accutane is a dangerous, powerful drug that needs to be closely regulated. Members learned that the SMART Program was questionable.

However, Members of Congress also learned first hand that the FDA was dragging its feet. The FDA failed to provide relevant documentation until the day of the hearing, when they dropped off a number of boxes filled with information requested by the committee. It was impossible to review this "just dropped" information before the hearing.

Had the FDA provided these documents in a timely manner, members would have realized that the FDA had received evidence of the failings of the SMART program from its inception. For instance, FDA received evidence that doctors were pre-dating the yellow stickers that signify the female patient had received a negative pregnancy test. A medical clinic was predating prescriptions so the patient could fill more than one prescription within the seven day limit of the negative pregnancy test. The FDA knew of at least one patient purchasing Accutane with no pregnancy testing, no prescription, no consent forms. Some health care plans, which electronically dispense their prescriptions, were not using the yellow negative pregnancy sticker. Also, pharmacies were not giving out the Med Guides for Accutane and that compliance with these toothless regulations were simply not working. In fact, approximately 50 percent of the doctors were not using the informed consent forms since it was voluntary. The FDA withheld this information on the SMART program from the committee until after the December 11, 2002 hearing.

Now, Roche has said they will support a mandatory registry and has submitted a proposal. Please understand my skepticism after numerous Advisory Committee hearings, reading thousands of pages of internal FDA documents recognizing the problems, and calling for solutions that never get acted upon. I still do not believe the FDA and Roche will ever institute a registry and certification program similar to S.T.E.P.S. for Thalidomide. The FDA has said no women can become pregnant on Thalidomide, or the drug will be taken off the market. Equivalent effects, call for equivalent restrictions. There must be a mandatory Isotretinoin registry for patients, doctors, and pharmacists. Pregnancies will continue to occur if any element is left out of the registry. There must be consequences for failure to comply with any part of the program.

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[11] December 11, 2002 hearing of Oversight and Investigations subcommittee of the Energy and Commerce Committee, pages 62-64.

The FDA has testified and warned of a "black market" that would result if a mandatory registry and certification is implemented. Yet, it is the FDA's own complacency that has exacerbated a foreseeable black market problem in other ways. In 1999, Congressman Ron Klink and I introduced legislation to stop Internet sales of pharmaceuticals, including Accutane. This legislation has been reintroduced and I still have not been successful in getting the FDA to even comment, support or oppose my proposal.

Shipments of pharmaceuticals to individuals in this country is another black market concern expressed by the FDA. Yet, the Oversight and Investigation subcommittee has held numerous hearings and on-site inspections of mail facilities and found the breakdown in the system is due to a lack of guidance from the FDA to U.S. Customs on how to handle these shipments. Failure of the FDA to enforce current regulations encourages mail orders of Accutane and other potentially harmful drugs. I'm not alone in my belief that the FDA needs to do more in this area. The bottom line is the FDA's inaction has created this "black market" for drugs entering this country through Internet and mail order purchases.

The manufacturer of Accutane, Hoffman-LaRoche is just as culpable as the FDA in allowing Internet and mail orders of Accutane into the country. While Roche complains of Internet sales, it is they who distribute Accutane to wholesalers and others. As the December 11, 2002 hearing showed, Roche hides behind the FDA's inaction to complain of Internet sales. Yet, Roche product coding allows them to determine the exact location of where their product is shipped, to whom, and when. If unscrupulous distributors are selling Accutane over the Internet and shipping it into this country, where is Roche's commitment to limit Accutane sales to reputable distributors who will only provide Accutane to licensed pharmacies to ensure person to person sales?[12]

And it can be done. In fact, the Oversight and Investigations subcommittee has confronted another pharmaceutical company on its distribution of oxycotin in Mexico. The committee was successful in reaching an agreement with the manufacturer, Purdue Pharma, to stop shipping oxycotin to Mexico as it was being brought back across the U.S. southern border. Yet, when it was pointed out that Mexico does not have the same regulatory scheme to prevent birth defects along our southern border, Roche refused to stop the shipment of Accutane to Mexico.[13]

Answers as to why Roche isn't really serious about entering into a mandatory registry for Accutane patients, physicians, and pharmacies can be summarized in a document provided during our December 11, 2002 hearing. Roche did all it could to

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12 December 11, 2002 hearing of Oversight and Investigations subcommittee of the Energy and Commerce Committee, pages 132 and133.

[13] December 11, 2002 hearing of Oversight and Investigations subcommittee of the Energy and Commerce Committee, pages 119, 120, 127, 128,132-134.

defeat the registry for Accutane as recommended by the September 2000 Advisory Panel. In fact, Roche staff viewed the defeat of the Advisory Committee recommendations as a cause to "celebrate," proclaiming "no psychiatric registry!" Not only did Roche view the defeat of the registry as cause to celebrate, they protected their $450 million in Accutane sales. Roche does not want any form of registry that would limit sales, prescribers, especially dermatologists (AAD), or provide insight into the psychiatric effects on patients.[14]

Roche is so fearful that a registry may provide evidence of Accutane causing psychiatric injury to young, developing brains that it will stop at nothing to prevent a registry. For instance, our Oversight and Investigations subcommittee has discovered that Roche failed to provide to the FDA in its initial application a study which suggests that Accutane does adversely affect the central nervous system in mice. The committee has uncovered three more subsequent studies that also suggest that Accutane does affect the central nervous system. Roche had not submitted these scientific studies to the FDA in a timely manner. These studies may help unlock the keys to the causation of psychiatric injuries in young patients. Even the FDA, which has been working with the National Institute of Mental Health (NIMH) and the National Institute of Health (NIH), has kept from the Advisory Committee and the American people their preliminary studies which do suggest a causation between Accutane and psychiatric injuries. Both the FDA and Roche have misled and failed to protect the American people, unborn children, and young adults from the devastating effects of this powerful drug.

The fact of the matter is that the Advisory Committee was right four years ago. Accutane is a powerful drug with serious side effects that needs to be highly regulated. The FDA knew this long before the Advisory Committee called for a mandatory registry in 2000. It seems the FDA only calls an Advisory Committee when the writing is on the wall. Well, I hope this time the FDA does not allow the manufacturers of Accutane and its generics to come in and water down the recommendations of this Advisory Committee.

Frankly, I am not sure Congress is willing to let them do that anymore. I will be introducing legislation to establish a mandatory registry of patients, doctors and pharmacists, similar to the Thalidomide registry. A mandatory registry is needed to track the effects of the drug and to ensure that it is being distributed and regulated in a safe manner. The legislation is ready to go, and members have contacted to join me in this effort. In our Oversight hearing, it became clear that if Europe, with its numerous regulatory schemes, has little or no pregnancy exposures to Accutane, then why can't the United States?

Within the documents provided by the FDA there is a statement from an exasperated FDA investigator who cries out, how could the FDA grant a patent extension

[14] December 11, 2002 hearing of Oversight and Investigations subcommittee of the Energy and Commerce Committee. Exhibits 36, internal Roche e-mail, and Exhibit 48, internal presentation by Roche's "Accutane Team."

on Accutane for use in young patients with all the devastation this drug has caused? One begins to ask, what special powers or charm does Roche have over the FDA?

It is time to put strict restrictions on the users, prescribers, dispensers and marketers of Accutane and its generics.