ISSUES RELATING TO THE SAFETY OF ACCUTANE

HEARING

BEFORE THE

SUBCOMMITTEE ON
OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON ENERGY AND
COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED SEVENTH CONGRESS

SECOND SESSION

DECEMBER 11, 2002

Serial No. 107–143

Printed for the use of the Committee on Energy and Commerce

Available via the World Wide Web: http://www.access.gpo.gov/congress/house

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U.S. GOVERNMENT PRINTING OFFICE

83–921CC WASHINGTON : 2003

For sale by the Superintendent of Documents, U.S. Government Printing Office
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CONTENTS

Page IV Blank Page 1 Follows

ISSUES RELATING TO THE SAFETY OF ACCUTANE

WEDNESDAY, DECEMBER 11, 2002

HOUSE OF REPRESENTATIVES,
COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
Washington, DC.

The subcommittee met, pursuant to notice, at 9:39 a.m., in room 2123, Rayburn House Office Building, Hon. James C. Greenwood (chairman) presiding.

Members present: Representatives Greenwood, Stearns, Gillmor, Deutsch, Stupak, DeGette, John, and Rush.

Also present: Representatives Waxman, Brown, and Green.

Staff present: Alan Slobodin, majority counsel; Casey Hemard, majority counsel; Will Carty, legislative clerk; Chris Knauer, minority counsel; and Nicole Kenner, minority research assistant.

Mr. GREENWOOD. Good morning. The committee will come to order. We welcome all of our guests and witnesses this morning.

This morning, the subcommittee examines the heart-wrenching and very complicated issues relating to the safety of Accutane, a tremendously powerful drug approved for treating severe recalcitrant cystic acne. Manufactured by Hoffmann-LaRoche, Accutane is the only drug that has the potential to clear severe acne that is resistant to standard treatment. Although the severe lesions Accutane treats are not life-threatening, patients, as a medical reviewer at the Food and Drug Administration has noted, quote, know all too well the very real suffering caused by this disfiguring disease.

Yet, as powerful as Accutane is in relieving suffering and improving lives, its adverse effects can be just as powerful and have required extraordinary vigilance over the years. Just like the sleeping pill thalidomide linked 40 years ago to gross birth deformities in Europe, Accutane is a teratogen, and is known to cause miscarriages and birth defects. Its use also poses risks of potentially serious problems affecting several vital organs. Finally, mounting reports of patients who committed suicide or violent acts while on Accutane have raised concerns about serious psychiatric effects associated with the drug.

Accutane is a unique and complicated case. The drug was approved in 1982 with the knowledge that it had the potential to cause birth defects, and it has always been labeled that way and measures have always been in place to limit these risks. Indeed, throughout the 20 years of Accutane's marketing in the United States, the FDA has used almost all the risk management tools at

its disposal to address patient safety concerns, chief of which that the drug must be avoided under all circumstances during pregnancy. Indeed, the only remaining risk management tools more restrictive than what FDA has already imposed on Accutane's marketing are mandatory patient and physician registries, or the outright withdrawal of the product from the market, which brings us to this morning's hearing.

Given Accutane's very serious adverse event profile, the subcommittee will focus on the nature of two major safety concerns, birth defects and psychiatric side effects, and examine whether current risk management programs are adequate to protect the public health, and, if not, what actions should be taken.

To help encourage the careful balanced and considered attention to today's testimony, I think it will be helpful before we commence to acknowledge the major issues and disputes and the arguments on both sides. The first major issue is whether a mandatory registry for Accutane should be imposed despite, among other measures, at least five FDA advisory committee meetings, numerous Dear Health Care professional letters, black box labeling warnings, company-sponsored educational campaigns, use of signed informed consent, as well as a national pregnancy program. Accutane use has more than tripled over a 10-year period, which suggests further increases in already extensive off-label, unapproved use of the drug.

Moreover, substantial numbers of pregnancy exposures continue to be reported, with probably many more not reported, and data from the company's program show that many women have not been receiving the necessary pregnancy testing prior to starting Accutane.

Meanwhile, European countries with restrictive distribution schemes for Accutane have use rates eight to 10 times lower than here in the United States. Recognizing these troubling results, in September 2000, an FDA advisory committee, which included dermatologists, unanimously recommended a restricted distribution system for Accutane with patient and physician registration and other safeguards designed to ensure Accutane would be used as safely as possible. The FDA initially supported and pursued implementation of this recommendation. However, in the face of medical and legal concerns raised by Roche and the medical community, the FDA did not follow the advisory committee's recommendation, and agreed instead to a risk management plan more restrictive than the existing pregnancy prevention program.

One of the criticisms of this pregnancy prevention program has been the suboptimal voluntary participation in the patients' survey portion of the program, with an estimated 40 to 50 percent enrollment rate of women receiving Accutane at its peak, and falling to an estimated 25 percent enrollment in the last few years.

One of the targets of the new program called SMART, for System to Manage Accutane-Related Teratogenicity, is to achieve a 60 percent enrollment rate. This would be one metric by which an FDA advisory program next year will evaluate the program's effectiveness and whether it should be continued.

Early data from SMART indicate, however, that the enrollment number and enrollment rates so far are actually below the num-

bers in the previous program and are well short of the 60 percent target.

In response to these points, Roche notes that the 40 percent participation rate in the patient survey was high compared with the 10 percent usually observed in voluntary surveys. Roche further notes that the rate of pregnancy reports is far lower than the rate of pregnancies anticipated in the population. Roche also insists the overwhelming amount of use of its drug is in accordance with its label or appropriate off-label use, such as for oncology and to treat severe acne in its early stages to prevent scarring. Given that the SMART program was implemented in April 2002, both FDA and Roche maintain that it is too early to judge the effectiveness of the program, and to let the FDA and advisory panel next summer assess the program.

Both FDA and Roche agree that there has been about a 20 percent decline in the use of Accutane over the past year. Although the drug went off-patent in February, Roche believes that the decline in use is tied to the SMART program.

Some at the FDA have also expressed the concern that mandatory registration would have the unintended effect of generating gray and black-market sales of Accutane, especially on the Internet, without direct physician interaction. FDA is already struggling in its attempt to curtail current Internet sales of Accutane, and there is a belief that a mandatory registry would exacerbate this problem.

There also appears to be a serious question over whether FDA has the authority to impose a mandatory registration on a drug already on the market where the agency is not prepared to withdraw the drug as an imminent hazard.

The second major issue is whether Accutane causes depression and suicide. Those arguing that there is such an association point to the following: The cases of de-challenge/re-challenge, where the patient gets less depressed taken and then worse when put back on it; the higher prevalence of depression with Accutane than with antibiotics; a higher ranking for Accutane in reports of adverse effects involving depression than other medications; and, the fact that depression rates for Accutane is underreported.

It is also argued that there seems to be a plausible biological mechanism by which Accutane could lead to depression and suicide. This involves retinoid receptors in the brain that can bind Accutane and the association of high doses of retinoids—of which Accutane is a derivative—and behavioral mood effects of in humans.

Finally, the individual case reports, although anecdotal, appear to show powerful and real connections to the drug.

Those arguing against such an association point to the following: The background incidents of suicide is more than 10 times greater than reported for Accutane patients. The spontaneous reports for suicides are poorly documented. None with psychological autopsy.

A proportion of the reports contain information about known risk factors for suicide, no plausible direct pharmacological link between Accutane use and suicidal behavior. The de-challenge/re-challenge cases may only reflect the cyclical nature of depression. Proportional analysis of the report shows that rates of suicide and depres-

sion for Accutane are only slightly higher than the rates seen in antibiotics and oral contraceptives. And reports show a tremendous diversity in the dose and temporal relationship to suicide and depression rather than expected similarities.

Notwithstanding the dispute, FDA has taken the precautionary approach by assuming such as an association exists, and strengthened the warnings on their psychiatric side effects. Efforts continue to develop ethical clinical trials to research these side effects. The recent introduction of the generic version of Accutane further complicates some of these issues. Mindful of the millions who have used this drug, many with positive experiences, and of thousands of fetal exposures in many others who may have been harmed, we forge ahead with our questions with an eye toward a constructive examination of this matter and with the hope that a consensus can be formed on how to best move forward in the public interest.

Today's hearing begins with testimony from Dr. Janet Woodcock, the director of the Center of Drug Evaluation and Research at the FDA. Later, we will hear individuals with compelling testimony, both painful and positive, about Accutane. We will also hear from a representative of the March of Dimes, a representative of the Office of Teratology Information Services, and a dermatologist.

And at this time I want to express my appreciate to the FDA for the extensive time its staff spent briefing Congressman Stupak and the committee personnel recently. I also want to compliment FDA Commission McClellan and Deputy Commissioner Crawford for their understanding and cooperation in making certain FDA experts available this morning for the hearing.

The last panel will feature testimony from George Abercrombie, president and CEO of Hoffmann-LaRoche.

Finally, a word about my colleague, Bart Stupak, a respected member of our subcommittee. As many of you know, the gentleman from Michigan lost his son, B.J., while he was using Accutane. My heart goes out to him and to his family. He has become intimately involved with the safety issues related to Accutane over the past 2 years of subcommittee work and has made an enormous effort to learn and investigate the issues. I salute him for his valuable service in raising these important public health issues.

I welcome the witnesses, look forward to working with my colleagues in considering these matters carefully and fairly, and recognize the ranking member, the gentleman from Florida, Mr. Deutsch, for his opening remarks.

[The prepared statement of Hon. James C. Greenwood follows:]

PREPARED STATEMENT OF HON. JAMES C. GREENWOOD, CHAIRMAN, SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

This morning the Subcommittee examines the heart-wrenching and very complicated issues relating to the safety of Accutane, a tremendously powerful drug approved for treating severe, recalcitrant, cystic acne. Manufactured by Hoffman LaRoche, Accutane is the only drug that has the potential to clear severe acne that is resistant to standard treatment. Although the severe lesions Accutane treats are not life-threatening, patients—as a medical reviewer at the Food and Drug Administration (FDA) has noted—"know all too well the very real suffering caused by this disfiguring disease."

Yet as powerful as Accutane is in relieving suffering and improving lives, its adverse effects can be just as powerful and have required extraordinary vigilance over the years. Just like the sleeping pill thalidomide, linked 40 years ago to gross birth deformities in Europe, Accutane is a teratogen. It is known to cause miscarriages

and birth defects. Its use also poses risks of potentially serious problems affecting several vital organs. Finally, mounting reports of patients who committed suicide or violent acts while on Accutane have raised concerns about serious psychiatric effects associated with the drug.

Accutane is a unique and complicated case. The drug was approved in 1982 with the knowledge that it had the potential to cause birth defects and it has always been labeled that way—and measures have always been in place to limit these risks. Indeed, throughout the twenty-years of Accutane's marketing in the United States, the FDA has used almost all the risk management tools at its disposal to address patient-safety concerns, chief of which: that the drug must be avoided under all circumstances during pregnancy. Indeed, the only remaining risk-management tools more restrictive than what FDA has already imposed on Accutane's marketing are mandatory patient and physician registries or the outright withdrawal of the product from the market, which brings us to this morning's hearing.

Given Accutane's very serious adverse event profile, the Subcommittee will focus on the nature of two major safety concerns—birth defects and psychiatric side effects—and examine whether current risk management programs are adequate to protect the public health and if not, what action should be taken.

To help encourage the careful, balanced, and considered attention to today's testimony, I think it will be helpful, before we commence, to acknowledge the major issues in dispute and the arguments on both sides.

The first major issue is whether a mandatory registry for Accutane should be imposed. Despite, among other measures, at least five FDA advisory committee meetings, numerous "Dear Healthcare Professional" letters, "black box" labeling warnings, company-sponsored educational campaigns, use of "signed informed consent," as well as a national "Pregnancy Prevention Program," Accutane use has more than tripled over a 10-year period, which suggests further increases in already extensive off-label—unapproved—use of the drug. Moreover, substantial numbers of pregnancy exposures continue to be reported (with probably many more not reported), and data from the company's program show that many women have not been receiving the necessary pregnancy testing prior to starting Accutane. Meanwhile, European countries with restrictive distribution schemes for Accutane have use rates 8 to10 times lower than in the United States.

Recognizing these troubling results, in September 2000 an FDA advisory committee (which included dermatologists) unanimously recommended a restricted distribution system for Accutane, with patient and physician registration and other safeguards designed to ensure Accutane would be used as safely as possible.

The FDA initially supported and pursued implementation of this recommendation. However, in the face of medical and legal concerns raised by Roche and the medical community, the FDA did not follow the advisory committee's recommendation and agreed instead to a risk-management plan more restrictive than the existing Pregnancy Prevention Program. One of the criticisms of this Pregnancy Prevention Program had been the suboptimal voluntary participation in the patient survey portion of the program, with an estimated 40% to 50% enrollment rate of women receiving Accutane at its peak and falling to an estimated 25% enrollment rate in the last few years. One of the targets of the new program—called S.M.A.R.T., for System to Manage Accutane Related Teratogenicity—is to achieve a 60% enrollment rate. This would be one metric by which an FDA advisory program next year will evaluate the program's effectiveness and whether it should be continued. Early data from S.M.A.R.T. indicate, however, that the enrollment number and enrollment rate so far are actually below the numbers in the previous program, and are well short of the 60% target.

In response to these points, Roche notes that the 40% participation rate in the patient survey was high compared with the 10% usually observed in voluntary surveys. Roche further notes that the rate of pregnancy reports is far lower than the rate of pregnancies anticipated in the population. Roche also insists the overwhelming amount of use of its drug is in accordance with its label or appropriate off-label use, such as for oncology or to treat severe acne in its early stages to prevent scarring. Given that the S.M.A.R.T. program was implemented in April 2002, both FDA and Roche maintain that it is too early to judge the effectiveness of the program and to let the FDA advisory panel next summer assess the program. Both FDA and Roche agree that there has been about a 20% decline in use of Accutane over the past year. Although the drug went off patent in February, Roche believes the decline in use is tied to the S.M.A.R.T. program.

Some at the FDA have also expressed the concern that mandatory registration would have the unintended effect of generating gray- and black-market sales of Accutane, especially on the internet without direct physician interaction. FDA is already struggling in its attempt to curtail current internet sales of Accutane and

there is a belief that a mandatory registry would exacerbate this problem. There also appears to be a serious question over whether FDA has the authority to impose a mandatory registration on a drug already on the market where the agency is not prepared to withdraw the drug as an imminent hazard.

The second major issue is whether Accutane causes depression and suicide. Those arguing that there is such an association point to the following: the cases of "dechallenge"/"rechallenge," where the patient gets less depressed when taken off the Accutane and then worse when put back on it; the higher prevalence of depression with Accutane than with antibiotics; a higher ranking for Accutane in reports of adverse events involving depression than other medications; and the fact that depression rates for Accutane is under-reported.

It is also argued that there seems to be a plausible biological mechanism by which Accutane could lead to depression and suicide. This involves retinoid receptors in the brain that can bind Accutane and the association of high doses of retinoids—of which Accutane is a derivative—and behavioral mood effects in humans. Finally, the individual case reports, although anecdotal, appear to show powerful and real connections to the drug.

Those arguing against such an association point to the following: the background incidence of suicide is more than 10 times greater than reported for Accutane; the spontaneous reports for suicides are poorly documented, none with psychological autopsy; a proportion of the reports contain information about known risk factors for suicide; no plausible direct pharmacological link between Accutane use and suicidal behavior; the "dechallenge"/"rechallenge" cases may only reflect the cyclical nature of depression; proportional analysis of the reports shows the rates of suicide and depression for Accutane are only slightly higher than the rates seen in antibiotics and oral contraceptives; and reports show a tremendous diversity in the dose and temporal relationship to suicide and depression rather than expected similarities.

Notwithstanding the dispute, FDA has taken the precautionary approach by assuming such an association exists and strengthened the warnings on the psychiatric side effects. Efforts continue to develop ethical clinical trials to research these side effects.

The recent introduction of the generic version of Accutane further complicates some of these issues. Mindful of the millions who have used this drug (many with positive experiences) and the thousands of fetal exposures and many others who may have been harmed, we forge ahead with our questions with an eye toward a constructive examination of this matter and with a hope that a consensus can be formed on how best to move forward in the public interest.

Today's hearing begins with testimony from Dr. Janet Woodcock, the Director of the Center of Drug Evaluation and Research at the FDA. Later we will hear individuals with compelling testimony, both painful and positive, about Accutane. We will also hear from a representative of the March of Dimes, a representative of the Office of Teratology Information Services, and a dermatologist.

At this time I want to express my appreciation to the FDA for the extensive time its staff spent briefing Congressman Stupak and the Committee personnel recently. I also want to compliment FDA Commissioner McClellan and Deputy Commissioner Crawford for their understanding and cooperation in making certain FDA experts available for this hearing. The last panel will feature testimony from George Abercrombie, President and CEO of Hoffman-La Roche.

Finally, a word about my colleague, Bart Stupak, a respected member of our Subcommittee. As many of you know, the gentleman from Michigan lost his son, B.J., while he was using Accutane. My heart goes out to him and his family. He has become intimately involved with the safety issues related to Accutane over the past two years of Subcommittee work and has made an enormous effort to learn and investigate the issues. I salute him for his valuable service in raising these important public health issues.

I welcome the witnesses and look forward to working with my colleagues in considering these matters carefully and fairly.

Mr. DEUTSCH. Thank you, Mr. Chairman. And I want to thank you and Mr. Tauzin for scheduling what is an important public health hearing. Your willingness to return to Washington during the busy holiday recess period to focus on this important matter is commendable.

I also want to join you in recognizing the outstanding work done by our colleague, Congressman Stupak. During the past 2 years, Mr. Stupak has provided extraordinary leadership, working as

hard as I've ever seen a member work on an issue. He has reviewed thousands of documents and conducted countless interviews with key public health officials. The committee and the public owe Mr. Stupak a great deal of gratitude for his steadfast determination to focus on this important public health issue.

The subcommittee has investigated extensively a number of key safety issues related to the prescription drug Accutane. Beneficial drugs often come with serious risks, and Accutane is no exception. Accutane is a known teratogen, which means it can cause severe birth defects. It may also cause psychological changes in some users, resulting in depression, suicide attempts, and even suicide itself. Today's hearing will examine nearly two decades of the FDA's attempts to manage the risks associated with Accutane. Moreover, it will examine whether existing controls, namely, what is now called the SMART program, will adequately protect the public health.

The history of Accutane is more troubling than what is generally known to the public. Both the FDA and CDC early on determined that Accutane was an extremely potent teratogen. As early as the mid-1980's, senior officials at both the FDA and CDC believed that these risks were compelling enough to argue that the drug should be removed from the market as the only viable means of preventing fetal exposures. Such a view was offered by the section chief of an FDA branch more than a decade ago who wrote a 1990 memo which I will quote from the following:

"Accutane poses an immediate hazard to the public health, requiring immediate withdrawal from the market." He goes on to say, "The severity and harm has been recognized and undisputed from early in Accutane's premarketing history. The drug is a potent teratogen, capable of causing severe disabling or fatal birth defects in offspring of women. As the data on drug use and contraceptive failure show, there probably have been 15,000 to 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 1,000 Accutane birth defects."

Despite such concerns, the prescription rate for Accutane has only increased since these words were written. From about 1990 to the present, Accutane sales has risen by as much as 300 percent. This increase may be the result of the Roche direct-to-consumer ad campaign. While some experts believe that much of the increase is attributed to off-label use, some health experts have questioned whether the risks of birth defects are justified by off-label use. Again, the section chief of FDA raised a warning flag in his 1990 memo. Over 90 percent 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 percent of them experienced pregnancy exposure to it.

Throughout Accutane's history, the FDA has struggled to effectively manage the drug's risk; yet despite patient education campaigns, labeling changes, package inserts, and a host of new materials for prescribers, many women using Accutane still become pregnant.

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A new effort to address this problem was made in September 2000 when FDA convened an advisory committee to yet again examine the drug. Panel experts, one of whom will testify today, ultimately recommended that FDA require Roche to implement a formal mandatory registry. Yet for reasons unclear to us, FDA has never implemented such recommendations. Instead FDA agreed to a voluntary plan called the SMART program. Unfortunately, as some experts will testify today, the SMART program may prove unsuccessful in preventing women using the drug from becoming pregnant.

As noted by Dr. Green, who is the medical director for the March of Dimes, "The March of Dimes firmly believes that the SMART system is inadequate to ensure 100 percent participation. We strongly recommend FDA-mandated implementation of a single program that is designed to put in place a more stringent system that would reduce exposure to developing fetuses from Accutane. We further recommend using as a model the highly effective program that is already in place for thalidomide."

In conducting this investigation, it was difficult not to have the word "thalidomide" used in the same sentence as Accutane. Countless public health experts interviewed told us they believe Accutane is as dangerous and perhaps even more dangerous to pregnant women than thalidomide. Several internal documents at FDA and CDC make similar conclusions.

What is odd, however, is that while both Accutane and thalidomide are potent teratogens, the drugs are managed differently by FDA. The system which governs thalidomide, a drug less likely to be used by women of childbearing age, is more tightly managed than Accutane, a drug widely used by women of childbearing age.

Just months before the September 2000 advisory committee, a top expert at FDA outlined the strange irony in a confidential e-mail obtained by this committee, where he wrote the following. "There is no doubt that Accutane is a potent teratogen. Pediatric groups and the CDC have concerns about the apparent asymmetry between the restricted distribution of thalidomide to a population less likely to become pregnant and the open and liberally promoted distribution of Accutane to a population more likely to become pregnant."

I am concerned over the situation and look forward to a full explanation from the FDA as to why these two drugs are treated differently despite their similar risks. Moreover, there are very troubling facts concerning psychological changes in some users. While the data for this issue may not be as well developed as the data concerning birth defects, I believe the committee should continue to examine this matter with great vigor. This aspect of this drug is troubling, and indeed needs more attention.

Mr. Chairman, a number of broader FDA policy issues have also surfaced as a result of this investigation. Similar to the committee's investigation of Oxycontin, Accutane raises a question of what actions the FDA can take when a drug has serious public health effects that surface after the drug has been approved. Both Oxycodone and Accutane have benefits associated with their use, yet in both cases these drugs have caused significant public health concerns which continue today. A central question is whether the

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FDA can forcibly implement an effective risk management plan over a problem drug that has already been marketed.

Mr. Chairman, based on the past 20 years, I fear we will struggle to manage the risks associated with this drug for a long time. It has been more than 15 years since some serious red flags were first raised by the CDC and FDA concerning the safety of this drug, and yet we sit here today still wondering if a sound system has been put in place. To complicate matters further, Accutane now appears widely available across the Internet and may also be available from the hundreds of Mexican pharmacies that now dot the U.S./Mexico border. Both such sources are notorious for lacking even basic regulatory controls and threaten any efforts toward a sound risk management plan. And yet after more than 6 years of this committee investigating border pharmacies and the Internet, the FDA only seems capable of surrendering ground.

I look forward to asking FDA what has become of the recommendation unveiled before this committee almost 2 years ago that the FDA would soon implement a plan to stop rogue Internet sites from shipping dangerous drugs to the U.S. Nothing but silence has come from the Department of Health and Human Services since the recommendation was made.

I will also ask the FDA about the new import alert on Accutane that was clumsily sent out only a few days ago. I find it curious that this alert was posted only 1 week after the committee raised the issue of Accutane Web sites with FDA, even though this has been a known problem for years, and Roche even went so far as to report this problem in writing to the FDA in 2000.

Finally, I intend to ask Roche why drugs appear so loosely controlled that we find them floating about the Internet. We don't see thalidomide widely available, but we do find Accutane.

Thank you, Mr. Chairman. And I yield back.

[The prepared statement of Hon. Peter Deutsch follows:]

PREPARED STATEMENT OF HON. PETER DEUTSCH, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF FLORIDA

Mr. Chairman, I thank both you and Mr. Tauzin for scheduling what is an important public health hearing. Your willingness to return to Washington during the busy holiday recess period to focus on this important matter is commendable. I also wish to recognize the outstanding work done by our colleague, Congressman Bart Stupak. During the past two years, Mr. Stupak has provided extraordinary leadership, working weekends and often past midnight, he has reviewed thousands of documents and conducted countless interviews with key public health officials. The Committee and the public owe Mr. Stupak a great deal of gratitude for his steadfast determination to focus on this important public health issue.

This Subcommittee has investigated extensively a number of key safety issues related to the prescription drug Accutane. Beneficial drugs often come with serious risk, and Accutane is no exception. Accutane is a known teratogen, which means it can cause severe birth defects. It may also cause psychological changes in some users resulting in depression, suicide ideation and attempts, and even suicide itself. Today's hearing will examine nearly two decades of the Federal Food and Drug Administration's (FDA) attempts to manage the risks associated with Accutane. Moreover, it will examine whether existing controls—namely what is now called the SMART program—will adequately protect the public's health.

The history of Accutane is more troubling than what is generally known by the public. Both FDA and the Centers for Disease Control (CDC) early on determined that Accutane was an extremely potent teratogen. As early as the mid 1980's, senior officials at both FDA and CDC believed that these risks were compelling enough to argue that the drug should be removed from the market as the only viable means of preventing fetal exposures. Such a view was offered by the Section Chief of FDA's

Epidemiology Branch more than a decade ago, who wrote in a 1990 memo the following:

> "Accutane poses an immediate hazard to the public health requiring immediate withdrawal from the market." [He goes on to say]... The severity and 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... 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 1,000 Accutane-related birth defects."

Despite such concerns, the prescription rate for Accutane has only increased since those words were written. From about 1990 to the present, Accutane sales have risen by as much as 300%. This increase may be a result of Roche's Direct-to-Consumer ad campaign.

While some experts believe that much of the increase in drugs is attributable to "off label" use, some health experts have questioned whether the risks of birth defects are justified by off label use. Again, the section chief of FDA's Epidemiology Branch raised a warning flag in his 1990 memo:

> "...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... 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 [sic] signed informed consent, pregnancy testing and contraception. The use of Accutane cannot be rendered safe for women even by such a controlled setting."

Throughout Accutane's history, the FDA has struggled to effectively manage the drug's risks. Yet despite patient educational campaigns, labeling changes, package inserts, and a host of new materials for prescribers, many women using Accutane still become pregnant.

A new effort to address this problem was made in September 2000 when FDA convened an Advisory Committee to yet again examine the drug. Panel experts (one of whom will testify today) ultimately recommended that FDA require Roche to implement a formal mandatory registry. Yet, for reasons unclear to us, FDA never formally implemented such recommendations. Instead, FDA agreed to a voluntary plan called the SMART program. Unfortunately, as some experts will testify today, the SMART program may prove unsuccessful in preventing women using the drug from becoming pregnant. As noted by Dr. Green, who is the medial director for the March of Dimes:

> "... the SMART program is inadequate for ensuring our real goal: prevention of Isotretinoin [Accutane] exposures during pregnancy. We strongly advocate FDA-mandated implementation of a single, stringent program to reduce exposure of developing fetuses to Accutane. A highly effective program is already in place for thalidomide."

In conducting this investigation, it was difficult not to have the word "thalidomide" used in the same sentence as Accutane. Countless public health experts interviewed told us they believe Accutane is as dangerous (and perhaps more dangerous) to pregnant women as thalidomide. Several internal documents at FDA and CDC make similar conclusions. What is odd, however, is that while both Accutane and thalidomide are potent teratogens, the drugs are managed differently by FDA. The system which governs thalidomide, a drug less likely to be used by women of childbearing age, is more tightly managed than Accutane, a drug widely used by women of child-bearing age. Just months before the September 2000 advisory committee, a top expert at FDA outlined this strange irony in a confidential e-mail obtained by this Committee, where he wrote the following:

> "There is no doubt that [Accutane] is a potent teratogen... Pediatric groups and the CDC have concerns about the apparent asymmetry between the restricted distribution of thalidomide to a population less likely to become pregnant and the open and liberally promoted distribution [of Accutane] to a population more likely to become pregnant."

I am concerned over this situation and look forward to a full explanation from the FDA as to why these two drugs are treated differently despite their similar risks.

Moreover, there are very troubling facts concerning psychological changes in some users.

Mr. Chairman, a number of broader FDA policy issues also have surfaced as a result of this investigation. Similar to the Committee's investigation of OxyContin, Accutane raises a question of what actions the FDA can take when a drug has serious public health risks that surface after the drug has been approved. Both OxyContin and Accutane have benefits associated with their use, yet in both cases, these drugs have caused significant public health concerns which continue today. A central question today is whether the FDA can forcibly implement an effective risk management plan over a problem drug that has already been marketed.

Mr. Chairman, based on the past 20 years, I fear we will struggle to manage the risks associated with this drug for a long time. It has been more than 15 years since some serious red flags were first raised by the CDC and FDA concerning the safety of this drug, and yet we sit here today still wondering if a sound system has been put in place.

To complicate matters further, FDA has now approved a generic version of Accutane which I believe will only make managing this risk more difficult. Even more troubling, Accutane now appears widely available across the Internet, and may also be available from the hundreds of Mexican pharmacies that now dot the U.S.-Mexico border. Both such sources are notorious for lacking even basic regulatory controls and threaten any efforts toward a sound risk management plan.

And yet after more than six years of this Committee investigating both border pharmacies and the internet, the FDA only seems capable of surrendering ground. I look forward to asking the FDA what became of the recommendation unveiled before this Committee almost two years ago, that FDA would soon implement a plan to stop rogue internet sites from shipping dangerous drugs to the U.S. Nothing but silence has come from the Department of Health and Human Services since that recommendation was made.

I will also ask FDA about their new import alert on Accutane that was clumsily sent out only a few days ago. I find it curious that an alert was posted only one week after the Committee raised the issue of Accutane Web sites with FDA, even though this has been a known problem for years and Roche even went so far as to report this problem in writing to FDA in April of 2000.

Finally, I intend to ask Roche why its drugs appear so loosely controlled that we find them floating about the Internet. We don't see thalidomide widely available, but we do find Accutane. I would like to know why.

Thank you Mr. Chairman and I yield back.

Mr. GREENWOOD. The Chair thanks the gentleman, and recognizes the gentleman from Michigan, Mr. Stupak.

Mr. STUPAK. Thank you, Mr. Chairman, and thank you for holding this hearing on the safety issues surrounding Accutane. I would like to thank the members of the committee who are present for today's hearing.

Two and a half years ago, Laurie, Ken, and I lost our son and brother, B.J., who took his own life. Anyone who knew B.J. Could not understand why a young man with such an outgoing personality and bright future would end his own life. B.J. Taking his own life is contrary to everything he believed in. Only a mother's intuition can sense, and Laurie asked me to check into the prescription drug B.J. Was taking for his acne, Accutane. Parents know their children. Mothers know their children the best. I remember telling Laurie I did not know how an acne medicine could possibly affect B.J.'s state of mind, but I'd check it out. Laurie did not wait for me. She checked on the Internet and found many disturbing facts about the adverse reactions to Accutane that we were never told. The most disturbing fact she found was the February 8, 1998 MedWatch stating, and I quote, "The FDA is advising consumers and health care providers of new safety information regarding the prescription anti-acne drug Accutane, isotretinoin, and isolated reports of depression, psychosis, and, rarely, suicidal thoughts and actions."

The MedWatch went on to say that the FDA and the drug manufacturing are strengthening this label warning even though it's difficult to identify the exact cause of these problems.

If Laurie and I had any idea that Accutane could cause depression, suicide ideation, or suicide, our sons never would have taken the drug. The thought that an acne medication would lead to such devastating side effects never occurred to us. For our family, the risks attributed to Accutane greatly outweighed any of the benefits.

Our dermatologist said that Accutane may cause chapped lips, bloody nose, and dry skin. The dermatologist did not say at any time that the Accutane may cause depression, suicide ideation, or suicide. Our oldest son Ken completed his treatment and appeared to tolerate the drug. The next year, the dermatologist prescribed Accutane for our younger son, B.J., before his acne was very bad. Once on Accutane, B.J.'s triglyceride levels skyrocketed, and he complained of sore joints and headaches. The dermatologist said this was a normal side effect of the drug, and to make sure B.J. Took his Accutane with a meal. B.J.'s triglycerides never really did get close to being normal. B.J. Died on Mother's Day, May 14, 2000, at the age of 17 from a self-inflicted gunshot wound.

After we found the MedWatch, I wondered why the FDA put out this warning 18 years after the drug was approved. What was the basis of the warning? Why were we not told about the risk of depression, suicide ideation, or suicide? Why didn't B.J.'s patient pamphlet mention anything about possible depression, suicide ideation, or suicide? More important, why weren't these warnings on B.J.'s Accutane package which had been revised 4 months after the MedWatch was issued?

Through the help of members of this committee, I was able to obtain the FDA's February 23, 1998 memorandum on isotretinoin and depression, spontaneous report data presented to the Division of Dermatologic and Dental Drug Products dated January 28, 1998. This memo—and we have it right here.

If you look at this memo, it studied 31 cases, 19 suicide attempts and 12 completed suicides. Of the 12 suicides, 10 were males with the median age 17. And it goes on and says, "For the majority, there was no antecedent history of depression, and the patients were not noted or known to be depressed at the time prior to their suicide."

A few days later, I showed the report to the Oversight and Investigation Subcommittee Chair, and asked for an investigation into the safety of Accutane. Today, more than 2 years later, after hours of reviewing thousands of pages of memos, reports, e-mails, medical and scientific literature, and meetings with grieving families, this investigation leads to one conclusion: In some cases, the acne drug Accutane results in cases of depression, suicide ideation, suicide attempts, and suicide.

Accutane is a powerful, dangerous drug, with dangerous consequences for some patients. The birth defects caused by Accutane are horrific. The FDA's response to birth defects and psychiatric events have been inadequate, irresponsible, and unacceptable. Thousands of babies, teenagers, and young adults have died prematurely. While the FDA has been aware of the birth defects since at least 1982 and the psychiatric injuries since 1985, their respon-

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sibility to protect the public has been inconsistent and without direction.

The drug manufacturer, Hoffmann-LaRoche—Roche here in the United States—has continued to put profits before people. They have done everything possible to prevent the American people from learning of the psychiatric injuries and deaths associated with Accutane. Even today I'm sure Roche will deny any causal effect of Accutane with the abortions, the deaths, and the suicides caused by their product.

This hearing, I'm sure, Mr. Chairman, will be much like the Firestone tire hearings where the manufacturer blamed the drivers for their injuries. Firestone blamed the compounding factors on the drivers for driving too fast, riding on underinflated tires, inexperienced drivers, reckless driving, and of course, the old standby—deaths and injuries were not significant when compared to the general population. The manufacturer's best statements were, "You cannot absolutely prove our tires caused the accident."

We will hear Roche make the same type of argument today that we heard in the Firestone tire hearings. We cannot allow the drug manufacturer and the FDA to continue to turn a blind eye to lives lost, families devastated, and dreams dashed by an acne drug. The American people, our children, are not collateral damage in the scheme of corporate profits.

When Laurie and I went public—and she's here today, along with the Pellazaro family, the Bencz family, Turney family, and White family. But when we went public to increase public awareness of the powerful drug and the deaths it caused, the FDA said at that time there were approximately 47 suicides. Today, 2 years later, there are at least 167 suicides attributable to Accutane. Last Friday my office reported another 37 suicides to the FDA. More than 200 suicides are now associated with Accutane. FDA officials indicate that this may only be 1 percent of the actual number of suicides. So, Mr. Chairman, is the number 2,000 or 20,000?

Mr. Chairman, this drug represents a public health concern for the American people. As Members of Congress, we have a responsibility to protect the public health and safety.

Mr. Chairman, in this investigation we found that the National Institute of Health and CDC have also been investigating this drug, and we should hear what they have to say about the health concerns of Accutane. Besides the birth defects and psychiatric injuries, Mr. Chairman, there are other safety—public safety and health concerns with Accutane. As has been mentioned, Accutane birth defects are similar to thalidomide, which is tightly controlled in this country and is used by a group unlikely to have children. Yet Accutane is not tightly controlled like thalidomide, and Accutane is marketed to women of childbearing years, despite its horrendous record of causing birth defects.

Mr. Chairman, this committee, we have spent a lot of time trying to deal with the devastating effects of Oxycontin because the FDA is unwilling or unable to control its use. We have the same, even worse devastation with Accutane, and the FDA is once again unwilling or unable to control its use.

Mr. Chairman, this committee has spent a lot of time dealing with Rohypnol, the date rape drug, pouring across our Mexican

border. Like Rohypnol, Accutane pours into this country from Mexico, where it can be purchased over the counter without a prescription, causing birth defects and deaths, here in this country.

Mr. Chairman, this committee has spent a lot of time trying to deal with the explosion of the sale of dangerous drugs over the Internet, and the FDA claims to be powerless to do anything about it. We find Accutane is being offered on the Internet at approximately 40 Web sites. We don't find thalidomide being offered on the Internet.

How will a pregnancy prevention program and the psychiatric warnings that the FDA relies on to prevent these birth defects and deaths be enforced on Internet sales? If the FDA cannot or will not regulate Accutane and these other drugs, then it is imperative for the U.S. Congress to act to protect the American public. The bottom line remains the safety of our citizens.

Thank you, Mr. Chairman, and thank you once again for having this hearing.

[The prepared statement of Hon. Bart Stupak follows:]

PREPARED STATEMENT OF HON. BART STUPAK, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Thank you Mr. Chairman for holding this hearing on the Safety Issues Surrounding Accutane. I would also like to thank the Members who are present for today's hearing.

Two and one half years ago, Laurie, Ken and I lost our son and brother, BJ, who took his own life. Anyone who knew BJ could not understand why a young man with such an outgoing personality and bright future would end his own life. BJ taking his own life, is contrary to everything he believed in!

As only a mother's intuition can sense, Laurie asked me to check into the prescription drug BJ was taking for his acne, Accutane. Parents know their children. Mothers know their children the best!

I remember telling Laurie, I did not know how an acne medicine could possibly affect BJ's state of mind, but I would check it out. Laurie did not wait for me, she checked on the Internet and found many disturbing facts about adverse reactions to Accutane that we were never told. The most disturbing fact she found, was the February 1998 MedWatch stating "The FDA is advising consumers and health care providers of new safety information regarding the prescription anti-acne drug Accutane (isotretinoin) and isolated reports of depression, psychosis, and rarely suicidal thoughts and actions." The MedWatch went on to say that the "FDA and the drug manufacturer are strengthening this label warning, even though it is difficult to identify the exact cause of these problems."

If Laurie and I had any idea that Accutane could cause depression, suicide ideation or suicide our sons never would have taken the drug. The thought that an acne medication would lead to such devastating side effects never occurred to us. For our family, the risks attributed to Accutane greatly outweigh any of the benefits.

Our dermatologist said that Accutane may cause chapped lips, bloody nose and dry skin. The dermatologist did not say, at any time, that Accutane may cause depression, suicide ideation or suicide.

Our oldest son, Ken completed his treatment and appeared to tolerate the drug. The next year, the dermatologist, prescribed Accutane for our younger son, BJ, *before* his acne was very bad.

Once on Accutane, BJ's, triglyceride levels skyrocketed and he complained of sore joints and headaches. The dermatologist said this was a normal side effect of the drug and to make sure BJ took his Accutane with a meal. BJ's triglycerides never really did get close to being "normal." BJ died on Mother's Day, May 14, 2000, at the age of 17, from a self inflicted gunshot wound.

After we found the MedWatch, I wondered why the FDA put out this warning, 18 years after the drug was approved? What was the basis of the warning? Why were we not told about the risk of depression, suicide ideation or suicide? Why *didn't* BJ's patient pamphlet mention anything about possible depression, suicide ideation or suicide? More important, why weren't these warnings on BJ's Accutane package which had been "revised" 4 months after the MedWatch was issued?

Through the help of members of this committee, I was able to obtain the FDA's February 23, 1998 Memorandum on Isotretinoin and Depression: Spontaneous Report Data presented to the Division of Dermatologic and Dental Drug Products on 1/28/98. This Memo studied 31 cases, 19 suicide attempts and 12 completed suicides. Of the 12 suicides, 10 were males with median age 17, "for the majority, there was no antecedent history of depression and the patients were not noted or known to be depressed in the time period prior to their suicide."

A few days later, I showed the report to the O/I subcommittee chair and asked for an investigation into the safety of Accutane. Today, more than two years later, after hours of reviewing thousands of pages of memos, reports, email, medical and scientific literature, and meetings with grieving families, this investigation leads to one conclusion. In some cases, the acne drug, Accutane results in severe cases of depression, suicide ideation, suicide attempts and suicide.

Accutane is a powerful, dangerous drug with devastating consequences for some patients. The birth defects caused by Accutane are horrific. The FDA's response to the birth defects and psychiatric events has been inadequate, irresponsible and unacceptable. Thousands of babies, teenagers, and young adults have died prematurely. While the FDA has been aware of the birth defects since at least 1982 and the psychiatric injuries since 1985, their responsibility to protect the public has been inconsistent and without direction.

The drug manufacturer, Hoffman-LaRoche, *Roche* here in the United States, has continued to put profits before people. They have done everything possible to prevent the American people from learning of the psychiatric injuries and deaths associated with Accutane. Even, today, I'm sure Roche will deny any casual effect of Accutane with the abortions, deaths, and suicides caused by their product.

This hearing, I am sure will be like the Firestone tire hearings, where the manufacturer blamed the drivers for their injuries. Firestone blamed the compounding factors in the drivers for "driving too fast, riding on under inflated tires, inexperienced drivers, reckless driving, and of course, the deaths and injuries were not significant when compared to the general population. The manufacturer's best statements were "you cannot absolutely prove that our tires caused the accident." We will hear Roche make the same type of arguments today that we heard in the Firestone tire hearings.

We cannot allow the drug manufacturer and the FDA to continue to turn a blind eye to the lives lost, families devastated and dreams dashed by an acne drug. The American people, our children, are not collateral damage in the scheme of corporate profits!

When Laurie and I went public (she is here today along with the Palazzolo, Bencz, Turney, and White families) to increase public awareness of this powerful drug and the deaths it has caused. The FDA said there were approximately 47 suicides in October 2000. Today, two years later, there are 167 suicides attributable to Accutane. Last Friday, my office reported another 37 suicides to the FDA. More than 200 suicides are now associated with Accutane. FDA officials indicate that this may only be 1% of the actual number of suicides. So is the number 2,000 or 20,000 Mr. Chairman?

Mr. Chairman, this drug represents a public health concern for the American people. As members of Congress, we have a responsibility to protect the public health and safety of the American people.

Mr. Chairman, in this investigation we have found that the NIH and CDC have been investigating this drug and we should hear what they have to say about the health concerns of Accutane.

Besides the birth defects and psychiatric injuries Mr. Chairman, there are other public safety and health concerns with Accutane.

The Accutane birth defects are similar to Thalidomide, which is a tightly controlled drug in this country and is used by a group unlikely to have children. Yet, Accutane is not tightly controlled like Thalidomide and Accutane is marketed to women of child bearing years despite its horrendous record of causing birth defects.

Mr. Chairman, this committee has spent a lot of time trying to deal with the devastating effects of Oxycontin because the FDA is unable or unwilling to control its use. We have the same, even worse devastation with Accutane and the FDA is unwilling or unable to control its use.

Mr. Chairman, this committee has spent a lot of time dealing with Rohypnol pouring across our Mexican border. Like Rohypnol, Accutane pours into this country from Mexico, where it can be purchased over the counter without a prescription, causing birth defects and deaths here in this country.

Mr. Chairman, this committee has spent a lot of time trying to deal with the explosion of the sale of dangerous drugs over the Internet and the FDA claims to be powerless to do anything about it. We find Accutane is being offered on the Internet

at approximately 40 web sites. How will the pregnancy prevention program and the psychiatric warnings that the FDA relies on to prevent birth defects and deaths are enforced on Internet sales?

If the FDA cannot or will not regulate Accutane and these other drugs, then it is imperative for the US Congress to act to protect the American public. The bottom line remains the safety of our citizens.

Mr. GREENWOOD. The gentleman is welcome, and the Chair thanks the gentleman.

Now, the gentlelady from Colorado is recognized for her opening remarks.

Ms. DEGETTE. Thank you, Mr. Chairman. And I want to thank everyone for their hard work on this issue.

Since 1971, Hoffmann-LaRoche, who makes Accutane, has been aware of its link to birth defects. In fact, the drug had been developed at that time in 1971, but Roche decided to withhold it from the market because of those risks. In 1982, 11 years later, Roche received approval from the FDA to put Accutane on the market to treat patients with severe acne and without other options. And in the same year, though, Roche began to learn about the cases of birth defects in the babies of women who had been taking the drug.

The next year, in 1983, a doctor employed by Roche told the CDC doctor that he would recommend that any woman exposed to Accutane during pregnancy have an elective abortion; that Roche was considering the drug to have nearly 100 percent teratogenicity. He went on to say, "Roche had no—no reports of normal outcomes in exposed women."

This was 19 years ago. Roche's own doctors knew that pregnant women exposed to Accutane had a nearly 100 percent chance of giving birth to children with defects, yet it took actions by the FDA in 1984 to make the warnings on Accutane stronger. Still this did not stop the occurrence of birth defects. In 1988, the director of the CDC's Division of Birth Defects in a letter to the FDA warned that the problems with Accutane are as serious as thalidomide in its ability to cause birth defects. He went on to say that something can be done about Accutane. He said, in this instance, we know how to prevent further cases; we simply need to remove the drug from the market.

Warnings like this continued, and in 1990, 8 years after Accutane was introduced to the market and 12 years ago, a memo was sent from the FDA Center for Drug Evaluation Research to the director of the FDA's Antiinfective Drug Products Division. It said, "Accutane poses an imminent hazard to the public health, and, as such, should be withdrawn immediately from the market."

These communications show that the FDA and Roche knew about the extreme risks of Accutane and could have taken precautions that would have better protected pregnant women. Although the FDA gave Accutane a category X rating, which should have restricted it from pregnant women, as early as 1990 the FDA believed that between 15,000 and 18,000 pregnant women had been exposed to Accutane, and that there had been between 11,000 and 13,000 abortions relating to the drug.

I was talking to committee staff about this last night. And the reason why we haven't seen the big public outcry around Accutane that we did around thalidomide is because people taking Accutane who get pregnant simply have abortions. Which is insane to me.

So why did the FDA not establish tighter controls, like a registry, as we have with thalidomide? What they have done, as we've heard, Roche and the FDA revamped their control program just this year finally, to try to reduce the risk of women getting pregnant while they are taking Accutane. But the program is voluntary and Accutane remains easily accessible on the Internet as well as in border pharmacies like in Mexico. In order to ensure that the threat to women is completely controlled, we—as with thalidomide, we must seriously consider establishing a strict prescription regime. The need to establish strict controls on Accutane is especially important considering the state of additional and very serious adverse side effects that are potentially linked to the drug and the availability of the recently approved generic drug, Amnesteem.

Just this year some people have reported, as we have heard, that Accutane could be linked with aggression and violent behavior, and there is now considerable evidence to believe that Accutane is linked to depression and suicide. Further studies on these issues are needed by the FDA and independent parties, and I hope that they will occur after these hearings. But there is one thing that is clear: If you get pregnant while you are taking this drug, you have a 100 percent chance of having a baby with birth defects. And that is why virtually everyone who gets pregnant while taking this drug has an abortion. I think that that's wrong. I think that the FDA needs to get a grip on this. And I think, if they don't, Congress needs to act.

And I thank you, and I yield back, Mr. Chairman.

[The prepared statement of Hon. Diana DeGette follows:]

PREPARED STATEMENT OF HON. DIANA DEGETTE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF COLORADO

Thank you, Mr. Chairman and thank you for holding this hearing today. Accutane is an extremely powerful and potentially dangerous drug approved to treat a very specific type of acne after other treatment options have failed. The safety of Accutane is a tremendously important issue for patients, parents, and physicians. I hope that this hearing will help to increase patient knowledge of the possible adverse reactions that can occur from the use of Accutane and reduce the number of people whose lives are damaged by its negative effects.

Since 1971, Hoffman-LaRoche, the makers of Accutane, have been aware of its link to birth defects. In fact, the drug had been developed at that time but Roche decided to withhold it from the market because of these risks. In 1982, Roche received approval from the FDA to put Accutane on the market to treat patients with severe acne and no other options and in the same year, they began to learn about cases of birth defects in the babies of women who had been taking Accutane. Then, in 1983, a doctor employed by Roche told a CDC doctor [as quoted by the CDC doctor] that he "would recommend that any women exposed to Accutane during pregnancy have an elective abortion, that Roche was considering the drug to have nearly 100% teratogenicity..." He went on to say that "Roche had had no reports of normal outcomes in exposed women." This was nineteen years ago.

Roche's own doctors knew that pregnant women exposed to Accutane had a nearly 100% chance of giving birth to children with defects, yet it took actions by the FDA in 1984 to make the warnings on Accutane stronger. Still, this did not stop the occurrence of birth defects.

Given this history, I believe this committee must look carefully at the actions and in-actions of the FDA, the CDC, and Roche. In 1988, the director of the CDC's Division of Birth Defects, in a letter to the FDA, warned that "the problems [with Accutane] are as serious as thalidomide..." in its ability to cause birth defects. He went on to say that something can be done about Accutane. He said, "In this instance we know how to prevent further cases. We simply need to remove the drug from the market." Warnings like this continued and in 1990, eight years after Accutane was introduced to the market, a memo was sent from the FDA's Center

for Drug Evaluation and Research (CDER) to the director of FDA's Anti-Infective Drug Products division. It said, "Accutane poses an imminent hazard to the public health, and as such should be withdrawn immediately from the market."

I am concerned by these communications because it appears that the FDA and Roche could have taken precautions that would have better protected pregnant women. The FDA gave Accutane a category X rating, which should have restricted it from pregnant women. However, as early as 1990, the FDA had reason to believe that between 15,000 and 18,000 pregnant women had been exposed to Accutane and that there had been between 11,000 and 13,000 abortions related to the drug.

So, why did the FDA not take precautions that had been taken with other drugs that cause severe fetal abnormalities, like thalidomide? Although thalidomide was never approved in the United States for use outside of investigational clinical trials, I believe we might learn a lot about how to stop these abnormalities from occurring by considering stronger control mechanisms like limiting the authority to prescribe the drug and maintaining patient registries. Just this year, Roche and the FDA revamped their control program to try to reduce the risks of women getting pregnant while taking Accutane. But, this program is voluntary and Accutane remains easily accessible on the Internet as well as in Mexico. In order to ensure that the threat to women is completely controlled, we must seriously consider establishing a strict prescription regime.

The need to establish strict controls on Accutane is especially important considering the spate of additional and very serious adverse side effects that are potentially linked to Accutane and the availability of the recently approved generic version of Accutane, Amnesteem. Just this year, some people have reported that Accutane could be linked with aggression and violent behavior and there is considerable evidence to believe that Accutane is linked to depression and suicide. But, further studies are needed by the FDA and independent parties. I would like to know what the FDA is doing to investigate these issues and to ensure that more and more people are not exposed to horrible negative effects.

I understand that Accutane can provide relief to those individuals suffering from severe acne and that many times it is the only method that works. But, this does not mean that we should allow a potentially dangerous product to flow through the market with inadequate controls.

Thank you, Mr. Chairman.

Mr. GREENWOOD. The Chair thanks the gentlelady, and recognizes the gentleman from Louisiana, Mr. John, for his opening remarks—who passes. The Chair then recognizes Mr. Rush for an opening statement.

Mr. RUSH. I pass.

Mr. GREENWOOD. All right. In that case, Mr. Waxman.

Mr. WAXMAN. Thank you very much, Mr. Chairman. I want to commend you for holding this hearing. It's important that we look into this issue, because Accutane obviously poses enormous risks to many people. I want to also join in commending my colleague Mr. Stupak for bringing this issue to the forefront and raising our consciousness about it and insisting that we delve into it and make sure that we do all that we can to protect people from the harms that Accutane may bring.

Although Accutane is the only effective drug for a very serious disfiguring form of acne, it poses severe risks. These risks include birth defects and organ damage, and the drug has also been linked to serious psychiatric disorders and suicide. Accutane is a powerful reminder that while drugs can provide miraculous cures for some people, they can be lethal for others.

When our government decides to permit the marketing of an effective but potentially lethal drug like Accutane, the government and the manufacturer have an unusually high responsibility to the patients who receive that drug. They have a responsibility to ensure that every possible precaution is taken to minimize the risks of the drug. And if they aren't successful in minimizing the risks, they have a responsibility to ensure that the drug is not being pre-

scribed for less severe conditions where the benefits of the drug do not outweigh its risks.

We are here today because despite a long and well-intentioned history of attempts to prevent pregnancies and associated birth defects in women taking Accutane, the government and the manufacturer have so far failed in their responsibility. It is simply unjustifiable to expose young people to severe side effects and expose babies to serious birth defects to gain only modest cosmetic improvements.

I would note that there was an FDA panel that made recommendations for carefully prescribing—proscribing the way this drug would be used. Unfortunately, the FDA's advisory committee recommendations were turned into a voluntary program. I think we need to review whether that was appropriate action and whether more needs to be done.

I am deeply concerned that we will continue to see pregnancies, birth defects, and other serious adverse effects unless and until there are mandatory restrictions on Accutane's distribution. We need firm rules that require pregnancy tests before the drug can be dispensed in compliance with contraception guidelines. We also must limit distribution to patients who truly have the serious disfiguring disease for which the drug is approved, and without these restrictions we cannot claim that we have fulfilled our significant responsibility to the patients who use this toxic drug.

I appreciate that we are holding this hearing, and I look forward to the testimony of our witnesses today.

[The prepared statement of Hon. Henry A. Waxman follows:]

PREPARED STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Today's hearing on the drug Accutane addresses an issue of great importance affecting the health of many Americans. I want to begin by commending the work of Congressman Bart Stupak. His tireless efforts to raise public awareness about the risks of Accutane have, I'm sure, already helped many families. His efforts have also been instrumental in encouraging Hoffman-LaRoche and the FDA to do more to learn about the risks of Accutane and to inform patients and families about those risks.

Although Accutane is the only effective drug for a very serious, disfiguring form of acne, it poses severe risks. These risks include birth defects and organ damage, and the drug has also been linked to serious psychiatric disorders and suicides. Accutane is a powerful reminder that while drugs can provide miraculous cures for some people, they can also be lethal for others.

A drug is approved only when the FDA concludes that its benefits outweigh its risks. When Accutane is used to treat the severe, physically and psychologically scarring form of acne for which it was approved, I agree that its benefits outweigh its considerable risks. Nevertheless, I believe that when our government decides to permit the marketing of an effective, but potentially lethal drug, like Accutane, the government and the manufacturer have an unusually high responsibility to the patients who receive that drug. They have a responsibility to ensure that every possible precaution is taken to minimize the risks of the drug. And, if they are unsuccessful in minimizing risk, they have a responsibility to ensure that the drug is not being prescribed for less severe conditions, where the benefits of the drug do not outweigh its risks.

We are here today because, despite a long and well-intentioned history of attempts to prevent pregnancies and associated birth defects in women taking Accutane, the government and the manufacturer have so far failed in their responsibility. Since Accutane's approval in 1982, Roche has received over 2,200 reports of Accutane-exposed pregnancies and 167 babies with birth defects. A majority of the exposed pregnancies occurred *after* the initiation of the Pregnancy Prevention Program in 1988, a program of enhanced labeled warnings, informed consent docu-

ments for patients, and educational materials for physicians. And over 150 cases of suicide and hospitalized depression have been linked to Accutane, despite increasingly strong warnings in the drug's label.

Perhaps most discouraging of all, even as the number of severe adverse events has continued to mount, use of the drug has both increased and shifted toward milder forms of acne. An FDA study published this year showed that use of the drug more than doubled between 1993 and 2000, and that prescriptions for mild to moderate acne increased from less than a third to almost half of all prescriptions for Accutane. It is simply unjustifiable to expose young people to severe side effects and expose babies to serious birth defects to gain only modest cosmetic improvements.

Accutane's manufacturer, which has aggressively marketed the drug and even embarked on a program of direct-to-consumer advertising, bears much of the responsibility for this inappropriate change in usage. Physicians who prescribe Accutane for mild acne and fail to ensure that their patients are adequately warned of the risks and do not become pregnant bear responsibility as well.

After reviewing the largely unsuccessful attempts to prevent pregnancies in patients taking Accutane, as well as the reports of psychiatric disorders, an FDA advisory committee recommended in September of 2000 that a new set of restrictions be placed on Accutane. Their primary goal was to ensure that no pregnancies would occur in patients taking Accutane.

To accomplish this, the advisory committee recommended: (1) required registration of all patients taking Accutane, and (2) required registration and certification of practitioners who prescribe Accutane. The purpose of these recommendations was to ensure once and for all that no Accutane would be dispensed without a negative pregnancy test and adequate use of contraception. These recommendations were a welcome change from past initiatives, all of which had been voluntary rather than mandatory. They would have finally imposed on Accutane the stringent restrictions that FDA imposes on another birth-defect producing drug, Thalidomide. And they would have imposed a system of restrictions more like the restrictions imposed on Accutane in Europe, where the incidence of birth defects is a tiny fraction of the incidence in the U.S.

Unfortunately, it appears that Accutane's manufacturer convinced FDA that required registration and certification were unnecessary for Accutane, and that yet another voluntary program should be tried. We will hear testimony today that reports of pregnancies in women taking Accutane have continued even after the initiation of this new program.

I am deeply concerned that we will continue to see pregnancies, birth defects, and other serious adverse effects, unless and until there are mandatory restrictions on Accutane's distribution. We need firm rules that require pregnancy tests before the drug can be dispensed and compliance with contraception guidelines. We also must limit distribution to patients who truly have the serious, disfiguring disease for which the drug is approved. Without these restrictions, we cannot claim that we have fulfilled our significant responsibility to the patients who use this toxic drug.

Mr. GREENWOOD. Mr. Brown.

Mr. BROWN. I thank the chairman. I want to welcome Dr. Woodcock and thank her for the good work she does, and thank my colleague Mr. Stupak for this work.

This issue has significant bearing on the well-being of young adults with the most severe forms of acne. As we know, it has significant bearing—despite the fact that Accutane is only indicated for severe cystic acne, 49 percent of prescriptions are actually going to teenagers with mild to moderate forms of acne. It's a drug that causes severe birth defects, may be linked to suicide; yet 49 percent of the prescriptions, as I said, are going to teens who don't have severe acne. What's going on here? Where is the Food and Drug Administration?

This hearing should have a bearing on the way FDA does business. Last year FDA testified before this committee that the Agency's obviously doing a good job because the market share of U.S. Drug manufacturers is growing. Let me say that again. They came in here, the first thing they told us was the Agency is obviously

doing a good job because the market share of U.S. Drug manufacturers is growing.

FDA was not created—it was not created to make the drug industry or the device industry more profitable; it was created to protect and promote public health. Taking a close look at the history of Accutane means evaluating FDA's performance against the job it's actually supposed to be doing: promoting the health of Americans.

Accutane has been on the market for 20 years. It may be more dangerous, as Mr. Stupak said, from a public health perspective than thalidomide because it reaches so many more patients. Yet, as Mr. Stupak also pointed out, it remains more loosely regulated than thalidomide. Why? What possible justification could FDA have for supporting voluntary approaches to the regulation of this drug? The only argument I've heard against a mandatory registry is something called diversion. The theory is to avoid a mandatory system. Teens will get Accutane from other kids or buy it off the Internet or get it from Mexico. With all due respect, it's the price of Accutane, not the regulatory scheme around it, that will lead kids to get it off the Web or get it from Mexico or from friends. As long as U.S. prices are two and three and four times higher than they are in other countries, Americans are going to look elsewhere for prescription drugs. That's why seniors are splitting pills in half, that's why Americans travel to Canada, that's why teens are buying Accutane from Mexico.

But between 1997 and 2000, Roche increased the price of Accutane 13 times. In those 3 years, the price of the drug increased 50 percent. It appears Roche was not concerned that affordability might drive adolescents to unsafe practices like taking a friend's prescription or buying it off the Internet or going to Mexico. FDA must provide a better reason than diversion for giving yet another voluntary scheme a chance at the risk of preventable disability and death. As I mentioned before, half of all Accutane prescriptions go to kids who don't have severe acne. In that context, I'm astounded by the nudge/nudge, wink/wink attitude toward off-label use of Accutane and FDA's complacency toward the broad-stroke promotion of this drug.

Until recently, Roche advertised Accutane indirectly through an acne education campaign. Roche never referenced Accutane directly in their acne education campaign. But let me quote from their 2001 product strategic plan for Accutane. About their direct or consumer acne campaign, Roche said: Historical Accutane data shows a strong relationship between DTC spending and unit sales of Accutane.

No kidding. Who is kidding whom here? Roche provided the education campaign to increase sales of Accutane. They didn't target just kids with severe, recalcitrant, nodular acne. And by no coincidence, the number of prescriptions for Accutane increased 250 percent in the last 8 years. No surprise there. Yet, in FDA's regulatory scheme, since the manufacturer did not use the word "Accutane," they weren't advertising for the drug.

Let me ask the question again. How is the consumer served by an FDA with far too much industry influence on FDA served by this head-in-the-sand approach? Over the last year, FDA's clearly—

has clearly significant soul-searching about the burden it places on the companies it regulates. This increasingly politicized Food and Drug Administration is now worried that it's overregulating advertising apropos of nothing: no lawsuit, no threatened lawsuit, just a bunch of political appointees too close to the industry.

The FDA's decided to solicit comments on whether it's appropriate for the Agency to regulate promotional materials. This is the FDA that with more and more drug industry executives opposed by President—appointed by President Bush is worried that it sends out too many warning letters. Since February, when FDA placed a new layer of bureaucracy between the determination of need and the actual issuance of these letters, the number of warnings has gone down 70 percent. Seventy percent. There is no data to suggest that compliance miraculously increased by 70 percent over that time period. There is no evidence that FDA is more stringently cracking down on the companies that receive a few letters that do go out.

I have one question, Mr. Chairman, in closing about FDA's compassion to conservatism. What about consumers? How does their well-being fit in? Accutane suggests that we should be more vigilant in regulating advertising, not less vigilant. It suggests FDA needs to distant itself from the industries its regulates, and truly consistently doggedly put the consumer first. Look at some of these promotional, these sort of—these promotional materials that the FDA has allowed Accutane and Roche to promote. It suggests that things have got to change.

I hope today's hearing will help us determine whether rethinking the regulation of Accutane should be a first step and that the FDA will return to its mission of promoting public health, not promoting the drug industry which seems to have more and more control over that Agency, Dr. Woodcock notwithstanding and her good work. Thank you.

[The prepared statement of Hon. Sherrod Brown follows:]

PREPARED STATEMENT OF HON. SHERROD BROWN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OHIO

Thank you, Mr. Chairman. This issue is important.

It has significant bearing on the wellbeing of young adults with the most severe form of acne.

It has significant bearing on the wellbeing of young adults with milder forms of acne. Despite the fact that Accutane is *only* indicated for severe cystic acne, *49%* of prescriptions are actually going to teens with mild to moderate forms of acne.

This is a drug that causes severe birth defects and may be linked to suicide. Yet 49% of the prescriptions are going to teens who don't have severe acne. What is going on here? Where is FDA?

This hearing *should* have bearing on the way FDA does business. Last year FDA testified before this committee that the agency is obviously doing a good job, because the market share of US drug manufacturers is growing.

FDA was not created to make the drug industry or the device industry more profitable. It was created to protect and promote the public health.

Taking a close look at the history of Accutane means evaluating FDA's performance against the job it is actually supposed to be doing—that is, promoting the health of Americans. A

ccutane has been in the U.S. market for 20 years.

It is more dangerous, from a public health perspective, than thalidomide, because it reaches so many more patients. Yet it remains more loosely regulated than thalidomide. Why?

What possible justification could FDA have for supporting voluntary approaches to the regulation of this drug?

The only argument I've heard against a mandatory registry is something called "diversion."

The theory is that to avoid a mandatory system, teens will get Accutane from other kids or buy it off the internet or get it from Mexico.

With all due respect, it's the price of Accutane, not the regulatory scheme around it, that will lead kids to get it off the web or from friends or from Mexico.

As long as US prices are 2 and 3 and 4 times higher in the United States than they are in other countries, Americans are going to look elsewhere for prescription drugs.

That's why seniors are splitting pills in half, that's why Americans are traveling to Canada to purchase their drugs, and that's why teens are buying Accutane from Mexico.

Between 1997 and 2000, Roche increased the price of Accutane 13 times. In those 3 years, the price of the drug increased more than 48%. It appears Roche was not concerned that affordability might drive adolescents to unsafe practices like taking a friend's prescription or buying off the internet.

FDA must provide a better reason than "diversion" for giving yet another voluntary scheme a chance at the risk of preventable disability and death.

As I mentioned before, about half of all Accutane prescriptions go to kids who don't have severe acne. In that context, I am astounded by the "nudge-nudge wink-wink" attitude toward off-label use of Accutane and FDA's complacency toward the broad-stroke promotion of this drug.

Until recently, Roche advertised accutane indirectly through an "acne education campaign."

Roche never referenced Accutane directly in their acne education campaign. But let me quote from their 2001 Product Strategic Plan for Accutane. About their DTC acne campaign, they say: "Historical Accutane Data shows strong relationship between DTC spending and unit sales" of Accutane.

Who's kidding who here. Roche provided the education campaign to increase sales of Accutane. They didn't target just kids with severe recalcitrant nodular acne. And, by no coincidence, the number of prescriptions for Accutane increased 250% in the last 8 years.

Yet, in FDA's regulatory scheme, since the manfacturer did not use the word Accutane, they were not advertising the drug. Let me ask the question again. How is the consumer served by this head-in-the-sand approach?

Over the last year, FDA has clearly significant soul-searching about the burden it places on the companies it regulates.

The agency is worried it is over-regulating advertising. Apropos of nothing—no lawsuit, no threatened lawsuit—FDA decided to solicit comments on whether it is appropriate for the agency to regulate promotional materials.

FDA is worried that it sends out too many warning letters. Since February, when FDA placed a new layer of bureaucracy between the determination of need and the actual issuance of these letters, the number of warnings has gone down 70%. *70%.*

There is no data to suggest that compliance miraculously increased by 70% over that time period. There is no evidence that FDA is more stringently cracking down on the companies that receive the few letters that do go out.

I have one question about FDA's compassionate conservatism. What about consumers? How does their wellbeing fit in?

The Accutane example suggests that we should be more vigilant in regulating advertising, not less. It suggest FDA needs to distance itself from the industries it regulates, and truly, consistently, doggedly, put the consumer first.

It suggests that things have got to change. I hope today's hearing will help us determine whether rethinking the regulation of Accutane should be the first step.

Mr. GREENWOOD. The Chair thanks the gentleman.

The other gentleman from Ohio, Mr. Gillmor.

Mr. GILLMOR. Thank you, Mr. Chairman. And I want to commend you for holding this hearing, and I am going to submit my statement and I thank you.

[The prepared statement of Hon. Paul Gillmor follows:]

PREPARED STATEMENT OF HON. PAUL E. GILLMOR, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OHIO

Mr. Chairman, with the number of patients taking Accutane on the rise, I appreciate the opportunity to hear from "Roche," this acne-fighting drug's manufacturer, the FDA, and others affected by its use.

Of note, the fact that Accutane, primarily prescribed to our nation's youth, ranks among the top 10 drugs in the FDA's database in terms of the number of reports of depression and suicide attempts among its users raises one of a number issues.

In particular, I look forward to learning more about what steps "Roche" and the FDA are taking to minimize risks associated with the drug such as its known birth defects and potential psychological effects. I am also hopeful that the programs advised by the FDA and implemented by "Roche" are both progressing and effective. Furthermore, I am anxious to know more about recent efforts such as appropriate labeling, preventive measures in the sale of Accutane over the Internet, as well as the witnesses' evaluations of the progress being made by the FDA and the drug's manufacturer.

I thank the Chairman and yield back my time.

Mr. GREENWOOD. The Chair thanks the gentleman.

The gentleman from Texas, Mr. Green, for 3 minutes.

Mr. GREEN. Thank you, Mr. Chairman. I would like to submit my complete opening statement. I appreciate the courtesy again, not being a member of the subcommittee, but allowing us from the Health Subcommittee to sit in because of the number of contacts we have had, and, of course, in respect for our colleague's loss. And I appreciate the Oversight and Investigations Subcommittee investigating it. Thank you.

[The prepared statement of Hon. Gene Green follows:]

PREPARED STATEMENT OF HON. GENE GREEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Thank you, Mr. Chairman, for allowing me to sit in on this Oversight and Investigations Hearing about the safety of the pharmaceutical Accutane.

Like many of my colleagues, I represent individuals who have suffered from the adverse events associated with Accutane.

Whether it's the plight of a young mother whose child has horrifying birth defects, or the parents of a normal, healthy teenage boy who, for no apparent reason, takes his own life, there are far too many Americans who have suffered from the side effects of this drug.

Since its approval in 1982, 2,261 pregnancies have been affected by Accutane. Of these, 1,328 were terminated, 252 ended in miscarriages, 195 resulted in normal babies, and 167 children were born with birth defects.

The figures are no less disturbing when it comes to psychological side effects. Accutane ranks among the top ten drugs in the FDA's database in terms of the number of reports of depressions and suicide attempts among its users.

In an odd coincidence, the FDA has received 167 reports of Accutane-associated suicide—the same number of children born with birth defects.

There is little doubt, however, that both of these numbers are low estimates, and do not reflect the many, many other unreported cases of suicide, depression, and birth defects associated with Accutane.

These problems raise important questions about whether the FDA, physicians, and the manufacturer are doing enough to prevent these adverse events.

One specific area of concern is the manufacturer's decision to disregard FDA recommendations that they create a mandatory registry of all patients receiving Accutane and all practitioners prescribing Accutane. Instead, they created a voluntary system that has been criticized as being insufficient.

Equally concerning is the FDA's decision to sign off on that system, despite the fact that a more stringent—and effective—system is in place for thalidomide—a drug that is less likely to be used by women of childbearing age.

The testimony we will hear regarding these problems will give us much insight and will hopefully aid us in crafting appropriate public policy to address this situation.

I would like to thank the witnesses who are here today, and would like to extend my deepest sympathies to those families that have endured the loss of a loved one who was taking Accutane.

This is undoubtedly a painful topic for all of you, and I applaud you for your courage and advocacy so that other families will not have to suffer the same fate.

I also thank Mr. Stupak for his unending commitment and dedication to this cause. You have fought tirelessly for better understanding of this problem and have

worked to find a solution. I thank you for all you have done to shed light on this important problem.

Mr. Chairman, this is an important issue, and I thank you for holding this oversight hearing. I hope that we can continue to study it and do more as a committee to ensure that all of the drugs and devices approved by the FDA are safe, and that the risks associated with these devices are widely known.

Thank you, and I yield back the balance of my time.

Mr. GREENWOOD. The Chair thanks the gentleman.

And without objection, all other opening statements will be made a part of the record.

[Additional statement submitted for the record follows:]

PREPARED STATEMENT OF HON. W.J. "BILLY" TAUZIN, CHAIRMAN, COMMITTEE ON ENERGY AND COMMERCE

Thank you, Mr. Chairman, for holding this hearing, which promises to provide a revealing case study of the drug called Accutane. Let me also thank you, Bart Stupak, for your tireless dedication to this issue, and join my colleagues in extending my deep sympathies to you and your family for your tragic loss. I commend you for your hard work for positive change to public health out of this tragedy.

The Accutane story is a story of what some have called a "failed regulatory experiment." It is a 20-year story of how FDA, industry, and the medical community have struggled to manage difficult safety and risk problems in a drug already approved and on the market. Accutane is a powerful drug that causes side effects in virtually all users, ranging from chapped lips to birth defects, organ damage, and, we are now learning, possible connection to psychiatric events.

But it is the drug's very dangerous power that makes it the only effective treatment for the disfiguring disease of severe, cystic, nodular acne and helps prevent scarring. People's lives have been positively transformed because of it. This drug, I also understand, has great promise for treating cancer, including in children.

But we cannot escape the fact that Accutane causes birth defects. Both FDA and Roche Pharmaceuticals, Accutane's maker, knew this when the drug was approved 20 years back. They first thought the problem could be minimized through warnings and labeling. Unfortunately, pregnancy exposures occurred—abortions, miscarriages, deformed babies followed.

Then, Roche proposed a Pregnancy Prevention Program, which FDA did not agree was an adequate program but nevertheless accepted because the agency apparently perceived it lacked the legal and scientific leverage to force Roche into a more restrictive management program.

Roche's program did reduce the pregnancy rates and those rates were extremely low relative to the background rate. But because of the skyrocketing usage, the number of fetal exposures went up. And limits in Roche's program mean we don't even know the true scope and nature of the pregnancy exposure problem.

So by 2000, outside experts and the FDA pushed for a mandatory registry, but Roche and the medical community again offered an alternative—a toughened pregnancy prevention program called SMART. Once more, it appears the FDA believed it lacked the leverage to force Roche into a mandatory registry. So FDA agreed to SMART as an interim action.

When FDA convenes the next advisory committee meeting, by the summer of 2003, judgment day will arrive for Accutane. Either SMART works sufficiently or it doesn't. The Subcommittee's investigation has shown there are real reasons to believe that, while SMART is a stronger program than Roche's previous one, it still suffers from some of the same flaws. Use of this product is down over the last year, but it is more widely available on Internet pharmacies outside the SMART program and we don't know what impact the launch of the generic version of Accutane will have on usage.

Now, misuse of this product is what concerns us. We have data that makes us suspicious. Even the voluntary survey data and anecdotal reports show many women getting Accutane had no cysts and did not suffer from severe acne.

Look, you can read in popular women's fashion magazines glowing profiles of Accutane as the skin-care drug of choice in Hollywood, downplaying the terrible consequences of this chemical on the body.

I understand that Roche denies the drug is overprescribed, but we have little recent data from the company supporting this assertion. If Roche maintains there is little misuse, show us the data. Roche, as a marketer of a powerful teratogen, has an obligation to know more about the epidemiology of the disease and the use of the product. Roche could put their marketing people to work, compensate the der-

matologists for their time, and get new and more detailed information. This is the kind of information that could help guide the FDA and the advisory committee.

Finally, Mr. Chairman, I think the message from today's hearing should be: no more band-aids. Child-bearing-age women and unborn children deserve the most rigorous safety program possible. There may be valid arguments against a mandatory registry for Accutane. However, without new market research data from Roche, we'll need spectacular results from SMART in the next six months to believe we have best safety possible for Accutane.

Thank you, Mr. Chairman, I'll look forward to the testimony.

Mr. GREENWOOD. The Chair now welcomes Dr. Woodcock. You are aware, Dr. Woodcock, that this committee is conducting an investigative hearing, and when we do that, it's our practice to take testimony under oath. Do you have any objections to giving your testimony under oath? Very well. And I would advise you that pursuant to the rules of this committee and the House, you are entitled to be represented by counsel. Do you choose to be represented by counsel this morning? No. Okay. In that case, if you would rise and raise your right hand.

[Witness sworn.]

Mr. GREENWOOD. Okay, you are under oath. Again, we welcome you, and you are recognized to make your statement.

TESTIMONY OF JANET WOODCOCK, DIRECTOR, CENTER FOR RUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION

Ms. WOODCOCK. Thank you. Mr. Chairman, and members of the committee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research at the FDA. I thank you for the opportunity to testify on the important issue of risk management for isotretinoin. I would also like to express FDA's gratitude to the patients and family members who are here to testify today. Your experiences and points of view are very important in these deliberations, and are always taken into account by the Agency.

Accutane, or isotretinoin, was approved for marketing by FDA in 1982. Its potential for causing birth defects, as has already been noted, was known at the time it was approved. Over the ensuing decades, FDA, the sponsor, and the dermatologic community have struggled with the issue of preventing the exposure of pregnant women to this drug. In the late 1990's, FDA observed that although the programs put in place by Roche had decreased the rate of pregnancy in Accutane users, the number of exposed women had not decreased because of increased use of the drug.

At the same time, there was increasing concern about the possibility that Accutane could cause neuropsychiatric side effects. A possible association with mood disorders had been added to the professional label in the 1980's. However, FDA reviewers were concerned about reports with severe outcomes, including suicide. As a result of these concerns, FDA held a 2-day public advisory committee meeting in September 2000. The issues relating to pregnancy exposure as well as possible additional risk interventions were discussed on day one, and the committee provided recommendations to the Agency, which have already been alluded to here.

The scientific data on neuropsychiatric side effects were discussed on day two. While it was agreed by the committee that no

causal link between Accutane and these effects has been demonstrated, the committee recommended that patient and prescriber education and warnings be strengthened. Subsequently, FDA worked with Roche to develop a program that met the risk management goals articulated at the advisory committee. This program is now in place, and we expect to begin evaluation of the results this summer.

Almost all effective drugs have side effects. FDA must constantly work to balance the public's need for access to effective therapies with the need to appropriately manage drug risk. No drug illustrates this better than Accutane, which has both unique benefits and potentially devastating side effects.

FDA has learned a lot about risk management for prescription drugs in the last decade. We have found that educational efforts alone are rarely sufficient to change behavior, particularly for well-established drugs. We understand how important it is to involve patients and pharmacists in programs. We have learned that we must focus strictly on the specific identified problem, not all problems related to the drug. And we must think through the unintended consequences lest we, with all good intentions, make the problem worse; and we have some preliminary evidence in some risk management programs we may have had these unintended consequences. And, finally, we must build evaluation strategies into our interventions so we can tell whether they are working.

The isotretinoin risk management program was designed with these principles in mind. The evaluation criteria are in place, and we expect that they will be met. If these are not met, or if out of experience we learn that we can do better, you should be assured we will do whatever is necessary to appropriately manage the risks of this drug. Thank you.

[The prepared statement of Janet Woodcock follows:]

PREPARED STATEMENT OF JANET WOODCOCK, DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA or the Agency).

I appreciate the opportunity to discuss the Committee's concerns regarding the prescription drug, Accutane (isotretinoin). Helping to ensure the safe and effective use of Accutane involves challenging scientific and ethical issues for FDA. We have taken our regulatory responsibilities concerning this drug very seriously. Since we last testified before Congress regarding Accutane, on December 5, 2000, we have been involved in many activities regarding this drug. These actions include updated labeling, educational programs for patients and prescribers, implementing an innovative, comprehensive risk management program, and on-going monitoring of both adverse event reports and performance of the risk management program.

FDA approved Accutane in 1982 for use in treatment of severe, recalcitrant nodular acne that is unresponsive to conventional therapy, including antibiotics. In most cases, cystic acne is disfiguring and painful, causing red cysts and deep nodules that can leave deep scars. Accutane is uniquely effective in treating patients with this disease, and in many cases is curative after a single 4 to 5 month treatment course. Accutane can, however, be associated with serious adverse events including birth defects. For these reasons, it continues to be one of FDA's most difficult challenges in the area of post-approval management.

This testimony will provide the Committee with an update on FDA's post-marketing activities regarding Accutane.

FDA must constantly balance the public need for access to effective therapies against the risks associated with their use. FDA has been proactive in addressing

the issue of risk management for Accutane. We recognize that FDA is but one of many players that can and must improve on the safety of health care in the United States.

During the review of a new drug application, FDA carefully reviews the data from the clinical trials to ensure that products are truthfully and adequately labeled. Approval of a drug product is based on FDA's assessment that the benefits of the drug outweigh the risks for the intended use and population. No drug, however, is 100 percent safe; no pharmacologically active medicine exists that does not have side effects. FDA realizes that when an approved new drug becomes widely used in clinical practice, health care professionals may observe differences from clinical trial results in both the incidence and/or types of adverse drug experiences. For this reason, FDA also conducts post-marketing surveillance to monitor rare, serious, unexpected adverse drug events (i.e., serious or unexpected adverse reactions not described in the approved labeling). The Agency monitors reports from manufacturers, consumers, and health professionals to determine if any safety problems or trends can be identified and takes action accordingly.

Once a drug is approved, the prescriber assumes primary responsibility for managing the product risks (and benefits) for the individual patient through specific knowledge of the unique circumstances surrounding each patient. In this situation, FDA's role has been to assist the prescriber by requiring a description of the risks and benefits in the labeling and promotional materials, and to assure, through analysis of reports of potential new safety information, that this new information about risk is relayed promptly to clinicians. To minimize risks, product labels often describe how to select patients, how to select and modify the dose schedule for individual patients, how to avoid interactions with other treatments, how to monitor for drug toxicity, and what measures to use to avoid or mitigate drug toxicity. FDA and manufacturers rely on practitioners to prescribe products with full knowledge of the prescribing information and limitations detailed in the product labeling. Likewise, practitioners presume their patients will use their medications according to directions given. We know, however, that this does not always happen.

Because all drugs have risks, it is critical that patients are fully informed about potential side effects as well as benefits before deciding to take a particular medicine. Once the choice to take a product is made, patients need to understand how to take the medicine properly, the precautions they should observe, and the signs of possible side effects. FDA has worked for over two decades to help ensure that patients get the full information they need to take medicines as safely as possible. For example, in 1980, the Agency published a rule requiring FDA approved patient labeling for ten drugs/drug classes, with the expectation that this would be extended to all prescription drugs. In 1982, the rule was revoked in favor of private sector efforts to provide patient information that FDA would monitor.

By 1994, FDA surveys showed that only 58 percent of patients were receiving some sort of information with prescriptions. Therefore, in 1995, FDA published a proposed rule, commonly called MedGuide, which set forth goals for the distribution of useful prescription drug information to consumers. It would have required manufacturers to include drug information for the patient when a product posed a serious and significant public health concern. In August 1996, Congress passed legislation that provided another opportunity for the private sector to achieve the MedGuide goals. Consequently, a private sector Action Plan was developed to meet the need. In 1998, FDA published a final rule requiring patient labels (MedGuides) for products that pose "serious and significant" public health concerns, anticipating that five to ten products would be subject to this requirement annually. This rule became effective on June 1, 1999, and provided the framework under which the Accutane MedGuide was developed. For the vast majority of products that will not have MedGuides, patient information distributed with prescriptions is expected to be provided by the private sector's voluntary efforts.

Following the approval of Accutane in 1982, it became evident that a formal risk management program would be needed due to the drug's harmful effects in pregnancy. In our testimony before the House Government Reform Committee in December 2000, we outlined the details of our activities up until the most recent advisory committee meeting in 2000.

On September 18 and 19, 2000, FDA convened a meeting of its Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) to re-examine the issues of pregnancy.

PSYCHIATRIC ADVERSE EVENTS

While the advisory committee did not express certainty that a causal relationship exists between Accutane and serious psychiatric events such as severe depression

and suicide, they recognized that the potential for adverse psychiatric events is of substantial concern. The advisory committee recommended a number of strategies to help manage this potential risk.

PATIENT EDUCATION

The committee recommended a "Medication Guide" for patients to provide more information in plain language about the possible side effects of Accutane than could be covered in the existing patient information on the actual medication package. The "Medication Guide" for Accutane was approved in January 2001. It must be distributed by the pharmacist to every Accutane patient each time an Accutane prescription is dispensed. The "Medication Guide" was developed in conjunction with FDA to emphasize key safety issues that patients should know about the use of Accutane. It summarizes, in layman's language, information in the Professional Package Insert, including the approved indication for Accutane and major adverse events reported in the package insert.

The advisory committee also recommended use of a consent form for all Accutane patients addressing possible psychiatric side effects. The Informed Consent form for Accutane is intended to be used by the prescriber after the prescriber has determined that a patient may be a candidate for Accutane, and has explained the proper use of this medication and its possible side effects. Patients then initial each of the items on the form and sign and date the entire form, thereby acknowledging their understanding of the information presented. The prescriber also signs this document. The signed and dated documents can then be placed in the patient's medical records.

To summarize, both the "Medication Guide" and the "Informed Consent" documents explain in plain language the benefits and risks of taking Accutane. These documents supplement other patient education materials provided by Hoffman LaRoche, such as *Important Information Concerning Your Treatment with Accutane® (isotretinoin)*—7th Edition (patient's brochure). Patient education materials are intended to be used by prescribers in discussions with patients to ensure they have information necessary for safe and effective use of Accutane.

FDA also established an Accutane Drug Information webpage on FDA's website and FDA Consumer Magazine published an article in March 2001 discussing the risks and benefits of Accutane in layman's language.

RESEARCH

The advisory committee recommended research to explore possible mechanisms, risk factors, and management options for psychiatric complications. FDA's Office of Pharmaceutical Sciences and the National Center for Toxicologic Research (NCTR) are conducting animal studies to identify possible experimental models to further these goals. Presently, NCTR is in the final stage of review for approval of their proposed research. Due to the nature and priority of this work, the experimental design took an unprecedented amount of planning and review.

FDA also began collaboration with the National Institute of Mental Health (NIMH) to address the need for independent research. Subsequently, NIMH held a workshop on November 19, 2002, to discuss basic scientific research into the effects of retinoids on the central nervous system. Retinoids are chemical compounds that act on the vitamin A recognition sites in the body. Accutane (isotretinoin), is a retinoid compound. Neuroscientists presented preliminary research results from animal and *in-vitro* studies. At the conclusion of the workshop the participants concluded that there was a need for additional basic research in this important area and the NIMH expressed interest in providing funding. We hope that this basic research into possible pathophysiologic mechanisms will generate specific, clinically relevant hypotheses. These hypotheses, in turn, can guide design of future clinical studies aimed at identification of risk factors and management options to allow the greatest number of patients who need isotretinoin to use it with maximal safety. This groundwork is of particular importance in the case of research on isotretinoin and psychiatric adverse events because there are a number of very significant technical and ethical problems with the type of trial usually conducted to settle causality questions (i.e., a large randomized controlled trial). These problems arise because the drug is already on the market and recruitment of patients with scarring acne for a controlled trial would be very difficult and poses ethical questions. In addition, the mucocutaneous side effects of the drug would make it impossible to do the study in a "masked" fashion, which is very important to avoid bias and false results. Obviously, we cannot do a study where suicide is the endpoint; the less objective, but related, psychiatric endpoint, depression, is a problem because patients already know this drug works, and patients in the study would ethically have to

need the treatment. Thus, there would be a large incentive to hide psychiatric symptoms in order to avoid being discontinued from the study, again greatly increasing the chance of a false negative result. This is particularly worrisome because such a result could likely seriously undermine the progress made to date in education and awareness.

PRESCRIBER EDUCATION

FDA has worked to improve prescriber awareness by a variety of avenues. These include:

- Developing with the manufacturer a new brochure for isotretinoin prescribers entitled: "Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Accutane (isotretinoin)." The brochure is referenced in the WARNINGS section of the package insert.
- Participating in an American Academy of Dermatology consensus conference.
- Establishing an Accutane Drug Information webpage on FDA's website.
- Submitting scientific papers for publication in the professional literature. These publications have included a scientific evaluation of studies of psychiatric events sponsored by the drug's manufacturer.
- Approving on-going label updates with notification of clinicians using "Dear Prescriber" letters.

Since our last testimony on this issue in December of 2000, Hoffman-LaRoche has issued three "Dear Accutane Prescriber and Dear Pharmacist" letters advising of changes made to the Accutane Package Insert regarding psychiatric events. The first (January 2001) notified prescribers about the availability of the two new communication tools, the Medication Guide and the informed consent forms for all Accutane patients. The documents themselves were also sent, as have been tear-off pads with copies of each update. Now that the major Accutane label revisions have been completed, the Medication Guide has been affixed by manufacturers onto the actual package dispensed to patients to help ensure that the most current version is dispensed. The manufacturer of Accutane plans a voluntary package exchange at the pharmacy retail level in December 2002. The second Letter advised of the new diagnostic brochure noted above. The third (June 2002) noted updated label information concerning reported aggressive and/or violent behaviors based on post-marketing safety reports. This information was also added to appropriate sections of the patient Medication Guide and Informed Consent form and is on FDA's Medwatch website.

ADVERSE EVENT REPORTS

The Adverse Event Reporting System (AERS)

AERS is a computerized database of post-marketing adverse events for all approved drug and therapeutic biologic products. It was designed to support FDA's post-marketing safety surveillance program. FDA receives adverse drug reaction reports from manufacturers as required by regulation. Health care professionals and consumers voluntarily report either to the manufacturer or directly to FDA (direct reports) through the MedWatch program. Presently, all manufacturer reports of serious events and all direct reports are entered into the AERS database. Non-serious manufacturer reports are not usually entered into AERS. Each report may contain numerous coded adverse events that are both serious and non-serious. Any serious event renders the entire report serious. The reports in AERS are evaluated by clinical reviewers in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) to detect safety signals and to monitor drug safety.

AERS contains almost 23,000 reports for Accutane (isotretinoin) from approval in 1982 to December 2002. Approximately 90 percent of these reports are from the U.S. Among these reports the five most frequently reported reactions are, in descending order, alopecia, depression, headache, dry skin, and induced abortion. For 2002 thus far, AERS contains just over 1,100 adverse event reports of which 82 percent are from the U.S. During 2002, the five most frequently reported reactions are, in descending order, depression, pregnancy, induced abortion, suicidal ideation, and headache.

The Office of Drug Safety (ODS) within CDER maintains a quarterly cumulative count of reports of Accutane-exposed pregnancies and outcome, if known, based on the Hoffman LaRoche quarterly submission. The latest update as of June 2002 shows a total of 2,350 Accutane-exposed pregnancies and 172 babies born with a congenital defect or anomaly in the U.S. since the product was approved in 1982.

ODS has also kept a monthly cumulative count of psychiatric adverse event reports in AERS. As of November 30, 2002, AERS contains 3104 reports (U.S. and for-

eign) with at least one reported psychiatric event. FDA is aware of 173 reports of suicide in association with Accutane (includes U.S. and foreign, but excludes duplicates). FDA has requested quarterly summaries of psychiatric events from Hoffman LaRoche. The most recent summary through August 2002 indicates approximately 6000 additional reports that include psychiatric events. A subset of these reports have been sent to FDA as required under the regulations, but are not in AERS because they are not coded as "serious." The remaining reports (labeled, non-serious) are excluded from submission under FDA's Waiver Program. Under the Waiver Program, the following conditions are imposed: (1) the sponsor is to hold in their corporate drug product safety files the individual case reports of adverse experiences that are non-serious and labeled; (2) submit these individual case reports to FDA within five-calendar days after receipt of a request by FDA to do so; and (3) continue to include the non-serious, labeled adverse experiences in each periodic adverse drug experience report submitted to FDA for the NDA. The sponsor must include the non-serious reports in the section that includes a summary tabulation by body system of all adverse experience terms and counts of occurrences submitted during the reporting period.

BIRTH DEFECTS: THE S.M.A.R.T. PROGRAM

Following the September 2000 advisory committee meeting, FDA and the manufacturer initiated an extensive series of meetings to implement a workable program aimed at meeting the two principal goals articulated by that committee: no woman should begin Accutane therapy if she is pregnant and no pregnancies should occur while a woman is taking Accutane. FDA acknowledges that the second goal may never be 100 percent achievable but expects that the program developed will be highly effective because it involves Accutane prescribers, patients, and pharmacists in a partnership to prevent fetal exposure, while minimizing perceived threats to patient privacy and access to needed therapy. This is of critical importance, since a risk management program unacceptable to stakeholders might well drive significant numbers of patients into alternative sources of drugs.

S.M.A.R.T. stands for the System to Manage Accutane Related Teratogenicity. It replaces the previous Accutane Pregnancy Prevention Program that was implemented in 1989. While S.M.A.R.T. is the prototype program, it is important to note that any approved brand of isotretinoin will have a program alike in all material respects in content to S.M.A.R.T.

Under the S.M.A.R.T. program, pharmacists dispense isotretinoin only upon presentation of a prescription with the special yellow isotretinoin Qualification Sticker. Pharmacists dispense a maximum one-month supply of Accutane, fill prescriptions within seven days from the date of "qualification," and provide a Medication Guide for patients with each Accutane prescription. Requests for refills (i.e. more without a new prescription) and phoned-in prescriptions are not filled. The risk management components are described fully within the boxed Contraindications and Warnings (Black Box) and the Precautions sections of the Accutane package insert, which provides detailed conditions for prescribing isotretinoin to women of child-bearing potential. By affixing the special yellow Sticker to the prescription, the prescriber asserts that the conditions in the labeling have been met and that the patient is thus "qualified." In essence, this means that a female patient has a negative pregnancy test each month, has received repeat counseling about pregnancy avoidance and birth defects, has chosen and agreed to use two effective forms of contraception or abstinence, and has been encouraged to join the follow-up survey to help monitor program performance. In order for prescribers to obtain the special yellow Stickers, they must attest to their cooperation with the program and to their competence to treat acne and manage a teratogenic drug. Patient educational materials inform the patient of what the special Sticker means. This innovative program, based as it is on a 3-fold partnership, should enhance the program's effectiveness, since failure at 3 levels is less likely and liability in the event of failure should be clear.

S.M.A.R.T. includes a number of practical tools to help patients, prescribers, and pharmacists manage the risk of birth defects. These include an updated second informed consent form for female patients, information in the Medication Guide, a patient video, separate patient education kits for men and women, a Guide to Best Practices for prescribers, a pharmacist Dispensing Guide, and carton instructions.

Prescribers receive a Letter of Understanding from the manufacturers to which they apply for the special Stickers. At the time of S.M.A.R.T. introduction, FDA sent a letter to all state boards of pharmacy and is involved in on-going leveraging with pharmacy and prescriber professional organizations to enhance the likelihood of program success. Both of these important stakeholder groups have expressed enthusi-

astic support for working toward full participation by their memberships and achievement of program goals.

MEASURING PROGRAM PERFORMANCE

To measure the effectiveness of the S.M.A.R.T. program, isotretinoin manufacturers are using two independent outcome assessment approaches. These are the isotretinoin patient survey, and an independent audit of pharmacies to assess the use of Accutane Qualification Stickers by prescribers. Prescribers, patients, and pharmacists have all been asked to participate fully in these critically important measures because valid data to assess program effectiveness depends upon a representative sample of the population at risk.

One way to ensure a representative "sample" would be to include all women who take isotretinoin. To this end, development of a *mandatory* patient registry for Accutane was presented as an option at the September 2000 advisory committee meeting. Detailed plans were not discussed, but the committee advised, in a general way, complete patient registration. They did not advise registration of pharmacies. Mandatory patient registration, in and of itself, does not manage risk, rather, it is a risk assessment tool that might provide a improved understanding of the S.M.A.R.T. program performance due to elimination of bias. However, when contemplating any program elements, unintended consequences need to be evaluated. CDER has encountered such unintended consequences in other risk management programs we have implemented.

In working with the sponsor to design a detailed risk management program, we found that there are a number of significant complications in this case. The medical community has not been supportive of the idea of a mandatory registry for patients. Almost all Accutane precribers are dermatologists. The main dermatologic professional organization, the American Academy of Dermatologists, as well as the American Medical Association, have contacted FDA and expressed their views, that a mandatory registration or burdensome restrictions in the risk management program would not be receptive to the majority of their members. There are also significant perceived patient privacy concerns, and as noted earlier, very real concerns that risk management tools unacceptable to patients might drive them into alternative medication sources on the Internet. This is a very dangerous option for a drug with numerous potentially serious side effects in addition to birth defects. The alternative of seeking high voluntary patient participation was thus selected.

The metrics described above for S.M.A.R.T. were included in the official approval action for the program. In addition, specific performance goals have been prospectively stipulated. Hoffman LaRoche committed to 90 percent compliance with the prescription Sticker program and 60 percent participation in the patient survey within the first year of S.M.A.R.T. implementation. Assessment by FDA of program effectiveness will address a global review of S.M.A.R.T. performance metrics, including compliance with the sticker program, participation in the patient survey, and any other pertinent data.

If FDA concludes that the program has failed or that the collected data from the voluntary metrics are insufficient to determine program performance, manufacturers, prescribers, pharmacists, and patients are already on notice that more stringent and rigorous options designed to increase effectiveness will need to be explored. FDA and the innovator will develop back-up plans, but the hope is that education and awareness will lead to success of the S.M.A.R.T. program now in place, a program that is "owned and operated" by the partnership of patients, prescribers, and pharmacists, rather than by government.

GENERIC ACCUTANE

FDA approved the first generic version of isotretinoin, Amnesteem, on November 8, 2002. The generic product will be marketed by Bertek Pharmaceuticals of Research Triangle Park, NC, the branded arm of Mylan Laboratories. All generic brands of isotretinoin will utilize the labeling that is alike in all material respects to the name brand, educational tools, distribution requirements, and follow-up metrics in place under S.M.A.R.T. Like the innovator, generic manufacturers are on notice that failure of the risk management plan, or failure to collect valid data, will obligate consideration of more burdensome measures.

INTERNET SALES AND IMPORTS

As already mentioned, Internet sales of Accutane present a significant public health risk. Obtaining Accutane (Isotretinoin) on foreign websites can allow patients to bypass the risk management requirements for Accutane. Moreover, Accutane obtained through foreign websites is generally an unapproved version of the drug. The

Agency has posted a special alert on its home page warning consumers that certain restricted distribution drugs, including Accutane, should not be purchased over the Internet. FDA has also put these restricted distribution drugs on Import Alert, informing the Agency's import inspectors that shipments of these drug are not appropriate for admission into this country under FDA's Personal Importation Policy. We have also specifically informed Customs about the fact that these dangerous drugs should not be admitted.

Nonetheless, Internet purchases of Accutane will not be eliminated by these efforts. The Agency has identified a number of websites, primarily in foreign countries, which sell Accutane, either with no prescription, with only an on-line questionnaire, or based on a faxed prescription. Hoffman LaRoche sent a letter to FDA, dated November 26, 2002, which also identified Internet websites selling Accutane. FDA takes this problem very seriously and is in the process of actively investigating websites selling Accutane and evaluating options for enforcement action.

CONCLUSION

FDA has worked diligently with the manufacturers and the medical and scientific communities to assure that patients have access to Accutane under conditions that make its use as safe as possible. FDA will continue its vigilance and keep health professionals and consumers aware of the risks associated with isotretinoin and the circumstances under which it should be used and prescribed. We will vigorously evaluate the S.M.A.R.T. program, and, if it is not performing as expected, consider additional risk management interventions. Thank you for the opportunity to discuss this important issue.

Mr. GREENWOOD. We thank you, Dr. Woodcock.

The Chair recognizes himself for 10 minutes and advises the members that we are going to do one round of 10 minutes apiece with this witness in order to accommodate her schedule and everyone else's schedule.

Dr. Woodcock, on September 18 and 19, 2000, the Dermatologic and Ophthalmic Drugs Advisory Committee met to review risks associated with Accutane. The members of the advisory committee, which included dermatologists, recommended that additional steps needed to be taken to ensure the safe use of this drug. Included in this recommendation that the advisory committee made was a mandatory registry of all patients receiving Accutane.

On October 6, 2000, you sent a letter to Roche which can be found at Tab 4—I believe you have that—in which you, in accordance with the committee's recommendations, requested that, "Roche should initiate a program whereby there is complete registration of all patients, both male and female, receiving Accutane."

If you turn to Tab 29, you will find a May 20, 2001 e-mail from you to Dr. Kweder on Accutane. In this e-mail, you wrote, "It seems the privacy problems have us boxed in on the assessment side."

My question is, what did you mean by that? Is this the primary reason you decided to shift from a mandatory program you requested in your October 6 letter to the voluntary program on Accutane? And if so, is there no way to implement a mandatory registry properly to address a perceived patient privacy concern?

Ms. WOODCOCK. Well, if I may. In answering your question, I would like to go over some terminology so we are all on the same page here. The advisory committee did recommend a registration of all patients. However, they were extremely concerned about a mandatory restriction on distribution of the drug. When—and that's my understanding. I reread the transcript over the weekend; I was there at the hearing——

When we went back and started to work with these recommendations from the advisory committee, we recognized that restricted

distribution is probably necessary if you are going to have 100 percent enrollment of the physicians or patients, because if the drug is out there in the pharmacies, then you don't have that control. And that was the point in my understanding, is that the advisory committee stopped short of wanting—of recommending to us that sort of program. Do you follow my——

Mr. GREENWOOD. Well, I think I do. I think what you said is that in order to have this 100 percent registry, you would have to change the way that the product is distributed.

Ms. WOODCOCK. That's correct.

Mr. GREENWOOD. It would not be available in pharmacies anymore, but would be available only from the doctor himself. Is that what you are indicating?

Ms. WOODCOCK. There are many ways to do this, but you are right in the essential point that either the distribution pharmacies would have to be restricted, or restriction would—that getting the drug would have to come from a central pharmacy point or would have to be available only through registered physicians who would agree to meet certain conditions as a condition of getting that drug.

Mr. GREENWOOD. Well, let's assume that. And then the question recurs: So why didn't you do that?

Ms. WOODCOCK. Well, as I said, the advisory committee stopped short of recommending that type of program. We had other concerns about that program for this drug. We do—we have operated restricted distribution programs with—we have recommended and brought about restricted distribution of other drugs. With this drug we were concerned about use through other channels if distribution was restricted too tightly.

Mr. GREENWOOD. And by that, you mean gray market, black market?

Ms. WOODCOCK. Yes.

Mr. GREENWOOD. So you—and let me ask you this question. On what evidence did you base that decision? In other words, clearly you, the FDA, could have achieved a registry and restrict—by restricting distribution—and that would have gone a long way to enhance the protections for the patients. But the FDA concluded, as I understand it, that that effort would be thwarted or undermined by black market access. And my question then is: Upon what evidence was that based?

Ms. WOODCOCK. Right. Well, that was one of the considerations. And, for example, we are concerned about other drugs. We were concerned about thalidomide. For example, at the time we put a restricted program in place for thalidomide, it was widely available through buyers' clubs and other means, and we were very concerned about the public health consequences of that.

Mr. GREENWOOD. But you have—I'm sorry to interrupt you. But what we have now is, we don't have restricted distribution and we still have, as you have heard from many opening statements—I was on the Internet last night and was astounded at how many different Web sites there were and how easy it appeared to be to acquire Accutane without a doctor's prescription. So you have the gray and the black market in any event.

Ms. WOODCOCK. We recognize that. And we had—there were other considerations.

Mr. GREENWOOD. What were they?

Ms. WOODCOCK. Okay. Another was getting a program in place quickly. We do not believe that a registry per se will prevent pregnancy. All right, so a mandatory registry is really a tool for evaluation, and there—that's where some of the privacy problems come in, is going in and trying to determine were women pregnant on this drug. Both pregnancy as well as neuropsychiatric symptoms are very personal and private issues for patients.

Mr. GREENWOOD. Well, the FDA did use the registry for thalidomide.

Ms. WOODCOCK. Right.

Mr. GREENWOOD. And bosentan—am I pronouncing that right?

Ms. WOODCOCK. Yeah. As I said, we have that in place for a number of other drugs.

Mr. GREENWOOD. Okay.

Ms. WOODCOCK. That's correct.

Mr. GREENWOOD. How many reported pregnancies have you received with regard to those drugs?

Ms. WOODCOCK. You mean outside of——

Mr. GREENWOOD. Well, I'm trying to get at—what I'm trying to—I'm trying to understand what makes you choose to go one way with one drug and another way with another drug?

Ms. WOODCOCK. Right.

Mr. GREENWOOD. And with your experiences with thalidomide, for instance, did that support the argument, the reasoning for not having the registry and the restricted distribution for Accutane?

Ms. WOODCOCK. We felt that the essential part of the thalidomide program is that you can't get a prescription unless you've had a pregnancy test. And that we have put into place with the SMART program or Accutane. That's the essential risk management step here, is that you only get a 30-day prescription, and you must have a pregnancy test each time to get another prescription.

The data that we were presented by Roche at our advisory committee, for example, showed that, I think, 11 percent of women may have started Accutane already pregnant, because there wasn't—they weren't waiting for the results of the pregnancy test. It also showed that perhaps up to 14 percent of women didn't wait——

Mr. GREENWOOD. These were patients who had received the Accutane in which manner?

Ms. WOODCOCK. The old system?

Mr. GREENWOOD. In the old system.

Ms. WOODCOCK. Yes. And that about 14 percent of women who ultimately were pregnant on Accutane had not waited until the first menstrual period to begin taking the drug. So there were clearly things recommended there that weren't being done; and by putting this program in with the sticker, we feel we have an essential piece, the risk management intervention that is in the thalidomide program.

Mr. GREENWOOD. Well, let me ask you this. Did any of these registries have the unintended consequences of creating black or underground markets on these drugs?

Ms. WOODCOCK. Well, the one where it could have been likely would be thalidomide. But we did not have any restriction on the

use of thalidomide in that program. There is no restriction of use. Most of the use of thalidomide is off-label.

Mr. GREENWOOD. Why, for instance, do we not see thalidomide advertised on the web, on the Internet the way we see Accutane?

Ms. WOODCOCK. Probably because it depends on what the indication is. A consumer-directed indication such as acne, you're more likely to get people to order it themselves. They can diagnose their own condition. Currently, thalidomide is being used for the treatment of cancer and leprosy, something that consumers are unlikely to diagnose themselves.

Mr. GREENWOOD. As you sit—my time is about expired. As you sit here today, do you believe that the system in place now is the way to go or do you have concerns that maybe we should go to mandatory registry and the restricted distribution?

Ms. WOODCOCK. I have concerns about either path. I think for the pregnancy issue it is very difficult to achieve a zero percent pregnancy rate in women of reproductive age because of contraceptive failure, regardless of what system you have in place. And perhaps in 1982 when we approved this drug we did not have the sensitive pregnancy tests we have now. It may be that with advances in technology we can do better. But I'm afraid for the pregnancy issues that it is very difficult to get to an irreducible no woman—no pregnant woman being exposed.

As far as neuropsychiatric side effects and the other serious side effects of this drug, I think the most important thing is that, first of all, the physician prescribing a drug be completely aware of the risks and that the patient receiving the drug and the parents, if it's a minor, be completely aware of the risk.

Mr. GREENWOOD. Well, of course, we all agree with that. But when I asked you a moment ago whether you think the current regime would—is sufficient to the task or whether we ought to go to a more restrictive regime you responded by saying it's hard to get to zero. Let's assume that.

Ms. WOODCOCK. Yes.

Mr. GREENWOOD. If our goal is to get as close to zero as possible—and I think we probably all assume that if this product's going to be available there will be failures—my question is, which regime do you think is likely to get us closer to zero?

Ms. WOODCOCK. I am testifying under oath and I can tell you I do not know the answer to that. We have to look at the global public health impact; and if we were to increase use in the gray market in a totally unregulated fashion with a very restricted program, we might end up doing more harm than good. I do not know the answer.

Mr. GREENWOOD. And that is, admittedly, a speculative issue.

Ms. WOODCOCK. That is speculative.

Mr. GREENWOOD. It's not based on data. Because either you don't have data or you find a comparison with thalidomide not to be a one-to-one ratio.

My time has expired.

Ms. WOODCOCK. Well, if I could say one more thing. We do have reports of pregnancy exposures in people who've received the drug and gone to other countries and gotten the drug now.

Mr. GREENWOOD. The gentleman from Florida.

Mr. DEUTSCH. Thank you, Mr. Chairman.

Dr. Woodcock, I don't think anyone would expect literally zero percent success or zero pregnancies. But at what rate is the system just so unacceptable?

Now, I have the comments from Dr. Graham that I guess were 1990 of the number of abortion-related Accutane—or Accutane-related abortions and Accutane-related birth defects. I mean, what number would you estimate that this year on those two specific questions?

Ms. WOODCOCK. This year?

Mr. DEUTSCH. Well, last year.

Ms. WOODCOCK. I'd like to ask—Marilyn, are you the best person to answer that question?

Well, you want to know how many reported or——

Mr. DEUTSCH. What do we estimate? How many—I mean, what's the number? What number are we talking about?

Dr. Graham in 1990, in the 8 years I guess—and that at least is how I'm reading it—said that there were between 11 and 13,000 Accutane-related abortions and 900 to 1,000 Accutane-related birth defects in that 8-year period, which to me is just an incredibly staggering number.

Ms. WOODCOCK. Right. Well, that was an extrapolation that Dr. Graham did based upon the rate of contraceptive failures and other data. So we don't know that that's actually what's happening.

Mr. DEUTSCH. Was that methodology valid? I mean, what—I'm trying to get a sense of what is the downside that—the known downside or the best estimates of the known downside from last year.

Because let me just say something; that on this panel and in this country there are people that are both, you know, pro-choice and pro-life. But I don't—and I have a consistent, you know, pro-choice voting record. But I will tell you that any abortion is something that should be avoided at all costs. Because no matter what you say, no matter how you feel about it, there are severe repercussions both psychological and physical of abortions. So if we're talking about these kind of numbers, no matter how you feel about the choice issue, these are staggering numbers.

And then the staggering numbers also in terms of birth defects are absolutely staggering, because each one of those children, you know, the implications is also dramatic. So, I mean, do you have in front of you some type of statistics?

Ms. WOODCOCK. What we have—what I have here is the cumulative statistics over all years of Accutane marketing for what's been reported to the FDA. And the question that you asked is, how would we extrapolate that? How many are not reported? What is the total number? That's something that is very difficult to find out, and that's one of the things we were alluding to in the privacy issues that were alluded to in our——

Mr. DEUTSCH. Well, I'm going to push you a little bit harder.

Mr. GREENWOOD. If the gentleman would suspend for just 1 second. At our request you've brought additional staff with you, and I should let you know that if at any time you think any of your other staff members could respond more thoroughly bring them forward and then we'll swear them in.

Mr. DEUTSCH. Could we maybe have Dr. Graham come up? Because, I mean, the numbers I have in front of me are from his report. Can we get Dr. Graham to come up? You know, again, my understanding—you want them under oath?

Mr. GREENWOOD. Yeah, I have to do that.

Dr. Graham, please be seated for a moment. We'll get there. Do you have any objection to giving your testimony under oath? Do you wish to be represented by counsel?

Mr. GRAHAM. No.

Mr. GREENWOOD. Now you can stand and raise your right hand.

Mr. GRAHAM. May I affirm rather than swear?

Mr. GREENWOOD. You absolutely may.

[Witness affirmed.]

Mr. GREENWOOD. You are under oath and can respond to Mr. Deutsch.

Mr. DEUTSCH. Thank you, Mr. Chairman.

Well, first off, do you stand by the numbers of your 1990 statements?

Mr. GRAHAM. Yes, I do.

Mr. DEUTSCH. And from that point forward, for the last 12 years, what would you extrapolate at this point in time?

Mr. GRAHAM. Well, currently, there's only about 2,000 pregnancy exposures a year. This is based on the level, the number of woman who are—oh, sorry.

Currently, there are about 2,000 pregnancy exposures a year. This is based on the number of women of reproductive age who are treated with Accutane, the distribution of contraceptive methods that those women are believed to be using and the documented contraceptive failure rates that those methods have associated with them. And so, although it is an extrapolation because we don't enumerate all of the events, we can with a fair amount of certainty know that we're in the ball park.

Mr. DEUTSCH. So of the 2,000 that you're talking about how many are related both abortions and birth defects?

Mr. GRAHAM. My guess is that with the concerted efforts of both the company and FDA in terms of their labeling that the abortion rate is probably higher than it was early on and that it wouldn't surprise me if about 95 percent of those exposures ended in abortion.

Mr. DEUTSCH. And, Dr. Woodcock, where are we different at this point in terms of the exposure rate? I mean, it still is a staggering number.

Ms. WOODCOCK. Well, let me just say that what Dr. Graham has presented is an extrapolation based on contraceptive failure rates in people not in the program, all right, and a number of other assumptions, so we really don't know that the numbers that Dr. Graham has presented are the actual numbers.

Mr. DEUTSCH. We don't know. But we base our, you know, decisionmaking on educated scientific assessments.

Ms. WOODCOCK. That's correct.

Mr. DEUTSCH. Now if you want to fire him if you think he's incompetent, then fire him. But I'm being really serious with you. That's the best number. I mean, do you have a counter number? Is that accurate? Is Roche going to say that's not accurate?

Because, you know, let's say what this is. I mean, this is teenage girls that you're marketing to; and no matter who they are, we have all sorts of issues related to this in terms of their susceptibility to becoming pregnant. That's the reality of the situation. And obviously we're concerned about off-label or Internet uses, you know, because of the marketing issues. You know, there's this whole issue as well, 3 percent of, I mean, the percentage of the use of this drug that is for the actual on-label use. What would your prediction—I mean, what would your assessment of that be at this time? Either one of you.

Mr. GRAHAM. I believe that it is very low. If you look at the use patterns of Accutane, when it first came on the market, at that time it didn't have a treatment for severe nodular cystic acne. So you could have this big pool of demand, if you will, of people who needed the treatment. So at that point you'd expect the use to be relatively high. And then once you've used up—once you've treated those people—because this is a long duration, chronic disease, but if you treat it, it's over—the incidence itself is relatively low. Once you've dealt with that prevalent pool, then all you have to treat then are the new people developing the disease each year, which is a smaller number than that prevalence pool.

So what should have happened with the use of Accutane if it had been going in the way one would have expected in terms of being used for its approved indication is that you would have had a high—some level of use during the first few years that once the prevalence pool was treated would have fallen and then sort of should have gone at more or less a constant level for the incidents, the new cases that developed. Instead, what happened is it didn't drop down like that. What it did is it was already high we estimated in 1988, and then between 1990 and 2000 it went up 300 percent beyond that. So the curve should have been down here. Instead, it went up there. So I believe that the use outside of the labelled indication is worse than it was in——

Mr. DEUTSCH. So what percentage would you say?

Mr. GRAHAM. I would say that over 90 percent of use is off-label.

Mr. DEUTSCH. Dr. Woodcock, would you challenge that number?

Ms. WOODCOCK. I'm not here to argue about this. I think——

Mr. DEUTSCH. I mean, that's staggering numbers. This is unbelievable. Think about what he just said: 90 percent off-label use, 2,000 abortions or 2,000 unwanted pregnancies. We don't know how many birth defects per year.

Ms. WOODCOCK. The diagnosis of acne is a spectrum disorder. I have the consensus report from the American Academy of Dermatology on this, all right? It is very clear to me from information I've received from patients that many people who get this drug are being inappropriately treated. The drug should be a third-line therapy after all other acne treatments have been tried and exhausted. And if you'd like more discussion on this, Dr. Jonathan Wilkin, who's our head dermatologist, can provide more information on it. So there is no doubt that a proportion of the people who have been treated, say, in the last decade with this drug had mild acne that should have been treated with other interventions. That is true.

Mr. DEUTSCH. Right. Again, I don't like to personalize these hearings, but clearly the case of Congressman Stupak's son was

not—it was an off-label use—I mean, the description of his son. He knows what his son looked like. It was not within that category, the diagnosis on the on-label use.

So, I mean, it's—again, with the limited indication with our time, it just—it seems fast. We have this—and I'm very much open, but, you know, 2,000, whether 90 percent of them are being aborted or not, we are creating a level of tragedy in this country, a severe level. It's not one case in a million. It is thousands and tens of thousands. And next year we're looking at the same thing is going to happen.

Let me just shift because again we're going to try to stick with the schedule. The depressive issues. And some of the—and I'm sure there'll be others on our dais who will question that. But I'm really curious if we're—I mean, what amount of data is needed? How do we look at or have we looked at it more in terms of this—are we relying upon either Congressman Stupak or other parents to, you know, get data to you on these types of incidents? I mean, where is the failure of just the data gathering in terms of the situation, in terms of issues of depression or the ancillary things?

Ms. WOODCOCK. Right. Unfortunately, because of the background rate in the population, anecdotal reports, all right, we have a lot of those and we have positive challenge, dechallenge and rechallenge cases. We have quite a few of those. What's needed now is a scientific linkage that could be done by studies.

FDA is doing some animal work in this area, both at the National Center for Toxicologic Research as well as the Center for Drugs. We have worked with the National Institutes of Mental Health and we had a conference—a scientific conference last month on retinoids, and we are—we need to develop enough scientific information that a human study could be done that would—we would have enough confidence that if a signal were there we would see it, all right? That's what we need.

Some retrospective studies have been done by Roche, and they have failed to show an association between prescriptions of Accutane and neuropsychiatric symptoms. And this may be because of their design. That is why we need more scientific——

Mr. DEUTSCH. Let me ask one final question and that really is, at least your statements or your comments to the chairman to me actually, unfortunately, were very disturbing in a very specific way, which were that, you know, if we put this on a registry we're afraid of basically black market use. Are we at the point now that basically, as the United States of America, not only can we not deal with bioterrorism or terrorists coming to our country in terms of our borders and other issues but we effectively have given up the control of prescription drugs? That if we know the outcomes are so severe that we have an availability to restrict or we have——

Again, the thalidomide example is a very good example in terms of having a more restrictive approach. You've told us at least that that was a factor, and I understand it. I mean, kids are going to be kids, teenagers are going to be teenagers, and they're going to find a way to get on the Internet and find it or they're going to take trips to Acapulco on spring break or whatever or their bigger brothers or sisters are going to do it for them. I mean, have we effectively given up in terms of that?

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Ms. WOODCOCK. Well, I didn't get to finish my response to the chairman because of the time. But, as I said, there were other considerations. We feel that the essential piece for pregnancy prevention is within the SMART program and that is the link between a prescription and having a pregnancy test. That is the essential hallmark of the thalidomide program as well. The registry would provide us more information, to the extent people are willing to give it to us, about their outcomes, whether they had a pregnancy on the program or not.

Mr. GREENWOOD. The time of the gentleman has——

Mr. DEUTSCH. Just a very short follow-up question.

Mr. GREENWOOD. It has to be, because I gave you an extra 2 minutes before we turned the clock on.

Mr. DEUTSCH. Let me just say I guess the concern I have in your response—and, again, I'm not hearing it exactly, probably. But you're saying, you know, the pregnancy test—I mean, that means it almost—again, I am not putting words in your mouth, but you're saying, well, the abortion outcome is an okay outcome. That is the pregnancy test beforehand and the pregnancy test afterwards. And if people are still engaged in sexual activity or—while they're on the drug, then the whole concept—and we're talking about failure rates of contraceptive—then obviously we can reduce failure rates by double contraceptive which can be part of the modality in terms of that.

Unfortunately, as I said, just determining pregnancy and then having an abortion, no matter how you feel about choice, I mean in this situation I just think is totally unacceptable as an acceptable answer.

Ms. WOODCOCK. We think it is unacceptable as well.

But the part about having the pregnancy test—you return to the physician each month. You receive contraceptive counseling. Your use of contraceptives is verified. This is all to focus—keep focusing the attention of the prescriber and the woman on the absolute necessity of avoiding pregnancy. We completely agree. The goal here is to avoid exposure of pregnant women to this drug. That's the goal.

Mr. GREENWOOD. The time of the gentleman has expired.

The gentleman from Florida, Mr. Stearns, is recognized for 10 minutes.

Mr. STEARNS. Thank you, Mr. Chairman.

Dr. Woodcock, how long have you been in your present position?

Ms. WOODCOCK. Since 1994.

Mr. STEARNS. So okay. So 8 years.

Ms. WOODCOCK. Uh-huh.

Mr. STEARNS. So you followed the history of this product during those 8 years intimately and have followed the history of this and been involved from the beginning?

Ms. WOODCOCK. No, I became more involved in this in 1997-1998 as the neuropsychiatric side effects became discussed.

Mr. STEARNS. Okay. This program of Roche on the SMART guide, this was activated—what—in the last 6 months—last year?

Ms. WOODCOCK. Uh-huh. Yeah, that's—6 months. Yes, a year.

Mr. STEARNS. A year?

Ms. WOODCOCK. Uh-huh.

Mr. STEARNS. The information that's used, Roche submits the information to you regularly?

Ms. WOODCOCK. They submit reports about adverse events, and they're going to be submitting reports on the success of the program.

Mr. STEARNS. Okay. Do you think this program should have been instituted a lot earlier? I mean, is this just—I mean, was there enough evidence that we should have had a program like this before?

Ms. WOODCOCK. Probably in retrospect that would have been a correct thing to do, yes.

Mr. STEARNS. And do you feel that the information you're getting from Roche is sufficient, or do you think there should be information from the people who use it, too?

Let me just say, as a point of information for people who might not know what I'm talking about, this is the best practices for women to prevent genetic defects during pregnancy. So this provides information to teach them and also, in the event there is a problem, that they report it to Roche and Roche reports it to you. So this is sort of a registry through this program.

Ms. WOODCOCK. That's correct.

Mr. STEARNS. So the question is, do you feel that this is sufficient or do we need to have the patients report to FDA, too?

Ms. WOODCOCK. Well, patients, pharmacists and other people can report directly to FDA through med watch programs if they have an adverse event. And we do receive about 10 percent of adverse events overall for drugs directly from patients, prescribers and pharmacists.

To answer your question, we will look at other sources of information, the CDC program on birth defects, the teratology societies and their registries and so forth.

Mr. STEARNS. So when a young woman gets a drug she gets a copy of this.

Ms. WOODCOCK. She gets an extensive amount of educational materials, yes.

Mr. STEARNS. I notice in your statement you said that Accutane is really the third line of defense for acne prevention. But I see—when my son was a teenager, all his friends had it. And I didn't have it when I was young and I was able to solve the problem, so how do we make it clear that it's a third-line defense and should not be used so frequently, as it obviously has been used?

Ms. WOODCOCK. We feel that the publicity resulting from our advisory committee and the other warnings that have been sent out and our interactions with the dermatologic community have started to get this message across. People may have become overconfident or overused to this drug, and it does have very serious side effects. Prescribing, from our measurements, has dropped about 30 percent, the number of prescriptions since the publicity attendant to the advisory committee.

Mr. STEARNS. Does the FDA play into this idea that there is a lot of depression in teenagers in general?

The Surgeon General came out in a report that depression and suicide in this country among young people—CDC, National Center for Health Statistics reports that suicide is the third leading cause

of death for all—all the way from 10 to 24-year-olds and second for 25 to 34-year-olds. So I'm just saying, how does that play in—that there is, you know, in teenagers, health statistics that shows that suicide, depression is already existent, how does that play in with what you already—what you have here?

Ms. WOODCOCK. That's what makes it very difficult for us to tell if there's an increase in the frequency, all right, over what we see in people who aren't taking Accutane. It makes it harder to figure out whether people on Accutane are at higher risk than the general teenage population.

Mr. STEARNS. To make this effective and to be able to understand this, shouldn't we have a baseline before we try to make an analysis on this of what exists already without Accutane?

Ms. WOODCOCK. Those types of things are randomized studies.

Mr. STEARNS. Yes.

Ms. WOODCOCK. And we certainly have talked about this, and it's very hard to do a randomized study. We have tried to get the best minds together, both from the National Institute of Mental Health and the people at the FDA, who know a tremendous amount about this, to figure out what kind of study could be done.

Mr. STEARNS. It seems to me if I was prescribing this to a young man or a woman, I would say, what are your circumstances in your family? Are you away at school in a very serious situation where you don't have any friends, you're lonely? I mean, I would think there'd be a lot of other conditions before I'd prescribe it. You know, if he was home in a safe environment I would think—because the tendency toward depression would be higher under certain conditions which would make Accutane, I assume, more prevalent, more effective, would affect the teenager. So that whole idea of bringing what the baseline is and having the prescription based upon knowing the family and the child I would think would be important.

Ms. WOODCOCK. There is an entire program for educating practitioners about the risk of depression and neuropsychiatric side effects, how to screen the patients, how to follow them and so forth. And that's part of the educational program.

Mr. STEARNS. Okay. On Tab 51 you have that—you talk about the statistics from the cumulative Accutane-exposed pregnancies. And you report, of the 2,350 Accutane-exposed pregnancies, 172 babies were born with congenital defects or anomalies in the US since the product was approved in 1982. If you go to Tab 51, you'll see a table of Accutane-exposed pregnancy report information submitted by Roche to FDA. That table shows that, besides the 2,350 pregnancies and 172 babies born with a defect, there were also close to 1,400 elective abortions, 260 spontaneous abortions and 196 babies born normal. Yet you don't seem to talk about the information.

I guess the question is, why wasn't the information on the abortions and the babies born normal included in your testimony?

Ms. WOODCOCK. Well, I assume that—this is all public information, and the committee has this information. But these are the facts. This is what's reported to Roche and to the FDA. It's different than what David Graham presented, which is his extrapo-

lation from an epidemiologic model. These are the reports that we have received.

Mr. STEARNS. Can Mr. Graham—Dr. Graham come up here just a second?

Dr. Woodcock, I think you should also, you know, not exclude information that downplays the abortion issue; and the fact is that some Accutane-exposed pregnancies resulted also in babies born normal. So I think the full panoply of information should be provided in your testimony.

Dr. Graham, you might want to comment on this, too.

Mr. GRAHAM. Yes. Going back to 1988, we knew that not all children who were exposed to Accutane in utero would be born with birth defects; and by 1990, Franz Rosa, who is now deceased but was an internationally famous teratologist and the FDA's authority in birth defects, had done a study where he found that the rate was about 25 percent based on his assessment of the case reports that we were getting in. Subsequently, the company did a study, and they came up with a rate of 28 percent for birth defects among—so the other 70-some odd percent didn't have the structural birth defects.

At the same time, in 1988, the labeling for Accutane was approved by the agency that had language that basically implied that the rate of birth defects was 100 percent and didn't mention that normal pregnancies could come from that; and a number of people from our group sent memoranda to people informing them of that. We had an Accutane monitoring group where that was discussed, and a number of reports from the chair of that committee went to the office director who oversaw the drug. But the labeling was not changed, and I think it wasn't for another 4 or 5 years after that labeling change was made, which basically implied a 100 percent rate that was changed.

Mr. STEARNS. I think that the concern that we have is how many pregnancy exposures and abortions are tolerable? What statistically is tolerable? Can Dr. Woodcock—or, Dr. Graham, can you indicate, based upon this Tab 51 and the information I have here—I mean, what do we say is tolerable?

Ms. WOODCOCK. I would like to say that the goal is there be no pregnancy exposures.

Mr. STEARNS. I would hope so.

Ms. WOODCOCK. And an absolute necessity is there would be no preventable. Those are the worst, the ones that we actually knew you could prevent those pregnancy exposures.

Mr. STEARNS. So you're saying zero is what——

Ms. WOODCOCK. Would be a goal.

Mr. STEARNS. [continuing] what you would accept as tolerable.

Ms. WOODCOCK. Well, we have to think about—we can't just work on models.

Mr. STEARNS. Can you quantify it today for me, this morning?

Ms. WOODCOCK. These are very difficult judgment calls, and you have to look—you have to have the data and you have to look at the circumstances.

Mr. STEARNS. Doctor Graham.

Mr. STUPAK. Would the gentleman yield on that point?

Mr. STEARNS. Sure.

Mr. STUPAK. Would you go to Tab 20 in your book? Let me show you. On Tab 20 you ask about abortions. This is the quarterly report for the last quarter of 1999: 313 serious events, all the psychiatric parts, completed suicides. You had 93 pregnancies unwanted, 42 abortions. But please note this fact. Note that the abortions, however, were not included among the serious events, presumably because the dead fetus is not considered a patient.

Mr. STEARNS. Reclaiming my time. Thank the gentleman.

I'll just conclude by saying that I think, Dr. Woodcock, the concern we have in the opening testimony that we did not hear anything about this issue, the statistics that were in Tab 51, and we're just trying to understand why this information was excluded. We think it's important. It seems to be downplayed. In fact, it should be made known to the public; and you, as an FDA officer, should be able not only to talk about it but also to explain it and to give us some understanding of what's tolerable.

And I yield back.

Mr. GREENWOOD. The time of the gentleman has expired.

The gentlelady from Colorado is recognized for 10 minutes.

Ms. DEGETTE. Thank you, Mr. Chairman.

Dr. Woodcock, let me try to explore a little bit of this in layperson's terms. As I understand it, Accutane is really a drug that's for the very most serious, intransigent cases of acne. Would that be accurate?

Ms. WOODCOCK. Yes.

Ms. DEGETTE. And one of the problems that we're having is that it's being prescribed for a much broader group of patients than it really should be, is that correct?

Ms. WOODCOCK. Yes, that's correct.

Ms. DEGETTE. I mean, I was thinking about my colleague Mr. Stupak's opening statement where he said his older son had it, and then they said, well, let's just prescribe it as a preventative measure for your younger son. That would not be an appropriate use of Accutane, is that right?

Ms. WOODCOCK. Well, I'm not going to comment on any specific cases.

Ms. DEGETTE. No, but I mean if a doctor said, okay, you know, one family member had it. Let's just give it to you because we know you'll probably get it.

Ms. WOODCOCK. There are other effective treatments for acne, and those treatments should be tried first.

Ms. DEGETTE. Now it's also true, and this is what we've been talking about this morning, that Accutane is a very potent teratogen, right?

Ms. WOODCOCK. Yes.

Ms. DEGETTE. And what that means is a drug that causes birth defects, right?

Ms. WOODCOCK. Yes.

Ms. DEGETTE. Now would you agree with a lot of the folks I talked about in my opening statement and we've been talking about today who say that Accutane's teratogenicity is about equal to that of thalidomide?

Ms. WOODCOCK. That was the testimony of the experts we had at our advisory committee in 2002.

Ms. DEGETTE. So you would agree with that. You would agree that that's serious.

Ms. WOODCOCK. Yes.

Ms. DEGETTE. And thalidomide for a long time was banned in this country because of the concern of the birth defects, the effect that it would have on pregnant women, is that right?

Ms. WOODCOCK. Thalidomide was never approved in the United States; and Dr. Frances Kelsey, who is the medical officer reviewing that case, said she did not approve the drug because she had additional questions about its safety, not related to teratogenicity. Subsequent to that, the European experience was uncovered with teratogenicity and the drug was not submitted for marketing in the United States.

Ms. DEGETTE. And right now, though, we do allow thalidomide to be marketed in the United States under severely controlled conditions and a registry, correct?

Ms. WOODCOCK. Yes.

Ms. DEGETTE. Now could you just describe really briefly how that registry for thalidomide works?

Ms. WOODCOCK. All right. Well, I think that's the problem with calling it a registry. What we have for thalidomide is restricted distribution.

Ms. DEGETTE. Right.

Ms. WOODCOCK. And the pharmacy can't get thalidomide without participating in this program, a doctor can't prescribe thalidomide without participating in this program, a patient can't be prescribed thalidomide without participating in the same program.

Ms. DEGETTE. Right. So it's very restricted. If you're going to give someone thalidomide, the doctor has to be registered, the pharmacist has to be registered, and the patient all have to be registered, right?

Ms. WOODCOCK. Uh-huh. Uh-huh.

Ms. DEGETTE. And you testified earlier that the FDA didn't really consider this kind of process for Accutane because you were concerned that you'd get something in place quickly. Is that accurate? I don't want to put words in your mouth.

Ms. WOODCOCK. As I said, we had a whole series of issues around doing this that we were dealing with.

One of the important parts of the thalidomide program is that people have to have regular pregnancy tests.

Ms. DEGETTE. Right.

Ms. WOODCOCK. Thalidomide is usually taken chronically for a long time by patients.

Ms. DEGETTE. Uh-huh. Well, I mean it would seem to me, given the extremely high risk of birth defects for Accutane, that wouldn't be such a terrible thing to ask for. You know, here's the thing. Only a very small number of people should be getting Accutane anyway, just like thalidomide. It's not a drug that should be used in widespread distribution. So of that very small percentage, some small percentage of that group is going to be women of childbearing age. Given the extremely high risk of birth defects among that very small number of women of childbearing age, wouldn't it be reasonable to ask for pregnancy tests there?

Ms. WOODCOCK. We do.

Ms. DEGETTE. Right, under your SMART program. So that wouldn't be anything different than you're doing now. So why would that be a concern of having a registry?

Ms. WOODCOCK. No, the concern is different. If you're—as I said in my opening testimony, it's really important to consider what problem you're trying to solve. Obviously, a restricted distribution is one approach to this problem and is actually what the FDA originally considered, as you probably know if you've looked over the documents. But restriction—the thalidomide program, for example, there's no restriction on the indication, which is what you say you're concerned about. So in thalidomide a physician, as long as they're enrolled in the STEPS—the thalidomide program, can prescribe the drug thalidomide for a patient with a variety of diseases.

Ms. DEGETTE. Right. Okay. But you could still do—you could still do a restricted registration program and say people who are taking Accutane, if they're childbearing age, they should have pregnancy tests. But what you would do by registration is you would really have strict controls over who was taking the drug, who was prescribing the drug and who was dispensing the drug, right?

Ms. WOODCOCK. I——

Ms. DEGETTE. I mean, you would.

Ms. WOODCOCK. A problem like that would be run—usually, the companies we have that run programs like that, it's run by a third party.

Ms. DEGETTE. Right.

Ms. WOODCOCK. And they—to my knowledge, we have no program that controls who is taking the drug.

Ms. DEGETTE. Okay. Let me ask you another question. Now, you've got—you said that you've got this SMART program in place. You were concerned about black market distribution with the more restricted registry type of system, right?

Ms. WOODCOCK. Uh-huh.

Ms. DEGETTE. But the thing is the FDA didn't do anything to stop importation of Accutane or to give an alert until this week, December 9, did you?

Ms. WOODCOCK. We had—my understanding is we'd sent some cyberletters to—isn't that correct, David? Yeah—to sites that were advertising Accutane. But we had not done this alert. And we, you know, appreciate that being brought to our attention.

Ms. DEGETTE. You actually did that alert because of this committee investigation, wouldn't that be fair to say?

Ms. WOODCOCK. Well, the investigation brought it to our attention. But we had taken action.

Ms. DEGETTE. So, obviously, you were so concerned about the distribution on Internet sites and through border pharmacies that you didn't do anything official until this week.

Ms. WOODCOCK. No, we didn't do anything official. We had taken other actions against Internet pharmacies marketing Accutane, however.

Ms. DEGETTE. You sent them cyberletters.

Ms. WOODCOCK. Yes.

Ms. DEGETTE. Could we get copies of that documentation for the record?

Ms. WOODCOCK. Certainly.

Mr. STUPAK. Could you yield on that point?

Ms. DEGETTE. Sure.

Mr. STUPAK. Isn't it true that Roche sent you a letter in 2000 concerning the Internet sales?

Ms. WOODCOCK. Yes, Roche has brought this to our attention several times.

Mr. STUPAK. Right. Several times. So it's been a couple of years, and you still haven't dealt with this issue on the Internet other than the so-called cyberletter.

Ms. WOODCOCK. Yes.

Ms. DEGETTE. Mr. Chairman, I'd ask unanimous consent to put the FDA alert into the record of this hearing.

Mr. GREENWOOD. Without objection.

[The information referred to follows:]

Accutane (Isotretinoin)

Do Not Buy Accutane Over the Internet

- You should not buy Accutane over the Internet because you will bypass important safeguards designed to protect your health (and the health of others).
- Accutane has special safety restrictions on how it is distributed to the public. Also, drugs purchased from foreign Internet sources are not the FDA-approved versions of the drugs, and they are not subject to FDA-regulated manufacturing controls or FDA inspection of manufacturing facilities.

To learn more about buying drugs safely, please see

- Buying Prescription Medicines Online: A Consumer Safety Guide.
- FDA strengthens controls, issues consumer alert on importing certain prescription drugs
- FDA Import Alert

Ms. DEGETTE. Okay. I just have a couple more questions about the SMART program. As I understand it, a recent study showed that there's only about 40 to 50 percent participation in the SMART program because it's a voluntary program. Would that be accurate?

Ms. WOODCOCK. There was 40 percent participation, it's my understanding, in the prior PPP, pregnancy prevention program, and we don't have metrics yet. We're going to await the metrics on SMART. But we have higher targets for participation.

Ms. DEGETTE. What are your targets for participation?

Ms. WOODCOCK. I have them here. Our target is 60 percent, I believe, but let me——

Ms. DEGETTE. So you'd still have 40 percent of the people who weren't even in this SMART program, which is the program you were talking about where they have the stickers and the warnings and all of that.

Ms. WOODCOCK. No, the sticker program we plan a target eventually of 100 percent participation.

Ms. DEGETTE. So what's the 60 percent participation?

Ms. WOODCOCK. The 60 percent is people who are willing to interact with a third party contractor and give them their information and be followed up. Patients who are willing——

Ms. DEGETTE. Right. So the rest of them can get the drug without any of that counseling.

Ms. WOODCOCK. No, they have to have all the counseling. The physicians need to provide the SMART program to everyone. It is participation in follow-up of their personal information that is currently voluntary.

Ms. DEGETTE. Yeah. Now, I've got—I don't know if you can see this, but you know it. It's the symbol that says "don't get pregnant" that's part of this program.

Ms. WOODCOCK. Yes.

Ms. DEGETTE. It's got a pregnant woman with a little "no" sign through it. And I've got this study here that says that only 21 percent of the women understood that they were not to get pregnant while taking Accutane. Is that true? Do you know about that study?

Ms. WOODCOCK. I don't know about the study.

Ms. DEGETTE. Okay. It is a study in the magazine—it looks like the magazine is called Teratology. And it's the September, 2001, issue where they say only 21 percent of women interpreted correctly without prompting that they should not take the medication if they are pregnant or not get pregnant without taking the medication—while taking the medication. Do you know about that?

Ms. WOODCOCK. I understand. That's strictly about interpretation of this symbol, and we agreed that a single symbol is not all that helpful. In fact, I think somewhere else, perhaps in this article or other articles, some women interpreted that symbol to mean the drug was a contraceptive.

Ms. DEGETTE. Right. They thought that if they were taking Accutane then they wouldn't get pregnant because it was a birth control product.

Ms. WOODCOCK. But there have been many other surveys and efforts and some of the witnesses today may testify where they've interviewed people on Accutane and a much higher percentage—very high percentage of them recognized they should not get pregnant. We do not rely on this symbol.

Ms. DEGETTE. Mr. Chairman, I thank you for the questioning; and I think it's pretty clear that the SMART program is a very troubled program and not really getting to the people who need to know that they cannot get pregnant while they're taking this drug. Thank you.

Mr. GREENWOOD. The Chair thanks the gentlelady.

The gentleman from Michigan is recognized for 10 minutes.

Mr. STUPAK. Thank you, Mr. Chairman.

Mr. Chairman, I'm tempted to continue the discussion of birth defects relating to this drug which I and the committee have spent hundreds of hours examining. However, as you know, there are additional concerns about potential side effects related to this, depression, suicide and suicide attempts, with this drug.

Because of the history of birth defects caused by Accutane, I believe FDA should strongly consider a formal mandatory registry. For 20 years FDA has known about the dangers of this drug for

pregnant women, and for 20 years the FDA has failed to prevent fetal exposure of this drug. But as I intend to explore with Dr. Woodcock, I believe there's additional concerns that may in and of themselves warrant a registry and limited distribution of the drug. Yet because of the failures in the risk management program so far I remain highly skeptical, highly skeptical that the FDA will adequately explore the psychological, devastating effects of Accutane. So I've got just a few questions on pregnancy, and then I'm going to go to the psychiatric effects.

Europe learned from thalidomide, didn't they? Europe learned from the thalidomide experience. They had all these birth defects on thalidomide.

Ms. WOODCOCK. Yes.

Mr. STUPAK. And you know Dr. Ed Lammer, right? He's been to your advisory committees. He's right now probably the leading expert in birth defects associated with Accutane because he's been studying it for about 20 years, right?

Ms. WOODCOCK. Yes.

Mr. STUPAK. Okay. In interviews with Dr. Lammer, he says Europe—there it's marketed as Roaccutane—he can count on one hand all the birth defects they have in Europe. Is that correct?

Ms. WOODCOCK. I don't know. I don't have personal knowledge of that.

Mr. STUPAK. Okay. Well, if Europe, with the many countries that make up Europe and different regulatory schemes over there—if they had just a handful, according to the leading expert of birth defects, just a handful of birth defects in Europe, in this country we can't do anything about it? We have 2,000 according to Dr. Graham. Well, if Europe can do it, can't we do it?

Ms. WOODCOCK. I would hope so. As you know, Europe has national health care in most countries. They have a different distribution system.

Mr. STUPAK. Right. They don't have to pay $500 to get their Accutane. They get it a little cheaper over there. So you'd think there'd be greater use. But it's not. Because in Sweden and everywhere else they restrict it through registries and that. And they don't have the birth defects problems that we have in this country, do they?

Ms. WOODCOCK. I don't know that to my personal knowledge.

Mr. STUPAK. All right. Let me ask you this question. We've met with FDA officials on occasions as committee members. If Roche came with Accutane today, would Accutane, that was approved in 1982, based upon that application, would it be approved today by today's standards, by today's FDA standards?

Ms. WOODCOCK. I personally believe so. It is a highly effective drug. There is no doubt about that. And the question is managing the risks appropriately.

Mr. STUPAK. Okay. Well, they have a new drug formula that's currently pending and that has not been approved by the FDA, right?

Ms. WOODCOCK. Right.

Mr. STUPAK. And one of the reasons is there's 11 times more psychiatric injuries with the new formula than there is with the current formula, isn't that right?

Ms. WOODCOCK. I can't comment on that.

Mr. STUPAK. Well, there's a number of documents in these files that indicate that, right? Skin and Aging magazine had it in there, about seven times greater. So you can comment on Skin and Aging magazine, can't you? Isn't that what they reported? It's 11 times greater than the current formula.

Ms. WOODCOCK. Yes. Estimates from small numbers often have very wide confidence levels.

Mr. STUPAK. Sure. But that was based upon a controlled study of 300 arm with the current formula 300 arm of the new formula. And the new formula had 11 times more, correct? That's Skin and Aging magazine now. You can comment on that. Yes or no.

Ms. WOODCOCK. I don't know. I recognize that there were issues——

Mr. STUPAK. Right. Accutane was sort of rushed on the market and was approved in less than a year, isn't that correct? First applied for in 1981, approved in 1982, correct.

Ms. WOODCOCK. We answered that. You requested that in our letter, so you're in possession of that knowledge then.

Mr. STUPAK. Okay. I've got the knowledge, but you have to answer the question for me. I know I have the knowledge.

Ms. WOODCOCK. Yes.

Mr. STUPAK. It was approved in less than a year.

Ms. WOODCOCK. Yes.

Mr. STUPAK. Back then it took 3 to 4 years to approve drugs.

Ms. WOODCOCK. That's my understanding.

Mr. STUPAK. And the original marketing, if you will, the original test on humans was 523 individuals, 89 of which were young people, and only six had acne, isn't that correct?

Ms. WOODCOCK. I do not know the data base myself.

Mr. STUPAK. Okay. So, again, my statement's probably correct, because I have studied it and I know, right?

Ms. WOODCOCK. My understanding from Dr. Wilkin is that most of the individuals have keratinizing defects that were not acne in those early studies.

Mr. STUPAK. Were not acne. In fact, there were only six, so we don't know if they're severe nodular cystic acne, do we, of those six?

Ms. WOODCOCK. I do not, no.

Mr. STUPAK. Okay. Dr. Woodcock, isn't it true that the current label—the current label on Accutane says this. I'm going to quote:

Some patients have become impressed—I'm sorry. Some patients have become depressed or developed other serious mental problems while they're taking Accutane or shortly after stopping Accutane. Some patients taking Accutane have thoughts of ending their own lives, suicidal thoughts. Some people have tried to end their own lives, attempted suicide; and some people have ended their own lives, committed suicide. No one knows if Accutane caused these problems or behaviors or if they would have happened even if the person did not take Accutane.

That's the current label, right?

Ms. WOODCOCK. That's from the patient information, right.

Mr. STUPAK. That's on the current label, right, that you get with your box?

Ms. WOODCOCK. Yes.

Mr. STUPAK. The new box that finally came out in May 2001, right? The old boxes didn't have any of this on it.

Ms. WOODCOCK. Correct. Not always.

Mr. STUPAK. Now, Dr. Woodcock, isn't it true a great deal of study and concern is required before a black box warning such as the one for Accutane is required for a drug?

Ms. WOODCOCK. We have to have a reasonable amount of concern about the safety.

Mr. STUPAK. Right. So you study it, and if there's a concern you raise it and you put on there——

Ms. WOODCOCK. Yes.

Mr. STUPAK. Now the black box is one of the highest warnings you can give to health care professionals. You've got the pregnancies black box and so is the psychiatric injuries——

Ms. WOODCOCK. Correct.

Mr. STUPAK. Okay. Now, recent e-mail of Roche dated October 30, 2001, saying it's time to celebrate because there's no registry, no advisory committee prior to getting this approved success in getting patients—excuse me—success in getting physician education into label.

Four, father exposed and depression removed from the black box to be placed in the precaution section. Are you going to remove the depression part from the black box warnings to the precaution warnings in your labeling?

Ms. WOODCOCK. I'd ask Dr. Wilkin to comment on that.

Mr. GREENWOOD. Dr. Wilkin, do you have any objection to giving your testimony under oath?

Mr. WILKIN. No. I would like to affirm.

Mr. GREENWOOD. You'll have that opportunity. Do you wish to be represented by counsel?

Mr. WILKIN. No.

Mr. GREENWOOD. Okay. I'd ask that you stand and raise your right hand.

[Witness sworn.]

Mr. GREENWOOD. You're under oath, and you may respond to the gentleman's questions.

Mr. STUPAK. My question is, is it true the depression and the psychiatric injury which is currently in the black box is that going to be moved to the precautionary section in the labeling?

Mr. WILKIN. The boxed warning is intended to identify known risks and significant risks.

Mr. STUPAK. So the answer—yes or no—are you going to move it from the black box precaution section according to the e-mail of Hoffman Roche of October 30? Are you removing it from the higher warning?

The black box is the highest warning you can get. If you move it down to precaution, that's a lesser warning. So this e-mail would be in error then. You are not going to remove it from the black box to precaution?

Mr. WILKIN. That is not our intent.

Mr. STUPAK. Okay, I know what your intent is. But are you going to do it or not? Are you going to move it from black box to precaution? I'm not trying to make this difficult. It's a simple yes or no answer.

Mr. WILKIN. I understand sir. But if you're talking about at any time in the future, there may be a time when we learn from studies that will be——

Mr. STUPAK. Doctor, right now, today.

Mr. WILKIN. No.

Mr. STUPAK. We've got the new patient box here that a patient gets, okay?

Mr. WILKIN. Yes.

Mr. STUPAK. Are you going to remove it from the black box? Are you going to move it from the PDR, Physician Desk Reference? You've got to educate people we've heard all day. The people you want to educate are the health care providers prescribing this drug. In the PDR the black box, which is the highest form of warning you can give a health care provider on a drug, are you removing it from that black box to precautions now? I don't know what you might do 10 years from now. We're hoping this drug isn't even on the market 10 years from now. So let's just deal with the facts of today.

Mr. WILKIN. Well, we're not removing anything from the black box. It is in the warnings.

Mr. STUPAK. So you're removing it from the black box warnings now? What are you actually doing with the new labeling of the patients and the PDR? What are you actually doing? Can you tell us?

Mr. WILKIN. Do you have in your documents the labeling for the product that we could go to together and we could point out the different sections?

Mr. STUPAK. Could you just—I don't want to spend my whole 10 minutes. In fact, my time's up. The chairman's going to get on me in a minute here. Yes or no. If you don't know, you don't know.

Mr. WILKIN. Okay. For the important risks for which there are data there is a black box or boxed warning that appears at the very beginning of product labeling. There is also a section further back in the labeling called warnings.

Mr. STUPAK. Right. And the black box is right up front so the health care provider can get the attention that it deserves. Are you removing depression and the psychiatric injuries from that black box further down into the physician label insert, as you call it?

Mr. WILKIN. Well, we have the warnings in the warnings section. We're not removing anything from that black box.

Mr. STUPAK. Okay. Thank you. Thank you.

Mr. GREENWOOD. The time of the gentleman has expired.

The gentleman from California, Mr. Waxman, is recognized for 10 minutes.

Mr. WAXMAN. Thank you, Mr. Chairman.

Dr. Woodcock and anyone else from FDA to respond, FDA approved Accutane only for severe recalcitrant nodular acne, a relatively uncommon and serious disease, not for garden variety acne, yet an FDA study indicates that it is being widely prescribed for milder conditions than severe cystic acne. Thus, patients with ordinary acne are being subjected to the serious risks of this drug. Do you believe that the benefits of Accutane outweigh its risks for ordinary Accutane?

Ms. WOODCOCK. No, and we are making every attempt to discourage use in those populations.

Mr. WAXMAN. Do you agree with Roche that the off-label prescribing of this drug is insignificant?

Ms. WOODCOCK. Perhaps that's semantics. Almost all the drug is prescribed for acne. However, much of it is prescribed—an unknown percentage is prescribed for acne that probably would respond to other treatments.

Mr. WAXMAN. And what steps has FDA or Roche taken to limit the use the drug to severe, recalcitrant nodular acne?

Ms. WOODCOCK. We have tried to educate the dermatologic community to the risks of this drug, and the SMART program really goes through all the risks to make sure the patient is also educated so the patient can also participate in that decision.

Mr. WAXMAN. And how successful would you say these efforts have been?

Ms. WOODCOCK. We do not know the success of this program until we see the metrics. However, prescribing—my understanding is prescribing has dropped 30 percent.

Mr. WAXMAN. And that came from the advisory committee, that figure?

Ms. WOODCOCK. No, that figure comes from our data that we look at.

Mr. WAXMAN. Okay. Do you believe that Roche's marketing of Accutane is consistent with limiting its use to severe acne?

Ms. WOODCOCK. They are required to limit their advertising to the indicated use, and our Division of Drug Marketing and Advertising Surveillance oversees those ads.

Mr. WAXMAN. And in your best professional judgment, do you think that they're doing a good job of limiting the advertising of the drugs to those who most need it?

Ms. WOODCOCK. I can't comment on that. I can tell you that, in my professional observation, the use of this drug has extended beyond the labeled indication. There is no doubt about that.

Mr. WAXMAN. What more in your view needs to be done to limit the use of this dangerous drug to severe acne?

Ms. WOODCOCK. We are hoping that the program that we've instituted over the past 2 years since the advisory committee will go a long way toward doing that.

Mr. WAXMAN. And so you're satisfied that that's all that needs to be done?

Ms. WOODCOCK. No, we are going to look at the metrics, as I said in my opening statement, and if we feel that this isn't successful then we'll see what else needs to be done.

Mr. WAXMAN. It seems to me that the adverse effects of Accutane on fetuses would be preventable if physicians were diligent in complying with the restrictions on the use of this drug. The high rate of pregnancy suggests that prescribing physicians are either unaware of the risks or are not being diligent in restricting prescriptions to women who are not pregnant and who can comply with contraceptive guidelines. How do you explain the failure of physicians and patients to heed the clear labeled warnings and instructions on how to use this drug?

Ms. WOODCOCK. There are several situations. It was clear that, earlier, some people were receiving this drug without the proper warnings about pregnancy, were not having the pre-pregnancy

tests done before starting the drug, and were not waiting until the onset of their first menstrual period to start the drug. Those are preventable situations.

But, as you may hear from later witnesses, there are other situations where women who choose abstinence and later reverse that position and aren't on contraception, and there are contraceptive failures.

Now, the SMART program adds a lot more counseling and interventions that we hope will prevent those type of contraceptive failures.

Mr. WAXMAN. Do you feel that there are other things that you or others need to do to insure that physicians and patients comply with the restrictions on the use of this drug?

Ms. WOODCOCK. I think we need to look at the metrics of the program. We need to make sure that each party has adequate information, both the prescriber and the physician. And we need to recognize that the pharmacist is now in the loop, and that provides another safety measure for this program that hasn't been there before. But we don't know yet whether this program will be successful.

Mr. WAXMAN. Over the years, FDA has been forced to take increasingly strong steps to try to prevent patients from the serious adverse effects of Accutane as each prior action fails to curb the problem. Do you believe that the most recent actions taken by FDA will be effective in reducing the incidence of pregnancy and birth defects?

Ms. WOODCOCK. Yes, I believe that we will reduce the incidents of exposed pregnant woman through this program.

Mr. WAXMAN. Why do you believe that doctors, pharmacists and patients will be that much more likely to follow the new rules for use of Accutane under the SMART program than they were under previous programs?

Ms. WOODCOCK. Well, we will have a direct audit by looking at the compliance with the sticker program and so forth to see how well this is occurring. We also will be able to talk to 60 percent of the people who are enrolled in the follow-up and discussion and registration and see what their compliance has been.

Mr. WAXMAN. Has this new program resulted in a significant drop in reported pregnancy and birth defects?

Ms. WOODCOCK. We have seen a drop, but we've also seen a drop in prescribing, and the program we don't think has been implemented long enough.

Mr. WAXMAN. I'm going to yield, since I have a little bit more time left, to Mr. Stupak if he wants to use any of that time. Thank you for the responses to my questions.

Mr. STUPAK. Thank the gentleman for yielding.

Mr. Chairman, I'd ask the documents from which we've been referring to and those in the white committee book here be made part of the record.

Mr. GREENWOOD. Without objection.

Mr. STUPAK. Thank you.

Dr. Woodcock, isn't it true that senior FDA officials have been concerned about the association between Accutane and depression

starting way back in February 1985? And let me just read to you from a Dr. Phyllis Hune——

Who's Dr. Phyllis Hune? She's the medical officer?

Ms. WOODCOCK. Medical officer, uh-huh. One of our clinicians.

Mr. STUPAK. And she reported suicide—I'm quoting now—in this memo to her director, suicide was recently reported in a male on Accutane who had no prior history of depression with no apparent adverse circumstance which might precipitate depression. There have also been a number of CNS—central nervous system—effects reported in patients on Accutane. These have included severe headaches, seizures, tremors, disorientation, numbness and paralysis, blurred or double vision, memory loss and behavioral changes other than depression. We would appreciate a review of these adverse effects which have been reporting to your division. And then after that, the FDA put out the so-called first dear doctor letter, right? Correct?

Ms. WOODCOCK. Yes.

Mr. STUPAK. And again, in 1986, they put out another dear doctor letter.

Ms. WOODCOCK. Those are usually done by the company.

Mr. STUPAK. At your request.

Ms. WOODCOCK. Um-hmm.

Mr. STUPAK. And in 1988, there was another dear doctor letter from the report that we saw earlier today, correct?

Ms. WOODCOCK. Yes.

Mr. STUPAK. All right. And dear doctor letters, they don't go to the patients or families or consumers; it goes just to the health care provider.

Ms. WOODCOCK. Correct.

Mr. STUPAK. How is the families or patients ever going to know about this, these psychiatric effects, if we don't get the notification?

Ms. WOODCOCK. Right. Well, we feel that now, with the new program, it's very—which I've been—which is the SMART program. And pardon me for——

Mr. STUPAK. I'm just talking about the psychological.

Ms. WOODCOCK. Yes.

Mr. STUPAK. How would the people know if I'm not a female and I'm not part of the SMART program?

Ms. WOODCOCK. Everyone needs to be counseled.

Mr. STUPAK. So you are relying upon the physicians to do it?

Ms. WOODCOCK. Yes.

Mr. STUPAK. In fact, didn't you put out the informed consent in about January and February 2001?

Ms. WOODCOCK. That's correct.

Mr. STUPAK. And isn't it true that doctors are not required to have patients sign informed consents? And the FDA's position is we can't tell doctors how to practice medicine, so we can't make them sign an informed consent?

Ms. WOODCOCK. Well, they undergo an extensive educational program. And it says in the label that they should go through these steps.

Mr. STUPAK. The informed consent is voluntary, isn't it, Doctor?

Ms. WOODCOCK. It's voluntary. Um-hmm.

Mr. STUPAK. And you know from the investigation your agency has done, a lot of doctors aren't using the informed consent.

Ms. WOODCOCK. I don't know whether we know that under this program yet.

Mr. STUPAK. Well, I'm not talking about the SMART program. I'm talking about January 2001, before you did the SMART program. When we went public, my wife and I, we had had seven Members of Congress. One of the things we said you should do is put an informed consent.

Ms. WOODCOCK. Right.

Mr. STUPAK. And you wrote out this informed consent and you said, this is it, we've got informed consent. And then the FDA come back and told us, well, 50 percent of the doctors are using it, and it's voluntary. And, quite frankly, the chairman and I were shocked. You're saying we bring in our minor child to get Accutane, and the doctor doesn't have to tell us about informed consent, which is the only place the consumer gets the advisory about the psychiatric events.

Ms. WOODCOCK. The Med Guide is mandatory.

Mr. STUPAK. And we also know from your own agency investigation that pharmacies aren't using it. And you are now going to go—we are going to try to stick the Med Guide inside this pack of Accutane, and you hope someone is going to read it.

Ms. WOODCOCK. Correct.

Mr. STUPAK. Because the Med Guide wasn't being given out by the pharmacist even though they are required to do so.

Ms. WOODCOCK. By law. That's correct.

Mr. STUPAK. Right.

Ms. WOODCOCK. Not in all cases.

Mr. STUPAK. Right.

Ms. WOODCOCK. They were not giving it out in all cases.

Mr. GREENWOOD. The time of the gentleman has expired.

Mr. STUPAK. Thank you, Mr. Waxman.

Mr. GREENWOOD. And Mr. Strickland is recognized for 10 minutes.

Mr. STRICKLAND. Mr. Chairman, I'm going to yield my time to Mr. Stupak in just a moment, but I just have one question. And I'm sorry I wasn't here earlier; I just spent 2½ hours in the dental chair, so I'm happy to be here. But is it a safe assumption that probably every physician—every physician is aware of the dangers of thalidomide in terms of birth defects? I mean, is that a——

Ms. WOODCOCK. No. We have looked to some—I've done some informal surveys myself at the time of approval of thalidomide, and, you know, it's a generational thing. Younger people, even though they are medically trained, may not associate that.

Mr. STRICKLAND. Even today?

Ms. WOODCOCK. Um-hmm. Today, today people who are prescribing thalidomide are very well aware of its potential, but it may well be that others are not.

Mr. STRICKLAND. Well, I want to tell you, in my 101 psychology class, which I taught to undergraduates, that was certainly something that we talked about. It's almost unbelievable to think that a physician today would not know the potential dangerous effects of thalidomide. And I was hoping you would say yes, and then I

was going to ask you, is there a similar awareness in terms of Accutane? But if they aren't—if all of them aren't aware of the dangers of thalidomide, I—I find that just stunning and shocking.

Mr. Stupak, I yield my time to you.

Mr. STUPAK. Thank you. I thank the gentleman for yielding.

Dr. Woodcock, Dr. Kathryn O'Connell is the medical officer for Accutane; is that correct?

Ms. WOODCOCK. Yes.

Mr. STUPAK. And she has been since about 1996, correct?

Ms. WOODCOCK. Yes.

Mr. STUPAK. Okay. In a memo that she wrote, in fact you received the memo, you were copied on it, in February 1998, it states—and we've had it blown up here. It states, it concludes that: Given all the pieces of evidence available, it is difficult to avoid the conclusion that Accutane can adversely affect the adult human brain in clinically significant ways, and that Accutane's use is associated with severe psychiatric disease in some patients.

Is that correct?

Ms. WOODCOCK. That's what their memo states.

Mr. STUPAK. Right. And you received that memo.

Ms. WOODCOCK. Correct.

Mr. STUPAK. Okay. Dr. Woodcock, isn't it true there is more than one way to establish causation between a drug and an effect of that drug——

Ms. WOODCOCK. Yes.

Mr. STUPAK. [continuing] other than just studies? There's a number of ways to help establish causation.

Ms. WOODCOCK. To help establish causation, certainly.

Mr. STUPAK. Well, let me show you this memo done by Dr. Wilkin who testified. It's number 33 in our binders. If you go through it, he lays out nine ways in which these spontaneous reports prompted us to ask whether other information supports a causal relationship since you don't have the studies.

No. 1, reach the target organ of the observed adverse event; in other words, the brain. Does Accutane go to the brain? The answer was yes. Is Accutane associated with other nervous—central nervous system adverse events? Again, yes. And it's all supported by your documentation. Do we have challenge and dechallenge consistent with Accutane pharmacokinetics? Again, yes. Are there published reports of psychiatric adverse events associated with Accutane that predate the publicity of the 1998? Yes. Other retinoids, including natural retinoids, Vitamin A, when consumed in excess? Again, yes, yes. We go all the way down, all to the last one. It has a mechanism—a mechanism of action has been established to account for observed events? No. Indeed, dermatologists have managed for many years potentially serious side effects administered without delineation of it.

So, 8 out of the 9 other ways to prove causation we can prove just with the information that we have available to us; isn't that right?

Ms. WOODCOCK. Those are all supportive evidence for causality. They don't establish a link.

Mr. STUPAK. They are all supportive of causality.

Ms. WOODCOCK. Yes.

Mr. STUPAK. This is like Firestone Tire. Right? We have all these other factors, but we don't know what really caused the tire to blow out. Right? As I said in my opening statement, I don't mean to argumentative with you.

Okay. Dr. Woodcock, when you went through and you did a review of the 31 suicide and attempted suicide cases, that's the chart we had up here earlier, it's number 20 in your binder there in front of you. Again—wrong one. Look again in this one. It's number 18 in your binder.

Ms. WOODCOCK. Okay.

Mr. STUPAK. Okay? For the majority of these people, in fact, 10 out of 12, there was no antecedent history of depression, and patients were not noted or known to be depressed prior to their suicide. That also helps to establish causation, doesn't it?

Ms. WOODCOCK. With the background rate, it is very difficult for us to use this type of reporting.

Mr. STUPAK. Wait a minute. You went through—and this is about a five-page report. I didn't go through and put it all down here. But you made sure—and the memo is all there in front of you. You made sure there was no confounding factors with these 31 cases; 19 were attempted suicide, 12 were not. You ruled out all these extraneous factors so you could get a clean picture of what was going on; isn't that correct?

Ms. WOODCOCK. We try to do that as much as possible.

Mr. STUPAK. Sure.

Ms. WOODCOCK. That's correct.

Mr. STUPAK. And the same with Exhibit Number 16 in your book right there, which talks about 51 patients on Accutane therapy who committed or attempted suicide. And again, you ruled out all the confounding factors, and only 11 had a previous history, as Dr. O'Connell concludes by saying the overall impression of these sources is that Accutane may precipitate serious psychiatric disturbance and suicide; isn't that correct?

Ms. WOODCOCK. Yes. I note she also says that is—there is inherent limitations in attempting to use these data to demonstrate cause and effect.

Mr. STUPAK. And why is it? Because you have limited information in the Med Watch reports that come in, correct?

Ms. WOODCOCK. That isn't the underlying technical reason.

Mr. STUPAK. Okay.

Ms. WOODCOCK. When we do adverse events for any drug, we often see what could look like a compelling signal.

Mr. STUPAK. A compelling signal. Right.

Ms. WOODCOCK. And when we do a clinical trial, sometimes it isn't a cause.

Mr. STUPAK. Compelling signal. Let me ask you this. When we went public in October 5, 2000, my wife and I, to try to increase public awareness about Accutane, you said there were 47 suicides.

Ms. WOODCOCK. Um-hmm.

Mr. STUPAK. Your office as of October 31 has confirmed 167. In a document just handed to me today, you confirmed now you have confirmed 173 suicides. Last Friday I sent you another 37 suicides of people who have contacted my office. We've urged them to contact the FDA. We find they do not, so we forward them to you. So

that's over 200 confirmed suicides. Is that a big enough signal for you?

Ms. WOODCOCK. I really don't mean to argue with you about this. It's simply with spontaneous reporting data, it's not possible for us to separate out the underlying incidents in the population from——

Mr. STUPAK. Sure. Sure, it's hard to. But you know——

Ms. WOODCOCK. We are concerned——

Mr. STUPAK. We know from your adverse event reporting because it's only a signal.

Ms. WOODCOCK. Yes.

Mr. STUPAK. And you do agree there is a signal there.

Ms. WOODCOCK. And we are very concerned. We have been very concerned.

Mr. STUPAK. And we know that signal that you see of 200 deaths now, suicides, we know that that represents probably 1 percent of the actual number, because you can't catch all of them, and these are voluntary reporting, correct?

Ms. WOODCOCK. We do not know the percent that have been——

Mr. STUPAK. That's okay.

Ms. WOODCOCK. [continuing] submitted to us.

Mr. STUPAK. Dr. Woodcock, in all these documents, if you want to go through it, Dr. O'Connell, Diane Wysowski, others have all indicated it's 1 percent. You have met with us, you said it's approximately 1 percent, because the length of time the drug's on the market, the treatment, which is for acne which is not life-threatening, but the devastating results of suicide and other deaths associated with this drug. And based upon the history of it—and it's hard to relate acne can cause suicide. As I said to my own wife when she asked me about it, I don't know how it would affect his state of mind. It's less likely people are going to catch these signals. You have. And it's fair to say, based upon all the reports and the information we have, it represents only 1 percent of the actual number, 1 out of every 100; isn't that correct?

Ms. WOODCOCK. I can't comment on that. I don't think we know. We realize that publicity will increase reporting, for example, and we have had many public reports on this.

Mr. STUPAK. Yes. And maybe after today we will have some more of those, too.

Ms. WOODCOCK. Yes.

Mr. STUPAK. And we have—Dr. Woodcock, if you take a look at this, how many deaths are actually related? Just deaths. I'm not talking suicides. Total deaths with Accutane now that you have in your data base? Four hundred?

Ms. WOODCOCK. We have—thank you. We have 381 reports of death——

Mr. STUPAK. Right.

Ms. WOODCOCK. [continuing] in people who have been taking Accutane.

Mr. STUPAK. And then when you use that for your 380, some of that was 167 for suicide. So the other 200 plus, what is that from? That's from heart attack, right?

Ms. WOODCOCK. I'm going to ask to ask our safety evaluator Marilyn Pitts to come up.

Marilyn, would you be the right person to comment?

All right. Is that okay?

Mr. STUPAK. Sure. If you want. Go ahead.

Mr. GREENWOOD. I'm sorry. Dr. Pitts, do you have any objection to giving your testimony under oath?

Ms. PITTS. No.

Mr. GREENWOOD. Do you wish to be represented by counsel?

Ms. PITTS. No.

Mr. GREENWOOD. Would you stand and raise your right hand, please?

[Witness sworn.]

Mr. GREENWOOD. Okay. You are under oath, and you may respond.

Ms. PITTS. Right.

Mr. STUPAK. Dealing with deaths we have seen with Accutane, 200 and some others are related to heart attack, right?

Ms. PITTS. No. I can't say that specifically. I know that we have deaths related to pancreatitis.

Mr. STUPAK. To pancreatitis. Right.

Ms. PITTS. Right. Death related to pseudotumor cerebri. And there is a whole spectrum, but I cannot give you the actual number.

Mr. STUPAK. I'm not asking for a number.

Ms. PITTS. Well, but I don't know if they are all related to heart attack. In fact, I'm pretty——

Mr. STUPAK. You mentioned acute pancreatitis.

Ms. PITTS. Um-hmm.

Mr. STUPAK. The cerebral is really a stroke, right?

Ms. PITTS. A hemorrhage, yes.

Mr. STUPAK. A hemorrhage of the brain, and they die, right?

Ms. PITTS. Not all patients died——

Mr. STUPAK. No.

Ms. PITTS. [continuing] who had hemorrhage.

Mr. STUPAK. Some do. Some do. And heart attacks. Some have them, and some don't die. But of these other 200, I'm grouping them all together.

Ms. PITTS. No. We also have reports of deaths of especially elderly patients who are receiving Accutane for certain cancers.

Mr. STUPAK. Okay.

Ms. PITTS. So we have those.

Mr. STUPAK. Some lymphomata. Okay. The point being on this thing, besides just the suicides, strokes, acute pancreatitis—and these are occurring in relatively young, healthy populations, right?

Ms. PITTS. I don't have the demographics, but relative—Accutane is relatively used in young, healthy patients, but I don't have the specific demographics for those patients.

Mr. STUPAK. Sure. And some of these young, healthy patients have had strokes.

Ms. PITTS. Yes. I can say that, that some of them——

Mr. STUPAK. Okay.

Mr. GREENWOOD. The time of the gentleman has expired. We promised Dr. Woodcock we'd have her out of here by 12, and I have asked the Minority for permission to go out of order and just ask one final question of you myself.

Ms. WOODCOCK. Certainly.

Mr. GREENWOOD. In your May 2001 e-mail, you wrote: There seems to be a general consensus that we should go forward quickly with a voluntary program while continuing to develop the mandatory program and have it as the fallback if things don't improve.

And my understanding is that one of the parameters for you to define success is a 60 percent compliance rate with the voluntary registry, and I'm also informed it doesn't look like you're going to get that. Now, so my question is, first off, do you have a fallback? Are you prepared—if at the time of reevaluation you haven't reached 60 percent, are you prepared to go to a fallback program?

And, more broadly, I think what's been clear from all of your responses and the questions so far is that a mandatory registration registry and a restricted distribution would, in fact, outside of the black and gray market, probably reduce the incidence of tragic outcomes with this drug, but it is the fear of increased or enhanced utilization of the product in the gray and black market that causes the FDA to come short of making that final decision.

It would seem to me, and I think Mr. Deutsch alluded to this in his question, that an approach, a logical approach, would be a multifaceted approach where you, in fact, did go to the mandatory registry, the restricted distribution, and then had a very robust program to prevent the young people in this country from acquiring Accutane from the Internet and from across-border importations. Why not—after all that we've heard this morning, why not bite the bullet and say, we are going to go out in an all-out, all-fronts effort to try to prevent birth defects and psychiatric and other disorders resulting from this very useful drug?

Ms. WOODCOCK. We certainly have run scenarios on fallback positions, and we have relayed this to Roche, and they are aware of our position. We are not sure that these additional steps would be additionally effective. We would have to see if that—if we come to that.

As far as—with all due respect, as far as our ability to keep young people from taking drugs, I have reason for some skepticism about how effective we in the United States are, from what I hear from my teenage children about illegal drug use of their peers.

So I think, you know, as I said in my opening remarks, a program is being executed. We will evaluate the metrics. If the program isn't satisfactory, you can be assured that we will continue to take the steps that are needed to make sure there is appropriate use.

Mr. GREENWOOD. Is your concern about the inability—I mean, obviously you can't completely control behavior. That's never a reason to give up trying.

Ms. WOODCOCK. Right.

Mr. GREENWOOD. Is your concern about the FDA's ability to stop Accutane at the border, to stop it from being available as readily on the Internet—is that a resources concern, that you don't have the resources within the FDA to accomplish that?

Ms. WOODCOCK. Well, as you probably—as the committee, I think, is aware, there are a spectrum of issues, from authority issues, resources, and all the way through that are limitations. Even if those were solved, I'm not sure, given the problem with

drugs of abuse in this country, that we could be 100 percent effective.

Mr. STUPAK. Mr. Chairman, on a point, may I follow up?

Mr. GREENWOOD. Briefly, yes.

Mr. STUPAK. Just one question, because you've talked about it, Mr. Chairman; you've spent a lot of time dealing with the OxyContin issue of coming across the border, and we've spent a couple years of years this committee exploring it. I would like to submit for the record from Customs an e-mail on December 9, 2002, and it states, and I quote: As of this writing, Customs has no formal plan of action to deal with this situation—this is the import alerts on Accutane—FDA must provide the necessary guidance for O G A to develop and implement the interagency enforcement strategy.

There is not even any guidance from FDA on how to do it. To say we can't do something and not even try, and I understand why the kids are skeptical or why we are skeptical of it. You are not even trying. Treasury is asking for guidance from you, and you are not even giving it to them.

Mr. GREENWOOD. Dr. Woodcock, finally, you just mentioned in your response that resources was an issue and that authority was an issue. Does the FDA believe that it has the authority to require a mandatory registration and limited distribution; and if your—if the answer is no, that you don't think you have the authority, do you seek it?

Ms. WOODCOCK. We have the Office of Chief Counsel here to answer that question.

Mr. GREENWOOD. All right.

Ms. WOODCOCK. Seth Ray.

Mr. GREENWOOD. Do you object to giving your testimony under oath, sir?

Mr. RAY. No.

Mr. GREENWOOD. Do you wish to be advised by counsel?

Mr. RAY. No.

Mr. GREENWOOD. All right. Would you stand and raise your right hand, please.

[Witness sworn.]

Mr. GREENWOOD. You are under oath, and you may respond.

Mr. RAY. If it's determined that a mandatory patient registry would be appropriate, FDA would first try to get the sponsors to agree. I think the Agency's experience has been that working together with the sponsors results in the most success in managing the risks of particular drugs. FDA would invoke its legal authority only as a last resort, and that's because our ability to enforce such restrictions on the marketing of the drug is limited because certain restrictions, for example, patient registries, require the participation of physicians and patients, and FDA's regulatory authority is over the sponsoring companies. And you should also appreciate that if a sponsor does not agree to such restrictions, because of the limits of our legal authority, we could find ourselves in the position of having to choose between withdrawing the approval of the drug and making it unavailable, or leaving it on the market without such restrictions.

Mr. GREENWOOD. And what are you citing as your authority there?

Mr. RAY. Basically, the Federal Food, Drug and Cosmetic Act.

Mr. GREENWOOD. Okay. Can you be more specific to the reference, with regard to the reference?

Mr. RAY. Well, there are a number——

Mr. GREENWOOD. You certainly seemed to have anticipated my question this morning.

Mr. RAY. Yes. Yes, we were anticipating it.

As I said, I think you have to look at various provisions in the——

Mr. GREENWOOD. I would ask if you would provide the specific legal references from which you are reading.

Mr. RAY. Sure.

[The following was received for the record:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
March 5, 2003

The Honorable JAMES C. GREENWOOD
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

DEAR MR. CHAIRMAN: During the December 11, 2002, hearing entitled, "Issues Related to the Safety of Accutane:" a question was raised about the Food and Drug Administration's (FDA or the Agency) authority to restrict distribution of drugs. Our response is set forth below.

As Dr. Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research, testified during the hearing that if the Agency determines a mandatory patient registry is appropriate, 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.

When FDA promulgated Title 21, *Code of Federal Regulations* §314.520, which governs approval of a drug product with restrictions to assure safe use, the Agency relied on sections 501, 502, 503, 505, and 701 of the FD&C Act. These provisions provide authority for FDA to issue regulations to help ensure the safety and effectiveness of new drugs. They reflect Congress' objective of protecting the public health by requiring safety and effectiveness of new drugs under the conditions of actual use, through a variety of mechanisms. For example, new drugs may be approved under section 505(d) of the FD&C Act only if safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. FDA is also authorized by section 505(k) of the FD&C Act to require reporting of information after approval necessary to enable the Agency to determine whether there may be grounds for withdrawing the approval. Among the grounds for withdrawal specified in section 505(e) of the FD&C Act are that the evidence reveals the drug is not shown to be safe and effective under its conditions of use. Finally, section 701(a) of the FD&C Act authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act.

Thank you again for your interest concerning this matter. Please contact us if you have any further questions.

Sincerely,

AMIT K. SACHDEV,
Associate Commissioner for Legislation

Mr. GREENWOOD. Did the stenographer get the gentleman's name? Could you spell your last name, please?

Mr. RAY. Sure. R-A-Y.

Mr. GREENWOOD. Okay. Thank you, sir.

Dr. Woodcock, we thank you for your testimony this morning, and you are excused.

Ms. WOODCOCK. Thank you.

Mr. GREENWOOD. The Chair would then call the second panel forward consisting of Susan Turney, Michael and Caroline Bencz, Debra Wallace, David Shove-Brown, Dr. Nancy Green, who is the medical director of the March of Dimes, and Lynn Martinez, the manager of Teratology and the Birth Defects Program of the Organization of Teratology Information Services from the Utah Department of Health.

Is Dr. Berson present? All right. We will proceed without her until such time as she arrives.

We welcome all of the witnesses this morning. We thank you for your help in our analysis here. As you may have heard me ask the other—or say to the other witnesses that this is an investigative hearing, and that when this subcommittee holds an investigative hearing, it is our practice to take testimony under oath. And I would ask if any of you have any objections to offering your testimony under oath this morning?

Okay. Then I want to inform you that, pursuant to the rules of this committee and of the House, that you are entitled to be represented by counsel. Do any of you wish to be represented by counsel this morning? Okay. Then seeing no positive responses to that question, I would ask you if you would all please stand and raise your right hand.

[Witnesses sworn.]

Mr. GREENWOOD. Okay. You are all under oath. And we are going to begin with Mr. Shove-Brown because I believe that he has a time problem.

We ask you to offer your 5-minute opening statement. And please pull that microphone close to you. Make sure it's turned on with the little button there. And it's very directional, so you want to speak directly into it.

You are recognized, sir.

TESTIMONY OF DAVID SHOVE-BROWN; SUSAN TURNEY, REPRESENTED BY DAVID P. AFFINITO, DELL'ITALIA, AFFINITO & SANTOLA; MICHAEL AND CAROLINE BENCZ, REPRESENTED BY MICHAEL J. RYAN, KRUPNICK CAMPBELL MALONE BUSER SLAMA HANCOCK McNELIS LIBERMAN & McKEE, P.A.; DEBRA WALLACE; NANCY S. GREEN, MEDICAL DIRECTOR, MARCH OF DIMES; LYNN MARTINEZ, MANAGER OF TERATOLOGY AND BIRTH DEFECTS PROGRAM, ORGANIZATION OF TERATOLOGY INFORMATION SERVICES, UTAH DEPARTMENT OF HEALTH; AND DIANE S. BERSON, ASSISTANT PROFESSOR OF DERMATOLOGY, JOAN AND SANFORD I. WEILL MEDICAL COLLEGE, CORNELL UNIVERSITY

Mr. SHOVE-BROWN. Thank you.

Distinguished members of the Committee on Energy and Commerce, I would like to thank you for the invitation to come here today and present my experiences and opinions of Accutane. I believe that listening to and learning about the experiences of acne sufferers and their relatives is important in comprehending what Accutane does physically and emotionally.

Prior to presenting my history—and I apologize if some of this is somewhat a reiteration of what you have all heard very scientifically this morning. I will present the much more human side.

Prior to presenting my history of Accutane, I must reiterate the difference between a general basic adolescent acne and what I had, which was severe acne. Basic acne manifests itself through the occasional zit or blackhead, while severe acne provided me with constant breakouts, blackheads, whiteheads, progressing to red, irritated skin.

I endured severe acne during my high school years in West Hartford, Connecticut. I found high school to be an excruciatingly difficult process. I was beginning to establish who I was, what I was interested in, and who I would be making my journeys with while trying to fit in with the cultural mainstream of America. How would I explore the beauty of contemporary art and design yet find a date to the end-of-school dance? It seems frivolous yet all-encompassing to teenage life.

The real challenge to this time in my life was my physical appearance. I suffered from severe acne, constant breakouts with irritated skin. I was fixated upon the idea that my classmates were consumed by my freakish appearance. I was embarrassed at times to be seen. I avoided all cameras, especially this guy, and image-capturing experiences. I refrained from attending events during the most heinous of breakouts. I loathed the idea of presenting in front of any type of group, 20 sets of eyes fixated upon me and my acne. It was a daily gamble, how much worse would my face look than the day before?

I visited my dermatologist monthly, hoping at each visit I would be cured. We ran the gamut of medications, from the most proven creams and oral medications to the outlandish old wives' tales from fictional novels. Each of these methods failed, leaving me increasingly dejected with the way that I appeared and the way that my appearance determined who I was. I was convinced that I would spend the remainder of my days with horribly disfigured skin, scaring small children.

I very vividly remember the day my doctor suggested Accutane. "There's a new medication on the market with severe cases—for severe case of acne like yours," he said. We discussed the case, the future, this medication and its side effects. My parents and I examined the options, researched the possibilities. After several weeks of discussions and debate, we elected to try Accutane. I considered this moment critical in my adolescent years. I went through one complete treatment of Accutane. I endured dry skin, susceptibility to sun, the occasional nosebleed, all that had been expected.

What I didn't expect was my attitude adjustment. Within weeks I wasn't embarrassed to go to school. I wasn't afraid to be in photos. I gained self-confidence and composure. These medication breathed new life into my young existence.

I give tremendous credit to Accutane and its manufacturers for my change in attitude. At this very influential time, I believe that my improved condition and modified appearance—I was able to believe in who I was and what I was doing.

At the end of my Accutane treatment, I was able to confidently finish high school. I proceeded to a very successful college career

studying architecture. I grew and flourished, developing into an increasingly poised and assertive young man. I tackled new challenges, jumped at new chances, and dreamed bigger dreams. I never once was ashamed of who I was and what I looked like. I found tremendous success in college. I believe that through the use of Accutane I was able to focus my energies away from judging my physical appearance to developing my mental and emotional persona.

I no longer fear standing in front of groups. As an architect, I present regularly in front of clients, coworkers, contractors, and potential clients. I feel that they are listening to my ideas, not assessing my skin. I teach part time. I work with young adults at Catholic University. Three days a week, I speak on the beauty of the built form and the design process. I lecture about influential people and radical ideas. I talk about spacial relationships, building materials, and the marriage of the two. Never once do I wonder if the students are examining my skin condition.

I have been married for 2 wonderful years. Since my wife and I met 5 years ago, we have laughed, we have dreamed, and we have explored. Not once have I been afraid to leave the bathroom because I was amidst a harsh breakout.

While all these ideas may seem simple and, in the grand scheme of the universe, unimportant, I assure you to a 17-year-old growing up, one's physical experience is life-defining. Accutane does not grow self-confidence genes, it does not develop assertiveness cells, it simply clears one's skin. It is through this basic task that Accutane did, in fact, change my life. Thank you very much.

[The prepared statement of David Shove-Brown follows:]

PREPARED STATEMENT OF DAVID SHOVE-BROWN

Distinguished Members of the Committee on Energy and Commerce: I would first like to thank you for the invitation to come here today and present my experiences and opinions of Accutane. I believe that listening to and learning about the experiences of acne sufferers and their relatives is very important in comprehending what Accutane does physically and emotionally.

Prior to presenting my history with Accutane, I must reiterate the difference between general, basic adolescent acne and severe acne. Basic acne manifests itself through the occasional "zit" or blackhead while severe acne provides constant "breakouts" going beyond blackheads, to whiteheads and progressing to red, irritated skin. It is the later of which I suffered.

I endured severe acne during my high school years in West Hartford, Connecticut. I found high school to be an excruciatingly difficult process... I was beginning to establish who I was, what I was interested in and who I would be making my journeys while trying to "fit in"' with the American cultural mainstream. How would I explore the beauty of contemporary art and design, yet find a date to the end of school dance? Seems frivolous, yet all encompassing to teenage life. The real challenge to this time in my life was my physical appearance. I suffered from severe acne... constant breakouts with irritated skin. I was fixated upon the ideal that my classmates were consumed by my "freakish" appearance. I was embarrassed at times to be seen... I avoided all cameras and image capturing experiences... I refrained from attending events during the most heinous breakouts. I loathed the idea of presenting in front of any type of group... 20 sets of eyes fixated upon me and my acne. It was a daily gamble... how much worse would my face look than the day before?

I visited my dermatologist monthly, hoping at each visit that I would be cured. We ran the gambit of medications from the most proven creams and oral medicines to the outlandish old wives tales from fictional novels. Each of these methods failed leaving me increasingly dejected with the way I appeared and the way that my appearance determined who I was. I was convinced that I would spend the remainder of my days with horribly disfigured skin scaring small children. I very vividly re-

member the day that my doctor suggested Accutane. "There's a new medication on the market for severe cases of acne like yours," he said. We discussed my case, the future, this new medication and its side affects. My parents and I examined my options and researched the possibilities. After several weeks of discussion and debate, we elected to try Accutane. I consider this moment critical in my adolescent years.

I went through one treatment of Accutane. I endured dry skin, susceptibility to sun and the occasional nosebleed, all as I had expected. What I didn't expect was my attitude adjustment. Within weeks I wasn't embarrassed to go to school...I wasn't afraid to be in photos...I gained self-confidence and composure. This medicine breathed new life into my young existence.

I give tremendous credit to Accutane and its manufacturers for my change in attitude. At this very influential time, I believe that through my improved condition and modified appearance I was able to believe in who I was and what I was doing.

At the end of my Accutane treatment, I was able to confidently finish high school. I proceeded to a very successful college career studying architecture. I grew and flourished, developing into an increasingly poised and assertive young man. I tackled new challenges, jumped at new chances and dreamed bigger dreams. I never once was ashamed of who I was and what I looked like. I found tremendous success in college, graduating number two in my class. I believe that through my use of Accutane I was able to focus my energies away from judging my physical appearance to developing my mental and emotional persona.

I no longer fear standing in front of groups. As an architect, I present regularly in front of clients, co-workers, contractors and potential clients. I feel that they are listening to my ideas, not assessing my skin. I also teach part-time...I work with young college students at Catholic University. Three days a week I speak on the beauty of the built form and the design process. I lecture about influential people and radical ideas. I talk about spatial relationships, building materials and the marriage of the two. Never do I wonder if the students are examining my skin condition.

I have been married for two wonderful years. Since we met five years ago, we have laughed, we have dreamed and we have explored and not once have I been afraid to leave the bathroom because I was amidst a harsh breakout.

While all of these ideas may seem simple and, in the grand scheme of the universe, unimportant, I assure you, to a 17 year old growing up, one's physical appearance is life defining. Accutane does not grow self-confidence genes, it does not development assertiveness cells, it simply clears one's skin. It is through this basic task, that Accutane changes lives.

Mr. GREENWOOD. We thank you for your testimony.

And do I understand correctly that you do need to depart?

Mr. SHOVE-BROWN. Yes, I do.

Mr. GREENWOOD. Well, you look very good, sir.

Mr. SHOVE-BROWN. Thanks.

Mr. GREENWOOD. And you did very well, and you are excused. Thank you very much.

Mr. SHOVE-BROWN. Thank you.

Mr. GREENWOOD. And, Dr. Berson, you had not yet arrived when the others were sworn in, so I should inform you of that. Because this is an investigating hearing—investigation hearing, we take testimony under oath. Do you have any objections to giving your testimony under oath?

Pursuant to the rules of the committee and the House, you are entitled to be represented by counsel. Do you wish to be represented by counsel this morning?

Okay. Then would you stand and raise your right hand, please.

[Witness sworn.]

Mr. GREENWOOD. Okay. And we will get to you in a little while.

Mr. Turney and Mrs. Turney, you are recognized for 5 minutes. Thank you for being with us this morning.

TESTIMONY OF SUSAN TURNEY

Ms. TURNEY. Good morning, Mr. Chairman Greenwood and distinguished members of the committee. My name is Susan Turney,

and next to me is my husband Martin. We live in Watertown, New York, and are the proud parents of a beautiful daughter Kelly and a handsome son Matthew.

Matthew took his own life at the age of 16 on March 14, 2001. He was on Accutane at the time of his unfortunate death. Needless to say, his death had a profound effect on our family and Matt's friends.

Matt was a good student, who was well liked by his teachers and had many friends. Matt loved to play baseball, basketball. He enjoyed swimming. He also sang in the chorus. He would lift weights in his room, and he loved to play pool. He was a well-adjusted young man.

When Matt was in his early teens, he started to develop pimples. After trying over-the-counter medications, we took him to a dermatologist. Initially Matt tried the usual course of antibiotics and ointments, but he sometimes didn't remember to use them. He was more concerned about the white film on his face left by the ointments than he was about the pimples, and he had no qualms in telling his dermatologist about that.

At one point his dermatologist told him there was a medication that worked very well on acne, but had some side effects like dry skin and chapped lips. The doctor told him to think it over and they would discuss it at his next visit. With youthful impatience, Matt was bugging me to call his dermatologist for an appointment to discuss this new medication. The doctor prescribed Accutane and informed Matt that he needed to be aware of the side effects before beginning treatment. He was told that it would cause very dry skin and chapped lips. He was also told to avoid the sunlight and not to share Accutane with any female friends because it could be potentially dangerous. Matthew and I both listened carefully to the dermatologist, and we decided it would be a good treatment for his mild acne.

That evening, October 5, 2000, Marty and I were watching the last part of an interview on a program that I believe was Dateline NBC about a man and his wife discussing how their son had committed suicide while taking Accutane. At that time we did not realize that it was Congressman Stupak.Marty said, isn't that the medication that Matt just got? So I went to the kitchen to check the package, and sure enough, it was the same medication.

By this time, Matt came out of his bedroom and started to watch the remainder of the interview with us. When it was over, Matt said, I don't want to take anything that is going to make me kill myself. And we were all concerned. Needless to say, while we were all concerned about what the father on T V was saying, we thought to ourselves, there must be something more to this story than just Accutane. There must be something wrong with that family or that child.

Within a day or two, Matthew and I returned to his dermatologist. We went back to the dermatologist to discuss the story of the mother and the father on TV, their sad experience, and our concerns about Accutane. The dermatologist said that there had been a couple of unsubstantiated cases of depression and suicide, but that there was no scientific proof that Accutane could cause it, and Matt didn't fit the profile anyway.

Matt and I left the doctor's office feeling secure about what we had heard. We told my husband that the doctor said we should not be concerned.

Matt started taking Accutane, and sure enough, within several weeks he started developing dry skin and chapped lips. The pimples were improving. And we saw no other side effects.

On March 13, 2001, we had a very nice dinner, talked about the day's events, and joked and laughed about everything. Matt even showed off his dishwashing skills by showing us how quickly he could load the dishwasher with expert speed and skill that he had learned on his job, with a big smile on his face.

The next morning, Matt got up for school as usual and got on the bus. Matt had perfect attendance that year for school. Before leaving, he looked at his father and smiled and said good-bye. He also yelled to me as I was getting ready in my bathroom, good-bye, Mom, I love you, just as he did every morning.

Apparently Matt had a good day at school. He talked to his guidance counselor about a program she had recommended for him for next year. He asked a girl to the upcoming dance, and she said yes, that she agreed to go with him. He had taken a couple of tests that day and did well on them. On the ride home, Matt sat with friends and laughed and fooled around just like any other kid. He got off the school bus at approximately 3 o'clock and stopped by the mailbox, picked up the newspaper and mail for me as he always did. He took off his shoes in the entranceway as he was taught to do, placed the mail and the newspaper on the counter as normal, went into his room, and hung up his coat.

It was at this point that his normal routine changed. Matthew did not turn on the T V or get a snack or check his e-mail as usual. Instead, he went into our master bedroom and unlocked the gun case and shot himself.

His father came home from work and saw Matthew's car in the driveway. He entered the house and, as usual, yelled, hello. But there was no response. There are glass-mirrored closet doors in our bedroom where Marty could see part of Matthew. He thought Matt was playing a practical joke on him. He went down the hall and said, come on, Matt, this isn't funny. But there was no response.

After shaking Matt a little, Marty could feel that his face was cold. He placed his head against Matthew's chest to see if he could hear his heartbeat. He then noticed the gun lock on the floor and ran to the kitchen and called 911 for an ambulance. Martin continued CPR until he heard my car pull into the garage. He ran to the door and said, something bad has happened; it's Matthew, he shot himself.

Martin and I went to the bedroom, and I started screaming. We continued with CPR, hoping that Matthew would be revived. At the hospital they tried to revive Matthew and then pronounced him dead. We went to Matt's side one last time with a priest and prayed and said good-bye to our baby.

While we were answering the sheriff's questions at the hospital after Matt was pronounced dead, one of the questions he asked us is if Matt was taking any medication. I told him, yes, that Matt was taking Accutane for acne. As soon as I made that statement, Martin looked at me and said, "The Accutane. Remember the pro-

gram about the father whose son committed suicide while on Accutane?" It was like a bell went off in my head. We told him what we had seen on T V when Matt first started taking Accutane.

After talking to all of Matt's friends, family, teachers coworkers, we confirmed what we had already known: Matthew was not depressed. His sudden death came as a shock to every person who knew Matt, including us, his parents. Matt's suicide seemed to be spontaneous.

We found out that Accutane is reserved for the most severe cases of nodular cystic acne. Here is a school picture of our son which was taken approximately 2 weeks prior to the start of Accutane. As you can see, Matthew did not have severe cystic acne. There was no depression, there was no warning, there was nothing for us to look for. There was no reason for his death other than Accutane.

Having a dermatologist informed about the signs of depression would not have made a difference to Matthew. Having a dermatologist talk to our son regarding suicide would not have made a difference to Matthew. Having an informed consent form would not have made a difference to our son or our family. The only thing that would have made a difference is if Roche would finally admit to dermatologists that there is a causal relationship between suicide and Accutane, and admit that it can occur without warning. Then parents would have the information and the tools to stop using this drug. Remember, the dermatologist told us exactly what Roche continues to say and what every parent wants to hear: There is no scientific proof; that these are unsubstantiated reports. What they are really saying is, don't worry, there must have been something wrong with those kids, those families, their lives.

Roche must know exactly what parents of a child considering this drug want to hear: It can never and it will never happen to us. But it does.

We strongly request to you, Mr. Chairman and members of the committee, that stronger action be taken to make certain that no other people die from this drug. We believe this drug is dangerous. The dangers and the unpredictable nature of the dangers don't outweigh the need to eliminate pimples, especially when the FDA recognizes that most people are prescribed Accutane for relatively minor acne.

My husband and I wish to thank you for this opportunity to tell Matthew Turney's story.

[The prepared statement of Susan Turney follows:]

PREPARED STATEMENT OF SUSAN TURNEY

Good morning, Chairman Greenwood and the distinguished members of the committee. My name is Susan Turney and next to me is my husband, Martin. We live in Watertown, New York and are the proud parents of a beautiful daughter, Kelly and a handsome son, Matthew. Matthew took his own life at the age of 16 on March 14, 2001. He was on Accutane at the time of his unfortunate death.

Needless to say, his death had a profound effect on our Family and Matt's friends. Matt was a good student who was well liked by his teachers and had many friends. Matt loved to play baseball, basketball and enjoyed swimming. He also sang in the chorus and played the trombone in the junior and senior high school bands. Matt would lift weights in his room and he loved to play pool. He was a well-adjusted young man.

When Matt was in his early teens, he started to develop pimples. After trying over the counter acne medications, we took him to a dermatologist. Initially, Matt tried the usual course of antibiotics and ointments but he sometimes didn't remember to

use them. He was more concerned about the white film on his face left by the ointments, than he was the about the pimples, and he had no qualms in telling his dermatologist about that.

At one point, his dermatologist told him there was a medication that worked very well on acne but had some side effects, like dry skin and chapped lips. The doctor told him to think it over and they would discuss it at his next visit. With youthful impatience, Matt was bugging me to call his dermatologist for an appointment to discuss this new medication. The doctor prescribed Accutane and informed Matt that he needed to be aware of the side effects before beginning treatment. He was told that it would cause very dry skin and chapped lips. He was also told to avoid the sunlight and not to share Accutane with any female friends because it could be potentially dangerous. Matthew and I both listened carefully to the dermatologist and we decided that it would be a good treatment for his mild acne.

That evening, October 5, 2000, Marty and I were watching the last part of an interview on a program that I believe was Dateline NBC about a man and his wife discussing how their son had committed suicide while taking Accutane. At that time, we did not realize that it was Congressman Stupak.

Marty said, "Isn't that the medication that Matt just got?" So I went to the kitchen to check the package and sure enough, it was the same medication. By this time, Matt came out to the livingroom and started to watch the remainder of the interview with us. When it was over, Matt said, "I don't want to take anything that's going to make me kill myself!" Needless to say, while we were all concerned about what the Father on TV was saying, we thought to ourselves there must be something more to this story than just Accutane. There must be something wrong with that family or that child.

Within a day or two Matthew and I returned to his dermatologist. We went back to the Dermatologist to discuss story of the Mother and Father on TV, their sad experience and our concerns about Accutane. The Dermatologist said that there had been a couple of unsubstantiated cases of depression and suicide, but that there was no scientific proof that Accutane could cause it and that Matt "didn't fit the profile anyway." Matt and I left the doctor's office feeling secure about what we had heard. We told my husband that the doctor said that we should not be concerned.

Matt started taking the Accutane and sure enough, within several weeks he started developing dry skin and chapped lips. The pimples were improving and we noticed no other side effects.

On Tuesday, March 13, 2001, we had a very nice dinner, talked about the day's events and joked and laughed about everything. Matt even showed off his dishwashing skills by showing us how to quickly load the dishwasher with expert speed and skill that he learned on his job with a big smile on his face.

The next morning, Matt got up for school as usual and got on the bus. Matt had a perfect attendance at school that year. Before leaving, he looked at his father, smiled and said "Good Bye." He also yelled to me as I was getting ready in my bathroom, and said "Good Bye Mom. I love you" just as he did every morning.

Apparently, Matt had a good day at school; he talked to his guidance counselor about a program she had recommended for him for the next year. He asked a girl to the upcoming dance and she agreed to go with him. He had taken a couple of tests that day and did well on them. On the ride home Matthew sat with friends and laughed and fooled around just like any normal kid. He got off the school bus at approximately 3:00 PM, and stopped at the mailbox, picked up the newspaper and mail for me as he always did. He took off his shoes in the entranceway as he was taught to do, placed the mail and newspaper on the kitchen counter as normal, went into his room and hung up his coat.

It was at this point that his normal routine changed. Matthew did not turn on the TV, or get a snack or check his email as usual. Instead he went into to our master bedroom and unlocked the gun case and shot himself.

His father came home from work and saw Matthew's car in the driveway. He entered the house and as usual yelled "Hello," but there was no response. There are glass mirror closet doors in our bedroom where Marty could see part of Matthew. He thought Matt was playing a practical joke on him. He went down the hall and said "Come on Matt, this is not funny." But there was no response. After shaking Matt a little Marty could feel that his face was cold. He placed his head against Matthew's chest to see if he could hear his heart beat. He then noticed the gunlock on the floor and ran to the kitchen and called 911 for an ambulance. Martin continued CPR until he heard my car pull into the garage. He ran to the door and said, "Something bad has happened, it's Matthew, he shot himself." Martin and I went to the bedroom and I started screaming. We continued with CPR hoping that Matthew be revived. At the hospital they tried to revive Matthew and then pronounced

him dead. We went to Matt's side one last time with the priest and prayed and said good-bye to our baby.

While we were answering the sheriff's questions at the hospital after Matt was pronounced dead, one of the questions he asked us is if Matt was taking any medication. I told him yes, that Matt was taking Accutane for acne. As soon as I made that statement, Martin looked at me and said "The Accutane!! Remember the program we about the Father whose son committed suicide while on Accutane?" It was like a bell went off in my head. We told him about what we had seen on TV when Matt first started taking Accutane.

After talking to all of Matt's friends, family, teachers, and co-workers, we confirmed what we had already known. Matthew was not depressed! His sudden death came as a shock to every person who knew Matt, including us, his parents. Matt's suicide seemed to be spontaneous.

We found out that Accutane is reserved for the most severe cases of nodular, cystic acne. Here is a school picture of our son, which was taken approximately two weeks prior to the start of Accutane. As you can see, Matthew did not have severe cystic Acne.

To the contrary, he went to school that day. He was making plans for the future. Had done well on exams that day. He had made a date with a girl. He had left school joking with his friends.

There was no depression. There was no warning. There was nothing for us to look for. There was no reason for his death, other than Accutane.

Having a dermatologist informed about the signs of depression would not have made a difference to Matthew. Having a dermatologist talk to our son regarding suicide would not have made a difference to Matthew. Having an informed consent form would not have made a difference to our son or our family.

The only thing that would have made a difference is if Roche would finally admit to dermatologists that there is a causal relationship between suicide and Accutane, and admit that it occurs without warning. Then parents would have the information and the tools to stop using this drug. Remember, the dermatologist told us exactly what Roche continues to say and what every parent wants to hear—there is no scientific proof and these are unsubstantiated reports. What they are really saying is, "don't worry, there must have been something wrong with those kids, those families, their lives." Roche must know that is exactly what parents of a child considering this drug want to hear. It can never and will never happen to us. But it does.

We strongly request to you Mr. Chairman and members of the committee that stronger action be taken to make certain that no other people die from this drug. We believe this drug is dangerous. The dangers and the unpredictable nature of the dangers don't outweigh the need to eliminate pimples, especially when the FDA recognizes that most people are prescribed Accutane for relatively minor acne.

My husband and I wish to thank you for this opportunity to hear Matthew Turney's story.

Mr. GREENWOOD. We thank you very much for your bravery this morning.

Mr. And Mrs. Bencz.

TESTIMONY OF MICHAEL AND CAROLINE BENCZ

Mr. BENCZ. Mr. Chairman, respected members of the committee, I'm going to give an abridged version of my speech because you have a copy, for time's sake.

Mr. GREENWOOD. And all of your statements, written statements, will be entered into the record.

Mr. BENCZ. Okay. This is my wife Caroline, and she is going to hold up some pictures of James.

My name is Michael Bencz. I'm the father of James Bencz. This is my wife Caroline. James Bencz is our son.

James was born on August 7, 1971. He was a certified firefighter, a rescue diver, an athlete, a licensed appraiser, a homeowner, and a business owner. He was a magnetic individual. Anybody that met James fell in love with him right away. James was always a leader in everything he did, and most people naturally looked at him that way. He did not believe in giving up or feeling sorry for yourself,

but focused on making it right. He was witty, humorous, talented, and a great sportsman, intelligent, and highly competitive, but most of all, above that, a wonderful human being. He was an avid mountain biker, skier, snowboarder, hiker, and camper. He competed in triathlons, in firemen's Olympics, and he had several awards and medals to show for it.

During his last year of high school and first year of college, he held a job as a lifeguard EMT. I'm sorry. He enjoyed—yeah. She's going to read it.

Ms. BENCZ. James enjoyed being able to help people. James decided when he was 19 that he wanted to be a firefighter, graduated from the academy with honors, and was one of the three to be hired at the Orlando airport. James had been at the fire department for about 10 years before his death. He was a paramedic, an engineer, and was the next one in line for lieutenant. He was also the fitness coordinator for the fire department at the airport.

James was extremely happy with his job at the fire department and was excited about being able to continue his education in the field of saving lives. James was also a scholar, and encouraged all younger people he met to go to school and get a good education. You see, James knew who he was and where he wanted to go in life. He had his future all planned out.

James was a diver. James has taken the love of his diving and weaved a career in business interests. James was a licensed real estate appraiser. He had been working for about a year at that. He was a homeowner. He had a three-bedroom house that was immaculate inside and out.

James also had just bought a new motorcycle which only had a few miles on it, but yet he was practical. His primary car was just a basic stick shift pickup truck, perfect for all his sports and work equipment.

James was not the type of person to just sit around and do nothing. He was always doing something, working, playing golf, basketball, working out, grooming in the yard, or just thinking of what silly joke or prank he could play on us next.

He believed in the importance of quality time, and when holidays and your birthday came along, he made sure that he spent good one-on-one quality time with you to let you know how important you were to him, and that really meant a lot. He always looked out for his sister Kathy. She's married, and she has two children. Our family is a close one, and that has never changed.

James was, is, the son of all sons, and our memories of him make us the luckiest family in the universe because he is a part of us. He touched many lives at work, home, at play, and we thank God for giving us such a wonderful young man to be our son, but we know that God did not take our son away from us. Accutane did. We wish every minute of every day that we had never heard of that drug. It took our son, our life as we know it, and left us with huge craters in our hearts that can never be filled in again.

In late 2001, apparently a doctor prescribed Accutane for James. As you can see, James had never had an acne problem. Apparently the diving suit he wore on dives had irritated his skin on his neck and back. In the days before his death, James apparently was concerned about Accutane. He called the doctor to ask questions. We

have not heard the phone call, but we understand there was a message he left with the doctor that was somewhat upsetting and concerning regarding how he was feeling.

Even if James was calling for help, what would a doctor say that Roche has not told them to say: There is no scientific evidence. It cannot be the drug. It must be you.

On the last day we heard from James, February 23, 2002, he called to say he did not feel well, he had a headache. It was nothing concerning, just that he didn't feel well. His last words to us were, I don't feel too good. I'm going to try to get some sleep.

Over the next few days, we did not hear from James. That was very unusual. It was not like James to disappear for days at a time without anybody knowing where he was. A massive hunt was undertaken. Eventually James was found on March 4, 2002. James was found at the bottom of a lake with a 44-pound barbell weight strapped to him. We know from his suicide note that he had killed himself. The note makes no sense and provides no explanation. He had killed himself in the lake which him and his sister had jogged many times and rode their bikes. He had died under circumstances so bizarre for someone like James, a diver, a firefighter, and an athlete with so much to live for and so many future plans.

There was no warning. There was no warning to look for.James was not the person anyone would expect to commit suicide. He had friends and family. He had financial and personal success. He had plans for the future, both near and long term. The week James died, he was to leave on a skiing trip to Austria with a few of his firefighter buddies. James had plans for his future, and death was not in that plan.

Roche always says when somebody comes forward to say that Accutane caused suicide, that the person who committed suicide was a troubled high school child, or a child in the first year of college, or a person who is experiencing spiraling depression, or an adult with a personal or family history of depression or under any financial or family stress. James does not fit in Roche's explanation for these suicides. Instead, James is why something needs to be done about this drug.

You will never—or you have heard or you will hear from families and people who say this drug saved their complexion and gave them a better outlook on life. James could not have had a better outlook on life. He killed himself without warning. How many more suicides and deaths have to occur before someone says enough is enough?

In the end perhaps James was taken from us so we could sit here with you today to tell you what a perfect young man he was. Believe me, he was the son you would want, he was the neighbor you would want, he was the rescuer you would want. Perhaps in his final act he will still rescue others, but, I'm afraid, not without your help. Thank you.

[The prepared statement of Michael Bencz follows:]

PREPARED STATEMENT OF MICHAEL BENCZ

My name is Michael Bencz. I am the father of James Bencz. This is my wife of 33 years, Caroline. James Bencz is our son.

James was born on August 7, 1971. James was a certified firefighter, a rescue diver, an athlete, a licensed appraiser, a homeowner, and a business owner.

He was a magnetic individual. Anybody that met James fell in love with him right away.

James was always a leader in everything he did, and most people naturally looked at him that way. He did not believe in giving up or feeling sorry for yourself. He was not one to point the blame if things didn't come out right, but focused on making it right.

He was witty, humorous, talented, a great sportsman, intelligent, and highly competitive, but most of all, above all that, a wonderful human being.

James was an avid mountain-biker, skier, snow-boarder, hiker, and camper. James competed in triathelons and the firemen's Olympics and had several awards and medals to show for it.

During his last year of High School and first year of college, he held a job as a life-guard EMT. He enjoyed being able to help people. James decided when he was 19 that he wanted to be a firefighter, graduated from the Academy with honors, and was one of three to be hired at the Orlando Airport.

James had been at the fire department for about 10 years before his death. He was a paramedic, and an engineer, and was the next one in line for Lt. He was also the fitness coordinator for the fire department at the airport. James was extremely happy with his job at the fire department and was excited about being able to continue his education in the field of saving lives.

James was also a scholar, and encouraged all the younger people he met to go to school and get a good education. He was continuously on the honor roll at school. The results of his good study habits showed not only in his grades, but in planning for his future. You see, James knew who he was and where he wanted to go in life, he had his future all planned out!

James was a diver. James had taken his love of diving and weaved a career and business interest. He and another firefighter friend formed a business to repair sonars of the U.S. and British Navy submarines that came in to port. He also had the permits to retrieve dead head logs from the Swaannee River and then turned them in to wood flooring.

James was a licensed real estate appraiser. He had been working for about a year at that. He was interested in getting involved in the real estate market and buying some property in Orlando, maybe living there himself, closer to work.

James was a homeowner. He had a 3 bedroom house that was immaculate, inside and out. He worked on the house and made his own improvements. James had also just bought a new motorcycle, which only had a few miles on it; it was the bike he always wanted and next on his list was a Porsche. Yet, he was not frivolous in his spending. He was practical. His primary car was a basic stick shift pick-up truck—perfect for all his sports and work equipment.

James was not the type of person to just sit around and do nothing, he was always doing something, working, playing golf, basketball, working out, grooming his yard, or thinking of what silly joke or prank he could play on you next. He believed in the importance of quality time and when holidays or your Birthday came along, he made sure that he spent some good one on one quality time with you to let you know how important you were to him, and that meant a lot!

He always looked out for his sister Kathy. She is married and has two children. James was always involved in her life, concerned about her well-being and her future and wanted to do as much as he could for her. Our family is a close one and that has never changed.

James was a wonderful Uncle to his nephew, Brandon, who is now eleven years old. James always encouraged Brandon to do good in school and let him know that he could do and accomplish anything by just studying and applying himself.

James was, is, the son of all sons, and our memories of him make us the luckiest family in the universe because he is part of us. He touched many lives, at work, home, or at play and we thank God for giving us such a wonderful young man to be our son.

But we know that God did not take our son away from us, Accutane did. We wish every minute of every day that we had never heard of that drug. It took our son, our life as we know it, and left us with huge craters in our hearts that can never be filled in again.

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In the days before his death, James apparently was concerned about Accutane. He called the doctor to ask questions. We have not heard the phone call but understand there was a message he left with the doctor that was somewhat upsetting and concerning, regarding how he was feeling. Even if James was calling for help, what

would a doctor say that Roche has not told them to say—there is no scientific evidence. It can not be the drug, it must be you.

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Eventually, James was found on March 4, 2002. James was found at the bottom of a lake, with a 44 lb barbell weight strapped to him. We know from his suicide note that he had killed himself. The note makes no sense and provides no explanation. He had killed himself in the lake which his little sister and he had sat at as children and skipped rocks. He had died under circumstances so bizarre for someone like James—a diver, a firefighter, and an athlete—with so much to live for, and so many future plans. There was no warning. There was nothing to look for to warn us.

James was not the person anyone would expect to commit suicide. He had friends and family. He had financial and personal success. He had plans for the future—both near and long term. The week James died, he was to leave on a skiing trip to Austria with a few of his firefighter buddies. James had plans for his future, and death was not in that plan.

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In the end, perhaps James was taken from us so we could sit here with you today. To tell you what a perfect young man he was. Believe me, he was the son you would want. He was the neighbor you would want. He was the rescuer you would want. Perhaps, in his final act, he will rescue others. But, I am afraid, not without your help.

Mr. GREENWOOD. We thank both of you, and we know how terribly difficult this is for you, and we appreciate your courage as well.

Ms. Wallace.

TESTIMONY OF DEBRA WALLACE

Ms. WALLACE. Yes. First I would like to say to Congressman Stupak, his wife, and the families here how deeply sorry I am for their loss. Our story is very, very different.

My son started off with getting breakouts in the eighth grade, which was pretty early than his other classmates had this problem. So my son clearly stood out. We went to the drug store and we tried all the over-the-counter treatments, the creams, the cleansers, and clearly that did not work. We then approached our family physician who prescribed Minocin and Retin-A, and we kept Alex on that for quite a few months, probably longer than we should have, because we really just kept hoping this would work, and it did not.

By this time, my son's skin was really bad. It was very inflamed, and my son was having a very, very difficult time. We knew that we needed to see a dermatologist.

I would like to tell you how my son felt during that time. My son was a happy boy, and undergoing this acne, he became very quiet, withdrawn. He didn't laugh very much, and basically he almost tried to make himself invisible. And this was a time in eighth

grade, just going to high school, his body was changing, his hormones were kicking in. He was trying to fit in with his peers, find his place, and instead he had to put his life on hold. And for me, as his mother, it was hard for me to put him on the bus every day to send him to school because he did suffer the remarks, the cruelty, insensitivity that children do have.

We then went to our dermatologist, Dr. Sassmannshausen, and we were very much at ease with him, and he made a statement I will never forget. He said: I can clear your son's skin up. And I thought that was so incredibly bold. And he followed that statement up by giving us a time line. So he clearly had our attention. He also told us that there were dermatologists in our community who would not prescribe this medication because it was very controversial, and he then went on to outline the course of treatment, which would include a monthly follow-up where he would chart Alex's progress. And also, this was a time when he would get his prescription. We never got more than one prescription at any one given time. And also, he had to have periodic blood tests, and I think he ended up with about three or four of those.

We talked about it. We sat there in his office, and our family decided to go with the treatment of the Accutane. And we were very hopeful, but at the same time we were really cautious about the medication. We felt it was a very powerful drug and we were going to treat it with the utmost respect. So, the way our family works is we took a team player approach. We had our dermatologist leading us. He was there to give us his expertise, monitor Alex's progress, tell us where we needed to be. Our pharmacy was very helpful. They were also involved with us. Every time we filled our prescription, they were there to ask us questions and make sure everything was going fine. My son Alex, his job was to follow directions and to take the medication. And for my husband and I, we were to support Alex, encourage him, be there for him. And I also dispensed his medication daily.

And I remember not wanting to just ask my son, how was your day, honey, and get the typical teen response, which is usually, fine. I wanted more information. I sat down with him every day and I asked him how was he feeling, did he have a good day, did he feel sad, angry, did he feel weird, anything like that. And that's how we progressed through our treatment.

The conclusion is my son ended up on two courses of Accutane. That is how resistant his skin was. And, as promised, my son's face was completely clear. It changed my son's life, and our overall experience was flawless. It was successful. And we no longer called Accutane by its name, we refer to it as the miracle drug.

Our family is grateful for the availability of this medication. I would do it again. I would recommend it. It changed my son's life. And our family hopes that other families will have the choice. We feel it's important for families to have the information and make the choice that they know is best for them, and weigh the pros and cons of everything. I feel that every medication, including over-the-counter medications, they all come with risks and side effects, and everybody has to really weigh them very carefully.

As I said, we chose Accutane. Our son is now a junior in high school. We have put this so far behind us, and my son has his

smile back. His biggest complaint these days is if he gets a pimple, and for our family, we couldn't be happier.

[The prepared statement of Debra Wallace follows:]

PREPARED STATEMENT OF JEFFREY WALLACE AND DEBRA WALLACE

My son, Alex Wallace, began with his skin breaking out during eighth grade. We treated it the usual way with over-the-counter cleansers and creams. His skin continued to worsen to the point where we needed to schedule an appointment with out family physician to see what we could do about it. Our physician, Dr. Cabe, prescribed Minocin 100 mg twice daily along with Retin-A treatment that proved to be completely ineffective. His skin, in fact, was getting progressively worse and we certainly gave it sufficient time to work. Alex was very distraught about the state of his skin, especially since he said he was the one going through this and that none of his classmates were experiencing any breakouts of their skin at this point in time. We knew we needed to see a dermatologist as soon as possible. Dr. Cabe's nurse recommended we see Dr. Sassmannshausen as her daughter had gone to school with him and she was extremely impressed by him.

On 2/29/00 we got the referral to see Dr. Sassmannshausen. Upon meeting him, we were very comfortable with him. He was professional, kind and compaasionate. He told us that not only could he clear up the acne for good, but also he actually gave us a timeline. This immediately got our attention, as we could not believe that anything would truly get rid of it and that our son would at best end up with scarring. Dr. Sassmannshausen was very enthusiastic about a drug called Accutane based on his experience and told us about it. He indicated that not a lot of dermatologists in our community would prescribe this drug because it was felt to be controversial, but his experience with it was very successful and that he could help our son. This really got our attention. We actually had some hope for our son.

Although I have tried, I cannot remember specifically all that we talked about during our initial visit, but I do know that it was very clear to me for a number of reasons that this was very powerful drug and not to be taken lightly. Dr. Sassmannshausen informed us that the course of treatment would include monthly checkups at which time we would be given the scrip for the following month's dosage. He never gave us more than a 30-day scrip at a time. He also stated that Alex would need to have periodic blood tests. Last but not least, Alex would need to regularly take the medication and use recommended moisturizers, as this drug seemed to dry the patient from the inside out.

Our family agreed to treatment. We felt confident in Dr. Sassmannshausen's ability and experience to treat Alex and again we were given hope. We proceeded with the treatment using a team approach. We had Dr. Sassmannshausen as the lead, answering our questions and monitoring the treatment. Alex had to do his part, which included following directions and informing us of how he felt and what changes he experience. Our job as his parents was to dispense his medication as well as support and encourage him during this really difficult time for him. I clearly remember being very aware that Accutane was a powerful drug and not to be taken lightly. The fact that it could completely clear up severe cases of acne when antibiotics were ineffective, the fact that there was and actual time frame for it to work, the fact that there were other dermatologists who were "uncomfortable" prescribing the drug, the fact that it clearly stated on the packaging that if pregnancy occurred there would be birth defects, the fact that our pharmacist made a point of consulting with us each time we filled the prescriptio—all of these things made it abundantly clear that we needed to b extremely cautious and acutely aware of what was going on with our son.

Mindful of the above, we were excited and hopeful that Accutane was really going to work for Alex. His life was literally on hold during the time he had acne. It took a lot of courage for him to go to school. This was time when his body was changing, he was trying to find his place among his peers, his hormones were at full speed ahead and all he could see was his face. It was as if that was all he was—a face, and it was a face he didn't like and it caused him a great deal of pain. He was clearly a different person. He didn't smile or laugh very often; he became very reserved as if trying to be invisible. Of course, there were kids who made fun of him starting each morning on the bus. Every single day, I had heart-to-heart talks with him. We talked about what he had experienced each day. I was not satisfied to just ask him how his day went. I wanted to know if he felt angry, depressed, neutral, etc. He knew his home was his safe haven from the cares of the day and he was always happy to get home to his space.

In the end, Alex ended up going through two rounds of the Accutane and just as Dr. Sassmannshausen promised, Alex's face was clear of the acne and he no scarring to speak of. Life began again for Alex and for me. We refer to Accutane as nothing short of a miracle drug and I would not hesitate to recommend it to anyone facing this problem and would do it all over again. Our team effort worked flawlessly. As with any medication, including over he counter drugs, there are always side effects and risks. It is clearly up to the patient and his family and doctor to proceed with care and eyes wide open. I would be disheartened if this drug were removed from the market. I can't even imagine what my son's life would be like if we did not have the choice of taking this medication. Now when we see a young person with severe acne, we want to tell them that they don't have to go through this because there is a medication that clears it up. As for my family, we are extremely grateful that Accutane was available for us and we have never looked back. Alex is now a junior in high school and he is happy, healthy and he is just a regular kid who complains loudly when he gets a pimple. We couldn't be happier.

Mr. GREENWOOD. Thank you, Ms. Wallace.

Dr. Green.

TESTIMONY OF NANCY S. GREEN

Ms. GREEN. Good afternoon, Mr. Chairman and committee members. I am Dr. Nancy Green, medical director of the March of Dimes Birth Defect Foundation. I am pleased to have the opportunity to testify today on behalf of the 1,500 staff members of the March of Dimes and the over 3 million volunteers nationwide.

As you may know, the March of Dimes works to improve the health of mothers, infants, and children by preventing birth defects and infant mortality. The foundation is a unique partnership of scientists, clinicians, parents, members of the business community, and other volunteers in every State, the District of Columbia, and Puerto Rico. I am pleased to share with you the foundation's views on issues related to the safety of Accutane and generic forms of isotretinoin. Specifically, I will provide recommendations intended to minimize the risk for causing serious birth defects or fetal death by exposure to developing fetuses.

In brief, and as you have heard already today, oral isotretinoin is widely used in women of reproductive age and is a well-known potent teratogen, an agent that has a high risk of causing birth defects, very much on the same scale as thalidomide. Data published by FDA indicate that the number of prescriptions for Accutane has increased dramatically and has been even accelerating over the last 5 to 6 years.

In 2000, nearly 2 million—2 million—prescriptions for Accutane were filled in the U.S. Increasing numbers of prescriptions pose a risk to a greater number of women who have the potential for inadvertent fetal exposure. The experts agree on this: No pregnant woman should take isotretinoin, and no woman taking isotretinoin should get pregnant.

Despite current voluntary safety measures taken by the manufacturer, many pregnant women and their developing fetuses are continuing to be unnecessarily exposed to this drug, and major birth defects, as you have heard, have happened in their babies.

According to a January 2000 Morbidity and Mortality Weekly Report that's put out by the Centers for Disease Control, the 1999 Boston University Accutane survey found that despite warning labels and the availability of consumer-based educational information, 900 women became pregnant between 1989 and 1999, a rate of 3 women becoming pregnant for each 1,000 treatments of

Accutane. Now, CDC has published last year that that's likely to be an underestimate of pregnancy exposures to Accutane.

In 1999, both the Boston University survey and the California Teratogen Information Service reported the birth of infants who were affected by fetal exposure to isotretinoin. Roche reported to FDA—you heard this earlier today—that from 1982 to 2000, there were documented nearly 2,000 pregnancy exposures, 1,995 pregnancy exposures, and 383 live births, of which 162 of those live births had congenital anomalies, about 40 percent of those babies. That's through 2000. And you have heard from FDA earlier today that that number continues to increase since that time.

Past studies have shown that 25 to 30 percent of babies born to exposed mothers develop birth defects. These major defects include a syndrome of mental retardation, hydrocephalus, microcephaly, cleft lip and palate, cardiovascular anomalies, and ear and limb abnormalities.

Physically it primarily affects the development of the head and neck, including the brain and the heart. The March of Dimes believes that Accutane and generic isotretinoin must be regulated by a rigorous system such as currently used for thalidomide and these measures, including a mandatory doctor registration and certification for those who dispense the drug, a mandatory patient registration for those who take the drug, a mandatory pharmacist registration and certification to verify women using the drug, meet specific criteria. Women undergoing repeated pregnancy—ought to undergo repeated pregnancy tests both before and during treatment and only 1 month of the drug is dispensed at a time. There needs to be mandatory pregnancy exposure reporting. Currently that's not the case and in fact the reports that you've heard about are not mandated. They're voluntary. And in addition, FDA should reevaluate if any pregnancy exposure occurs during that program.

Now, I'm just going to read something from the FDA Web site about thalidomide since you've heard much about the analogy between thalidomide and Accutane and the fact that there is a type program in place for thalidomide. This is the FDA Web site I'm quoting—under frequently asked questions—concerning thalidomide. The question, what is the FDA going to do if there's a fetal exposure to thalidomide? And the answer that FDA gives, and I quote, is, "If there is even one fetal exposure to thalidomide the agency will reevaluate the entire distribution system and take the necessary steps to ensure that all deficiencies are corrected."

Again, that's for thalidomide. No such statement occurs for Accutane. The FDA's program to review in utero exposure to thalidomide is a more carefully monitored approach than the so-called SMART system currently used to monitor dispensing of isotretinoin. Though based on small numbers of women, the thalidomide system appears to be highly effective. The SMART program for Accutane introduced earlier this year was designed to improve the risk management program for Accutane but still depends upon voluntary participation, making the monitoring system even more difficult. And something that we've not heard about earlier today is the imminent release of at least one generic form of Accutane, isotretinoin. Roche is no longer going to be using the Boston University survey, again a voluntary survey, though the ge-

neric manufacturers will be and I've spoken to the head of survey at Boston University to verify this. Thus, there will be two separate isotretinoin surveys, one for the Roche formulation for the generics, another for the—I'm sorry—one for the Roche formulation of Accutane and another for the generic products. The March of Dimes firmly believes that this system is inadequate to ensure 100 percent participation. Furthermore, we are concerned that the complexity of the SMART program's expansion will further erode already suboptimal participation.

Half of the pregnancies in the U.S. are unintended and even amongst women who are college educated in their 30's, only about a third of pregnancies are planned, so exposures to isotretinoin can occur before a woman even knows that she is pregnant. We believe that the current system is inadequate to prevent pregnancy exposures and the serious consequences of both fetal death and serious birth defects. We strongly recommend FDA-mandated implementation of a single program designed to put in place a more stringent system that would reduce exposure to developing fetuses from Accutane or isotretinoin. We further recommend using as a model the highly effective program that is already in place for thalidomide.

In conclusion, on behalf of the March of Dimes I want to thank you, Mr. Chairman, for holding this hearing today. March of Dimes volunteers and staff around the country stand ready to work with you and other members of this committee to support public policies to prevent birth defects.

Thank you.

[The prepared statement of Nancy S. Green follows:]

PREPARED STATEMENT OF NANCY GREEN, MEDICAL DIRECTOR, MARCH OF DIMES BIRTH DEFECTS FOUNDATION

Good morning, Mr. Chairman and Members of the Subcommittee. I am Dr. Nancy Green, medical director of the March of Dimes Birth Defects Foundation. I am also Associate Professor of Pediatrics and Cell Biology at the Albert Einstein College of Medicine. As you know, the March of Dimes is a national voluntary health agency founded in 1938 by President Franklin D. Roosevelt to find a scientific prevention of the threat of polio to the public. Today, the Foundation works to improve the health of mothers, infants and children by preventing birth defects and infant mortality through research, community services, education and advocacy. The March of Dimes is a unique partnership of scientists, clinicians, parents, members of the business community, and other volunteers in every state, the District of Columbia and Puerto Rico.

I am pleased to have the opportunity to testify this morning on behalf of the over 3 million volunteers and 1500 staff of the March of Dimes, and to share with you the Foundation's views on issues relating to the safety of Accutane and generic forms of isotretinoin. Specifically, I will provide recommendations intended to minimize the risk for causing serious birth defects or fetal death via exposure to developing fetuses. As you know, one of the major difficulties with preventing fetal exposure to isotretinoin is that the target clients of this drug are people with acne, a sometimes serious but certainly not life-threatening condition, occurring primarily in young adults—of whom half are women of reproductive age.

The March of Dimes has reviewed the current medical literature on the pregnancy-related risks of oral isotretinoin and would like to make several points and recommendations for consideration by this committee.

In brief, oral isotretinoin is widely used in women of reproductive age and is a known potent teratogen (an agent with a high risk of causing birth defects), on the same scale as thalidomide. No pregnant women should take isotretinoin, and no women taking isotretinoin should get pregnant. Despite current voluntary safety measures taken by the manufacturer, many pregnant women and their developing fetuses are continuing to be unnecessarily exposed to this drug and major birth de-

fects have developed in their babies. We recommend a single, stringently monitored and restricted system for clinical use of Accutane, such as the system currently in place for thalidomide.

Accutane (isotretinoin) is an oral medication approved by the Food and Drug Administration (FDA) for treatment of recalcitrant nodular acne, an important but not a life-threatening disorder. FDA reports that retail pharmacies dispensed 19.8 million outpatient prescriptions for isotretinoin from 1982 through 2000. The Centers for Disease Control and Prevention (CDC) reports that Roche Laboratories began direct-to-consumer print advertisements in 1996, and added television and radio advertisements in 1997. Data published by FDA indicate that the number of prescriptions for Accutane has increased dramatically and has been accelerating over the past 5-6 years. In 2000, nearly 2 million prescriptions for Accutane were filled.

There are well-documented data pertaining to prescribed use of Accutane for less severe acne. In 2000, an FDA survey found that the proportion of treatment for mild and moderate acne was half of all treated cases. Half of these patients were female, and half of these female patients were 15 to 24 years old. Increasing numbers of prescriptions pose a risk to a greater number of women who have the potential for inadvertent fetal exposure.

The CDC and others have collected an overwhelming amount of data demonstrating that oral use of isotretinoin during pregnancy causes major birth defects and miscarriage. These data include a number of studies revealing that oral use of isotretinoin, especially early in pregnancy, poses a significant risk of multiple major birth defects in the exposed fetuses as well as a very large risk for spontaneous miscarriage. Early exposure may even occur prior to a woman's knowledge of her pregnancy. These major defects include a syndrome that includes mental retardation, hydrocephalus, microcephaly, cleft lip and palate, cardiovascular anomalies, and ear and limb abnormalities. The data supporting isotretinoin as causing birth defects are strengthened by findings of similar birth defects in multiple species of experimental laboratory animals exposed to isotretinoin *in utero.*

Many fetuses are at risk of exposure to isotretinoin and its effects. According to a January 2000 Morbidity and Mortality Weekly Report, the 1999 Boston University Accutane Survey (BUAS) enrolled over 450,000 women between 1989 and 1999; this number translates to about one million women exposed to the drug during this period. Despite warning labels and the availability of consumer based educational information, the BUAS identified 900 women who became pregnant during this period of time, a rate of 3 women becoming pregnant for each 1000 treatments of Accutane. CDC and others have documented continued occurrences of isotretinoin-exposed pregnancies, indicating that more needs to done to eliminate this known risk. 'Major birth defects have been reported in many babies exposed to isotretinoin *in utero.* In 1999, both the BUAS and the California Teratogen Information Service reported the birth of infants who had had fetal exposure to isotretinoin. Roche reported to FDA that, from 1982 to 2000, there were 1,995 pregnancy exposures and 383 live births of which 162 had congenital anomalies.

The prescription, dispensing and consumption of another known potent teratogen, thalidomide is currently carefully monitored. Due to the FDA's diligence 40 years ago, thalidomide was not licensed for use in the U.S. Nonetheless, 10,000 babies were affected worldwide. For thalidomide, a single registration program currently exists: only physicians registered with the program may prescribe the drug and only pharmacists registered with the program may dispense it. Patients must comply with mandatory education, contraception and monitoring measures. Pregnancy testing must be performed both before and during treatment, and only one month's supply of the drug is dispensed at a time to limit its availability. Though based on small numbers of women this system appears to be highly effective. The program to reduce in utero exposure to thalidomide is a more carefully monitored approach than the System to Manage Accutane Related Teratogenicity (SMART) program currently used to monitor dispensing of isotretinoin.

Half of all pregnancies in the U.S. are unintended. Even amongst college educated women in their 30's, one third of pregnancies are unplanned. These statistics, and their implications for the significant risk of exposure to a potent teratogen that is widely prescribed for use in women of child-bearing age, are a reality that should be recognized.

The voluntary registration and survey program (SMART), introduced earlier in this year, was designed to improve the system by applying pressure to join on providers and women consumers of Accutane. Making the monitoring system even more difficult is the release of generic forms of isotretinoin. Roche is no longer using the BUAS, though the generic manufacturers are; thus there will be two separate isotretinoin surveys: one for the Roche formulation and another for the generic products. The March of Dimes firmly believes this system is inadequate to ensure 100%

participation. Furthermore, we are concerned that the complexity of the SMART program's expansion will further erode participation. We strongly recommend FDA-mandated implementation of a single program that is designed to put in place a more stringent system that would reduce exposure to developing fetuses from Accutane/isotretinoin. We further recommend using as a model the highly effective program that is already in place for thalidomide.

In conclusion, on behalf of the March of Dimes, I want to thank you, Mr. Chairman, for holding this hearing today. March of Dimes volunteers and staff around the country stand ready to work with you and the other Members of this committee to support public policies to prevent birth defects.

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Mr. GREENWOOD. We thank you, Dr. Green.

Ms. Martinez.

TESTIMONY OF LYNN MARTINEZ

Ms. MARTINEZ. Thank you. I'm pleased to be here today. I'm representing the Organization of Teratology Information Services. That is a network of 36 reproductive hazard education and research centers in the United States and four in Canada. We have been in operation variably since the middle 1980's. The service that I work with in Utah has been around since 1984.

I have been at this for 18 years and have seen the Accutane exposed pregnancy rates go up, go down for a time during the 1980's, and then climb back up again. As we looked from the mid-90's to the present moment, we've seen cases of Accutane exposed pregnancies increase. And by the end of the 1990's, we had enough concern among the group, the Organization of Teratology Information Services—the acronym for that is OTIS—the OTIS group came together in 1999 at one of our annual meetings and we all started talking about the fact that we were getting Accutane calls again, that we were getting people who were pregnant, who were using the drug, not just folks calling with questions because they took Accutane last year and were wondering if there was a problem this year if they became pregnant but women who were actually pregnant who were taking the drug. Those calls had increased and so we went back through our various data bases that we each have and looked at the numbers of calls and, sure enough, they had increased significantly from 1996 through 1999. And we're happy that the FDA convened an advisory committee meeting in 2000 and invited us to talk with them at that time.

The recommendations we had at that time are the recommendations that we have today. And those recommendations are for a mandatory system, very similar to, if not exactly the same as the STEPS program that was instituted by Celgene, the manufacturer of thalidomide. As Dr. Green said, that includes mandatory registration of all prescribers, be they physicians, be they physicians' assistants, nurse midwives, nurse practitioners; whoever is pre-

scribing needs to be registered. The pharmacies need to be registered before dispensing and all patients that are given the drug need to be mandatorily a part of that system. Otherwise, we don't know how many people are pregnant. We don't know how many contraceptive failures there are. We don't know if people have the little yellow sticker on their prescription that they're supposed to have unless we have a mandatory system in place.

So that recommendation made at that time stands today. We still want to see the same system that's in place for thalidomide. We know that pregnancies—over half the pregnancies are unintended. We know from our experience of talking to women who've become pregnant on Accutane that they are variably informed of the birth defect risk, that they are also variably enrolled in whatever pregnancy prevention or SMART program is available, that there's a lot of slippage in the system.

I wanted to also give you a little more graphic understanding of the birth defects related to Accutane because we all think about thalidomide and those of us with gray enough hair are old enough to remember that thalidomide was a word that raised serious concerns. It was kind of the bogeyman of our generation. We don't see that about Accutane. So I wanted to give you a little graphic understanding of the birth defects associated with Accutane. We lump them in areas of central nervous system, cardiovascular, ear problems. But let me describe those for you because I think it's important that you hear this. They include complete absence of the thymus. They include complete absence of the—total absence of the inner ear and the outer ear. They include very serious birth defects of the heart. They're known as conotruncal defects. They require often serial surgeries and they are often lethal, which is one of the reasons the risk for miscarriage is so high and the reason that neonatal death is so high in this population.

So these are very serious heart defects, as well as hydrocephalus, fluid on the brain, which can lead to death and often does. Again it's a lethal disorder in a lot of these kids. But also, it's interesting to note that of the children who have none of those physical birth defects, up to half of the surviving children have moderate to severe mental retardation. That's based on the studies that have been done by Jane Adams, who's doing the follow-up of the kids that have been reported to Roche and to the FDA.

So I think it's important to understand the individual birth defects to see the significant impact that the birth defect condition has on individuals' lives, and I think that that's something I wanted to leave you with today as well as the understanding that we are still getting calls, that most of our calls this year have occurred after the SMART program went into effect. So we do have concerns that this is not a mandatory program, that there does need to be something beyond the voluntary system that's in place.

Thank you very much.

[The pepared statement of Lynn Martinez follows:]

December 5, 2002

Honorable JAMES C. GREENWOOD
Chairman, The Subcommittee on Oversight and Investigations
The Committee on Energy & Commerce
United States House of Representatives
2436 Rayburn House Office Bldg.
Washington, D.C. 20515

Honorable PETER DEUTSCH
Ranking Member, The Subcommittee on Oversight and Investigations
The Committee on Energy & Commerce
United States House of Representatives
2436 Rayburn House Office Bldg.
Washington, D.C. 20515

DEAR SIRS: OTIS (Organization of Teratology Information Services) is a non-profit, North American network of 22 state or regional Teratology Information Services (TIS), 14 individual members and four services in Canada. Each TIS is staffed with a minimum of a Medical Director and TIS specialist. TIS' are telephone consultation services that provide health care professionals and their patients with up-to-date, authoritative information regarding the effects of drugs and chemicals on the human embryo and fetus. As a constellation of services, OTIS receives approximately 56,000 calls per year. Half of these calls are initiated by patients or the general public while the remainder come from health care professionals. OTIS is organized exclusively to stimulate and encourage research, education, and the dissemination of knowledge in the field of teratology, and to improve the abilities of TIS' to provide accurate and timely information about prenatal exposures, with the overall objective of preventing birth defects and improving the public health.

At its 14th Annual Meeting in 2000, members of OTIS discussed the disturbing trend of continued occurrence of isotretinoin-exposed pregnancies. Data compiled from 16 of our TIS' for the period of 1995-1999 indicated that there was an increase in the numbers of women who called our services because they had become pregnant while undergoing treatment with isotretinoin (see Appendix A). Many of our members reported receiving calls from pregnant women who were being treated with isotretinoin, but had not been appropriately counseled by their health care professional regarding effective contraception. These reports were consistent with data subsequently published by the Centers for Disease Control and Prevention.[1] These continued pregnancy exposures to isotretinoin despite implementation of the Pregnancy Prevention Program (PPP™), and more recently the S.M.A.R.T. program, by the manufacturers are a great concern given the high teratogenicity of isotretinoin. Women who conceive during treatment with isotretinoin have a high risk for pregnancy loss or for having babies with severe birth defects. Anomalies of the brain, face, ears, heart, and thymus are present in about one-third of children whose mothers were exposed to isotretinoin during the first trimester of pregnancy. In some cases, the mothers had been treated with isotretinoin for less than a week. Subnormal intelligence with or without structural defects has also been observed in children prenatally exposed to isotretinoin.

Background

As you know, to prevent fetal exposure to Accutane® (isotretinoin), Roche instituted the PPP™ in 1989 with aggressive marketing to heath care providers and pharmacists. The PPP™ instructed prescribing physicians that women of childbearing potential should:

- Have two negative pregnancy tests
- Use two forms of birth control simultaneously, starting one month before the prescription. The drug should be started only after the second or third day of the next cycle.
- Be capable of carrying out the instructions herein
- Receive both verbal and written warnings of the risks of exposing the fetus to the drug.

However, the use of the PPP™ by physicians was voluntary. To assess the effectiveness of the PPP™, Roche commissioned a Survey of Accutane® Use in Women by the Slone Epidemiology Unit in 1989. Women treated with Accutane® were encouraged to enroll in the survey through their physician, by filling out a form in the medication package, or by calling a toll-free telephone number. They were ran-

[1] Honein MA, Paulozii LJ, Erickson JD: Continued occurrence of Accutane-exposed pregnancies. Teratology 64:142-147, 2001.

domly assigned to be followed by telephone or by mail.[2] Women who were followed by telephone were interviewed at the beginning of Accutane® therapy, in the middle, and six months following cessation of treatment. Those who were followed by mail were sent questionnaires six months after treatment ended. As of August 2000, the survey reported results on 494,915 women.[3] The pregnancy rate among these women was 2.8 per 1000 140-courses of isotretinoin. Among 28,016 women evaluated between 1995 and 2000, 195 identified themselves as being sexually active and not practicing contraception. Nearly all women in the Survey were advised to avoid pregnancy while taking Accutane® and 75% of the sexually-active women had signed a consent form. Nevertheless, only 67% of these women postponed starting treatment until the results of a pregnancy test were known and only 57% of the women surveyed postponed treatment until their next menstrual period as instructed by the PPP™. These results clearly illustrate that compliance to the PPM™ was poor.

Between the entire period of 1982-2000, Roche received reports of 1,995 Accutane®-exposed pregnancies 1. Roche reported that between 1982-1989, 71 infants were born with congenital malformations following prenatal exposure to Accutane®.[4] In addition, since the PPP™ went into effect in 1989 through 2000, the FDA's Adverse Events Reporting System database has reported 20 cases of congenital anomalies and 89 abortions (both induced and spontaneous) per year on average following prenatal exposure to Accutane®.[5]

The Slone Epidemiology Unit has also evaluated the effectiveness of the S.T.E.P.S. Program, a pregnancy prevention program initiated in 1998 for another highly teratogenic medication, thalidomide. This program differs from PPP™ in that it requires mandatory registration of prescribing physicians, patients, and dispensing pharmacies, and mandatory compliance with the program. So far, no pregnancies among 360 sexually-active women who are of reproductive age and currently taking thalidomide have been reported.[3]

FDA Meeting on Accutane®—2000

Because the number of Accutane® prescriptions to women of child-bearing age had tripled from 70,000/year in 1989 to estimates of almost 210,000 in 1999, there was concern that an increasing number of pregnant women were being exposed to Accutane®.[6] The FDA held a meeting of its Dermatologic and Ophthalmic Drugs Advisory Committee in September, 2000 to discuss what additional measures might help prevent further fetal exposures to Accutane®. OTIS was also invited to participate in this meeting. At that time, OTIS made the following recommendations to FDA:

1. Increased regulatory safeguards concerning the use of Accutane® in reproductive age women using the thalidomide S.T.E.P.S. program as a template to include:
   A. Mandatory enrollment of physicians, pharmacists and patients by the manufacturer.
   B. An improved monitoring system for reporting a greater proportion of Accutane® exposed pregnancies, including a substantial increase in the use of the patient survey
   C. Increased patient accessibility to the use of two reliable forms of contraception.
   D. Continued educational activities provided for physicians, pharmacists and patients concerning the teratogenic potential of Accutane®.
2. Incorporate OTIS toll-free number and web site information in all Accutane® packaging so that direct access to risk assessment and counseling concerning the use of Accutane® prior to and during pregnancy is available to the consumer.
3. Amend marketing strategies to include pregnancy warnings in all direct to consumer advertising.
4. Continued evaluation of the effectiveness of this program and modification if necessary.

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[6] Jones KL, Adams J, Chambers CD, Erickson JD, Lammer E, Polifka J: Isotretinoin and pregnancy [letter]. JAMA 285(16):2079-2080, 2001.

Introduction of the S.M.A.R.T. Program

In accordance with the recommendations made by the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee, Roche developed the S.M.A.R.T. program in April 2002 to further enhance the safe use of Accutane® in women of reproductive age. In addition to the requirements of the PPP™, the S.M.A.R.T. program also requires that women receive a pregnancy test each month before refilling their prescription. Physicians must register with Roche and agree to follow the new guidelines for prescribing Accutane®. They are also expected to provide patient counseling or referrals about effective contraception and write prescriptions for no more than a one-month supply. A bright yellow qualification sticker supplied by Roche must be applied to each prescription form for Accutane®, signifying that the patient has had negative pregnancy tests, education about risks associated with the use of Accutane®, and counseling regarding effective contraception. Pharmacists are expected to fill only those prescriptions for Accutane® that bear the yellow sticker, dispense a one-month supply at a time, and refuse to fill prescriptions that are more than seven days old. Furthermore, unlike the PPP™, the S.M.A.R.T. program prohibits call-in prescriptions (http://www.fda.gov/cder/drug/infopage/accutane/smart.pdf).

Limitations of the S.M.A.R.T. Program

Patient/Physician Compliance to the Program

The S.M.A.R.T. program is to be commended for its stricter control over the prescribing and dispensing of Accutane®; however, there is still concern that the regulations do not go far enough to prevent unintended pregnancies. For example, although physicians are required to register 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. For these reasons, it is likely that compliance to Roche's pregnancy prevention program for Accutane® will continue to be less than optimal. Indeed, pregnancies still continue to occur even under the tighter restrictions. Since April 2002, 17 cases of pregnancy exposure to Accutane® have been reported to 13 North American TIS'. Also, several of the women who called their local TIS reported that no yellow sticker appeared on the prescription form when they got their prescription filled. Although these reports are anecdotal and the S.M.A.R.T. program has not been in effect for very long, they nevertheless suggest that compliance to the requirements specified in the S.M.A.R.T. program continues to be a problem. The Pregnancy Riskline, a TIS in Salt Lake City, Utah, has recently received funding from a Cooperative Agreement between Association of American Medical Colleges and the Centers for Disease Control and Prevention to systematically study the reasons why Accutane®-exposed pregnancies continue to occur, despite the implementation of pregnancy prevention programs by Roche and the FDA.

The Danger of Overprescribing of Isotretinoin

There is evidence that isotretinoin is being used to treat conditions other than severe, disfiguring nodular acne. A survey of 670 dermatologists in the United States in 1992 found that dermatologists were prescribing isotretinoin for indications other than those contained in the official labeling.[7] More recently, a study published by Wysowski et al. evaluated prescription data from two pharmaceutical marketing research databases and two health plan networks. The authors reported that between 1993 and 2000, the proportion of prescriptions for isotretinoin for severe acne declined from 60% to 46%, whereas the proportion of prescriptions for isotretinoin for mild and moderate acne increased from 31% to 49%.[8] Since the proportion of prescriptions was evenly distributed between males and females, it is not likely that the increase in the proportion of prescriptions for isotretinoin for mild and moderate acne was due to more males receiving the prescriptions. Unfortunately, it is not always clear from these studies if isotretinoin was used as a first-line therapy or only after other treatments had failed. Some dermatologists advocate using isotretinoin to treat even mild cases of acne that are unresponsive to standard therapies, not

[7] Doering PL, Araujo OE, Frohnaple DJ, LaMarre A, Flowers FP: Patterns of prescribing isotretinoin: focus on women of childbearing potential. Ann Pharmacother 26(2):155-161, 1992.

[8] Wysowski DK, Swann J, Vega A: Use of isotretinoin (Accutane) in the United States: Rapid increase from 1992 through 2000. J Am Acad Dermatol 46:505-509, 2002.

just cystic acne.[9,10] Others believe that treatment with isotretinoin should be started in patients with severe acne before scarring occurs. These views illustrate the potential for more widespread use of isotretinoin than was originally intended.

Further evidence that isotretinoin may be overprescribed can be found in articles in popular women's magazines. For example, in the September/October 2002 issue of Elle, the increased use of Accutane by women is discussed in the article, "Small Wonders". On the front page of the article, a photo of a beautiful, nude woman with flawless skin is pictured. Accutane® is touted as "Hollywood's guaranteed panacea for the occasional blemish". The health risks associated with the use of Accutane® are not discussed until the second page, and only one sentence is devoted to the teratogenic risk of Accutane®. One dermatologist is quoted in the article as saying, "A very low dose of Accutane® is safe to take indefinitely if a condition like this [rosacea or psoriasis] is chronic and you have no intention of getting pregnant". Since 50% of pregnancies in North America are unintentional, what happens if a woman *does* become pregnant during chronic treatment with a low dose of Accutane® (however that may be defined)? What are her risks of giving birth to an infant with malformations or mental retardation? Unfortunately, we have no epidemiological evidence that a low dose of isotretinoin is safe to take during pregnancy in humans.

The Wysowski et al. study also found that dermatologists were not the sole prescribers of isotretinoin. During Accutane® marketing in the United States in 1982 through 2000, 8% of the physicians who prescribed Accutane® were family and general practitioners and internists.[8] In many rural areas of the country, opportunities to visit specialists, such as dermatologists, are infrequent. Since the diagnosis of acne is not perceived to be difficult and the drug is not very toxic to the adult, an increasing number of family practitioners prescribe Accutane®. Although the S.M.A.R.T. prescribing guidelines for Accutane® recommend that Accutane® should be prescribed only by prescribers who have "demonstrated special competence in the diagnosis and treatment of severe recalcitrant nodular acne [and] are experienced in the use of systemic retinoids", Roche nevertheless only requires that a physician sign the S.M.A.R.T. *Letter of Understanding* certifying that he or she "knows how to diagnose and treat the various presentations of acne". Therefore, although it may be implicitly understood that the likely prescriber would be a dermatologist, the S.M.A.R.T. program does not go so far as to prohibit other health care professionals from prescribing Accutane®.

In addition, a generic form of Accutane® has recently been approved for marketing in the U.S. by the FDA; other generic forms will surely follow. This, in addition to the potential for overprescribing, will likely increase the number of prescriptions filled for isotretinoin and consequently the number of isotretinoin-exposed pregnancies.

OTIS Recommendations

OTIS is supportive of the current efforts by the manufacturer, Roche Laboratories, Inc. and the FDA to decrease the number of exposed, pregnant women. However, our programs continue to receive calls from pregnant women who have taken isotretinoin, even under the current S.M.A.R.T. guidelines. And given recent trends to expand the number of skin conditions that can be treated by isotretinoin and the arrival of generic forms of isotretinoin on the market, OTIS cannot see how the current S.M.A.R.T. guidelines can possibly prevent the continued and *unacceptable* occurrence of isotretinoin-exposed pregnancies. Therefore, further restrictions are essential to assure appropriate protection for the embryo and fetus. For this reason, OTIS recommends implementation of the following:

1. Increased regulatory safeguards concerning the use of oral isotretinoin in women of reproductive age, using the thalidomide S.T.E.P.S. program as a template to include:
   A. Mandatory enrollment and compliance of physicians, pharmacists and patients with the S.M.A.R.T. program as set forth by the manufacturer.
   B. Mandatory participation of patients, prescribing physicians, and pharmacies in an independent registry established to monitor compliance and pregnancy outcomes of exposures to all forms of oral isotretinoin.
   C. Increased patient accessibility to the use of two reliable forms of contraception.

[9] Layton AM, Knaggs H, Taylor J, Cunliffe WJ: Isotretinoin for acne vulgaris—10 years later: a safe and successful treatment Br J Dermatol 129:292-296, 1993.

[10] Cunliffe WJ, van de Kerkhof PCM, Caputo R, Cavicchini S, Cooper A, Fyrand OL, et al.: Roaccutane treatment guidelines: results of an international survey. Dermatology 194:351-357, 1997.

D. Continued educational activities provided for physicians, pharmacists and patients concerning the teratogenic potential of isotretinoin.

2. Availability of all forms of oral isotretinoin should be strictly limited to only those women who meet the clinical criteria for severe recalcitrant cystic acne.
3. Prescribing of oral isotretinoin should be strictly limited to dermatologists who have enrolled in the S.M.A.R.T. program and have agreed to comply with the guidelines.
4. More effective and comprehensive contraceptive counseling techniques should be used to eliminate common misconceptions about contraceptive methods and to ensure that women understand their responsibility in preventing pregnancy.
5. Incorporate OTIS toll-free number and web site information in all isotretinoin packaging so that direct access to risk assessment and counseling concerning the use of oral isotretinoin prior to and during pregnancy is available to the consumer.
6. Continued evaluation of the effectiveness of this program and modification if necessary.

Given the nature of human reproduction, OTIS is aware that all exposures to isotretinoin cannot be prevented. However, we feel that our combined efforts can make a significant impact on the number of exposed pregnancies. Therefore, we would like to see an increase in the use of TIS' to provide accurate risk assessment and counseling for pre-, peri-, and post conception exposures to isotretinoin. Specifically, the potential teratogenic effects should be clearly discussed with those individuals who have been exposed during pregnancy.

Sincerely,

JANINE E. POLIFKA, PH.D.
President, OTIS

Appendix A

AGGREGATE DATA COLLECTED FROM PARTICIPATING TIS'—9/2000

Year	Total Calls Concerning Reproductive Effects of Accutane	Calls From Accutane Exposed Pregnant Women	# TIS' Reporting
2002*	40	27	13
2001	90	39	20
2000	86	28	16
1999	62	17	13
1998	68	16	11
1997	57	15	9
1996	48	11	8
1995	49	13	6
1994	27	3	6
1993	57	13	5
1992	61	9	5
1991	18	9	5
1990	8	4	4
1989	9	4	3
1988	5	1	2
1987	3	-	1
TOTALS	**558**	**143.**	

*These numbers are incomplete because data have not been received from all TIS' as of December 9, 2002.

Mr. GREENWOOD. We thank you, Ms. Martinez.
Dr. Berson.

TESTIMONY OF DIANE S. BERSON

Ms. BERSON. Good afternoon, Mr. Chairman and members of the committee. My name is Dr. Diane Berson and I'm a dermatologist at Cornell Medical College in New York. I thank you for allowing me the opportunity to testify before you today.

Acne can be a disfiguring disease. Cystic acne is a serious condition which can be both painful and unsightly. The life long scarring

can be physical as well as emotional. Isotretinoin, brand named Accutane, is the most effective medication for the treatment of severe cystic and inflammatory acne. Because of its efficacy and lack of alternatives for treating recalcitrant acne, isotretinoin is an extremely valuable drug which I hope will remain available for dermatologists to prescribe to those patients who clearly need it.

Since the inception of this drug, dermatologists have been keenly aware of the risk of birth defects in women who might become pregnant while taking isotretinoin. As a result of strict adherence to guidelines established by the FDA, the rates of pregnancy in women taking the drug have actually dropped despite increased use by women of child bearing age. We are dedicated to ensuring that even more improvements are made regarding the rates of pregnancy. The introduction of the SMART program will take this one step further. We are doing all we can to ensure the success of this program.

A vital component of the risk management effort is a survey on female patients with experience with isotretinoin. Female patients voluntarily complete survey forms and submit them to enroll in the survey. The data is analyzed by the FDA to measure the success and effectiveness of efforts to manage the risk of pregnancy in female isotretinoin patients.

As dermatologists we really think it is imperative that we do what we can to ensure that the current risk management programs do succeed. We play a vital role in distributing the survey forms to our patients and motivating them to enroll in the confidential survey of program outcomes.

Another potential safety issue regarding isotretinoin is the possible connection between the use of isotretinoin and psychiatric incidences. No biological mechanism has been shown to explain the possible association between the drug and aggressive behavior. While that connection is as yet unproven, dermatologists do take these concerns seriously.

Recently a scientific consensus conference was held to address this issue. At this conference the most up to date scientific information on isotretinoin and the psychiatric and pregnancy issues were reviewed. Some of the conclusions from the scientific consensus conference include calling for future studies to examine the possible link between isotretinoin and mood changes or suicide drawing upon multidisciplinary teams of dermatologists, adolescent medicine specialists, psychologists, psychiatrists and pharmacologists.

Additionally, a major effort is needed to combine basic science research with large prospective controlled incidence studies. The safety of our patients is of paramount concern. For many otherwise healthy adolescents the dermatologist may be the only physician that they see regularly. We as dermatologists thoroughly educate and counsel our patients prior to prescribing Accutane. We review the potential side effects and risks associated with its use and the vigilant need to prevent pregnancy in female patients of child bearing age. I always frankly discuss the issue of depression and encourage my patients to inform their parents or me immediately if they experience any changes in mood or emotional problems. If I suspect preexisting depression, a referral is made to the appropriate specialist.

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Accutane has been called a miracle drug by many patients who have suffered from the pain and embarrassment of acne. It has changed the lives of so many young adults who were forced to avoid interactions with their peers at the very age when association awareness peaks. Successful treatment can restore their self-confidence and emotional well-being.

In the last 15 years I have prescribed Accutane to hundreds of patients. So many individuals are grateful that I was able to offer them medication which cleared a condition many had suffered with for years and had not responded to any other medications.

Thank you very much.

[The prepared statement of Diane S. Berson follows:]

PREPARED STATEMENT OF DIANE S. BERSON, ASSISTANT PROFESSOR OF DERMATOLOGY, WEILL MEDICAL COLLEGE

Acne can be a disfiguring disease. Cystic acne is a serious condition which can be both painful and unsightly; the lifelong scarring can be physical as well as emotional. Isotretinoin, brand name Accutane, is the most effective medication for the treatment of severe cystic and inflammatory acne. Because of its efficacy and the lack of alternatives for treating recalcitrant acne, isotretinoin is an extremely valuable drug which should remain available for dermatologists to prescribe to those patients who need it.

Since the inception of this drug, dermatologists have been keenly aware of the risk of birth defects in women who might become pregnant while taking isotretinoin. As a result of strict adherence to guidelines established by the FDA, the rates of pregnancy in women taking the drug have actually dropped despite increased use by women of child bearing age. We are dedicated to insuring that even more improvements are made regarding the rates of pregnancy.

The introduction of the SMART program will take this one step further—we are doing all we can to insure the success of the SMART program and other programs for generic versions of isotretinoin.

The new regulatory program took effect on April 10, 2002. Prescribers are required to enroll with the risk management program in order to continue prescribing this drug. This effort includes yellow Qualification Stickers, patient information/labeling and patient consent forms.

A vital component of the risk management effort is a survey on female patients' experience with isotretinoin. Female patients voluntarily complete survey forms and submit them to enroll in the survey. The data is analyzed by the FDA to measure the success and effectiveness of efforts to manage the risk of pregnancy in female isotretinoin patients. As dermatologists, we realize that it is imperative that we do what we can to ensure that the current risk management programs succeed. We play a vital role in distributing the survey forms to our female patients and motivating them to enroll in the confidential survey of program outcomes. Another potential safety issue regarding Isotretinoin is the possible connection between the use of Isotretinoin and psychiatric incidences. While this connection is as yet unproven, dermatologists take these concerns seriously. Recently a scientific consensus conference was held to address this issue. At this conference, stakeholders were informed of the most up-to-date scientific information on isotretinoin and the psychiatric and pregnancy issues.

Some of the conclusions from the scientific consensus conference include calling for future studies to examine the possible link between isotretinoin and mood changes or suicide, drawing upon multidisciplinary teams of dermatologists, adolescent medicine specialists, psychologists, psychiatrists, pharmacologists, epidemiologists, and other appropriate professionals. Additionally, a major effort is needed to expand and integrate basic science research starting at the molecular level with large-scale epidemiologic studies, and large, prospective controlled incidence studies.

The safety of our patients is of paramount concern. For many otherwise healthy adolescents the dermatologist may be the only physician they see regularly. We (as dermatologists) thoroughly educate and counsel our patients prior to prescribing Accutane; we review the potential side effects and risks associated with its use, and the vigilant need to prevent pregnancy in female patients of childbearing age. I always frankly discuss the issue of depression and encourage my patients to inform their parents or me *immediately* if they experience any changes in mood or emo-

tional problems. If I suspect preexisting depression a referral is made to the appropriate specialist.

Accutane has been called a "miracle drug" by many patients (and their families) who have suffered from the pain and embarrassment of acne. It has changed the lives of so many young adults who were forced to avoid interactions with their peers at the very age when social awareness peaks. In the last 15 years I have prescribed Accutane to hundreds of patients. So many individuals are grateful that I was able to offer them this medication which cleared a condition many had suffered with for years.

Thank you.

Mr. GREENWOOD. Thank you, Dr. Berson.

The Chair recognizes himself for 5 minutes. This is a tough one. We've had from this panel descriptions of different kinds of pain, the obvious pain of the loss of a child, which is, I can tell you from personal experience, the deepest pain that there is. But we've also heard from those who've experienced the pain of being ostracized, of being humiliated and being—loss of self-esteem at school because of these severe issues. And it's a very difficult one.

I want to ask Dr. Berson, when you counsel you said that if you suspect a preexisting depression that you'd make a referral. Do you prescribe Accutane anyway, or do you wait for a report from a clinical psychologist or psychiatrist?

Ms. BERSON. I would recommend that the patient see a psychiatrist and I would not prescribe Accutane right away until I consulted with that psychiatrist after the patient was examined.

Mr. GREENWOOD. You heard the testimony of attorneys and of the Benczes and you're probably familiar with Mr. Stupak's personal tragedy. In each of these instances what appears to happen is a sudden, without any warning, without a long history of any kind of depression or even personal problems, this immediate sudden change of behavior and this almost compulsion to end one's life as quickly as possible. How do you advise a young—I mean, do you say that to a young person? How do you advise a young person with regard to the psychiatric effects? Because if you say if you start to feel blue or you feel sad as you're taking this medication report to me right away. And yet, all of these parents would tell you that, and did, that that wouldn't have helped because it was like that. And I think probably under that compulsion to end one's life, there's no rational thought patterns going on about perhaps I can call, get help, have this changed. This changes one's whole perception of their existence.

Ms. BERSON. I do discuss this entire issue with every patient whom I start on Accutane, especially the adolescents and the young adults, and I do really let them know that if they do feel blue or depressed or down that they must let me know right away. I do also let them know that there have been reports of incidents such as these. I haven't experienced this within my own practice, but I certainly can't explain it.

Mr. GREENWOOD. What about—let's get to the question with you of utilization because we've heard that this is recommended only for the most severe cases of acne, recalcitrant nodular acne. Where do you draw the line specifically with regard to when you think it's appropriate to utilize this drug?

Ms. BERSON. Well, certainly Accutane is indicated for severe cystic nodular acne or inflammatory acne with scarring. I never use it as a first line therapy. I will usually place patients on regimens,

including topical therapies and oral antibiotics and even oral hormone therapy for young women.

Mr. GREENWOOD. But do you use it as a third line in cases that are less severe than recalcitrant nodular cystic acne?

Ms. BERSON. I think every patient on whom I place Accutane has some degree of cystic acne. Inflammatory acne is a cascade where there can be lesions described as papules, pustules and cysts. But I would rarely give it to a patient——

Mr. GREENWOOD. What's your definition of severe? I'm sorry to sort of pepper you with questions here, but my time is limited.

Ms. BERSON. Cystic acne would be referred to as having at least five cysts.

Mr. GREENWOOD. And is that how you define severe case?

Ms. BERSON. I think very often it becomes an individual basis type of decision. If I have a patient with inflammatory acne, the evidence of scarring, who's been on a regimen that hasn't worked for over a year, and who is not responding to any other therapies, I might consider treatment with Accutane. I certainly would never use it in any patient with mild acne, and I can tell you I have had a lot of instances where I've had a teenager will come in with very mild acne, hardly any pimples on their face begging me to give them Accutane because they have a friend who is on it or who's just finished it who looks great. And certainly I will explain to them that there's no way I'd be willing to do that and this is a serious medication, and it's not for them.

Mr. GREENWOOD. Thank you. Very quickly for Dr. Green and Dr. Martinez. Ms. Martinez. If there were a—if the FDA took the strongest course of action that they think that they can under the current statutory authority to require mandatory registry of physicians and patients, and they changed the distribution schemes so that the only place you could get this medicine was at that registered doctor's office as opposed to the pharmacy, and—well, let's just stop there. What impact do you think that would have on the incidence of this drug causing birth defects?

Ms. MARTINEZ. You know I think we can look to what's happening with thalidomide to understand what impact that might have because thalidomide is less widely prescribed. But if the restrictions were in place, Accutane maybe would be less widely prescribed as well and would be reserved for those cases in which other things had not worked. So I think it would have an impact that would decrease the likelihood of pregnancy among those folks who are taking Accutane just because of experience we've seen.

Mr. GREENWOOD. The reason I have trouble comparing those two, they seem very much like apples and oranges to me, because obviously you have a different population interested in thalidomide. You have the terror that it strikes in people with my hair and your hair and you don't have all of these desperate teenagers clamoring for this miracle drug.

Ms. MARTINEZ. But I think we can also look at the European experience with this drug, with the same drug, and look at the rates in Europe of the embryopathy, the birth defects related to Accutane. Significantly lower. Much, much lower by, you know, many times what we're seeing in the United States. And those are set up by direct restricted distribution as well. So I think that

there are reasons to believe, at least, that we have fewer of the birth defects.

Mr. GREENWOOD. Do you think that when the advisory panel made its recommendations to FDA that was clear in your mind that you wanted and that the advisory panel wanted a mandatory registry and the limited distribution system?

Ms. MARTINEZ. It was clear that that's what we wanted. It was clear to me that there were many other members of the panel who were interested in that. It was less clear to me what the overall recommendation was that came out of that panel.

Mr. GREENWOOD. Okay. My time has expired. The gentleman from Florida, Mr. Deutsch, is recognized for 5 minutes.

Mr. DEUTSCH. Thank you. And again I just want to thank everyone who's here. I know I can at least have some sense of how difficult it is. And hopefully your testimony is really hopefully part of a process that will lead to better results.

Dr. Berson, I want to follow up on some of the questions that my colleague has asked. First off, how do you feel about nondermatologists prescribing Accutane?

Ms. BERSON. Personally I feel that Accutane should be prescribed by dermatologists who are the specialists in skin diseases and I think that we have a lot of experience in diagnosing and treating all the different forms of acne.

Mr. DEUTSCH. I mean, is it medically responsible because again, you know, we obviously know that a certain percentage of physicians who are nondermatologists are prescribing it presently?

Ms. BERSON. I personally feel that a patient with any skin disorder should be evaluated by a dermatologist, and——

Mr. DEUTSCH. Okay. Let me also mention another statistic. I don't know if you were here when the FDA was here. But the FDA official testified under oath that in his judgment 90 percent of the Accutane is off label use. In your practice, you know, you were getting right near the edge of potential off label use. Would you consider any of the prescriptions that you provide off label use of Accutane?

Ms. BERSON. I think I really try to adhere to the indication for prescribing this for nodular cystic acne. I think there is off label use.

Mr. DEUTSCH. But I mean for you personally in your practice what percentage, 1 percent, 2 percent, 5 percent?

Ms. BERSON. Maybe 2 to 5 percent.

Mr. DEUTSCH. And let me, the reason why I mention that is, I don't know you but you come from a facility that is a world renowned facility. I mean, you are the—you know, your facility, you know, is the paradigm of the way medicine should be practiced. And if everyone in America practiced like you, you know at least in terms of the birth defect issue, or even in terms of the suicide issue I think we'd be in much better shape. But not every dermatologist in America practices at Cornell Medical School. And you know we have people from Orange, New Jersey and we have people from Fort Wayne, Indiana, and we have people from Fort Lauderdale, Florida that are not going to medical centers, international medical centers like you to get this type of treatment. I mean, you know, we've talked about 2 million prescriptions a year. And I

think that's the contrast in a sense. And what I do want to have a sense of from your case, I mean, how—the percentage of your prescriptions for Accutane for teenage girls, how many—just a rough estimate. How many teenage girls are you presently prescribing Accutane to in your practice?

Ms. BERSON. I would say—percentage of?

Mr. DEUTSCH. Well, the numbers. How many teenage girls are you providing Accutane for?

Ms. BERSON. Right now?

Mr. DEUTSCH. Right now, today.

Ms. BERSON. Maybe 10.

Mr. DEUTSCH. Okay and the age range of those girls?

Ms. BERSON. I would say 14 to 20.

Mr. DEUTSCH. You know, again, one of the things which is obviously at least disturbing me and I think other people as well, is, you know, you're going through these discussions about sexual activity with a 14-year-old; is that correct?

Ms. BERSON. I am, and very often I try to have a conversation alone with the patient in addition to having a conversation with the parent present.

Mr. DEUTSCH. Okay. And so the 14-year-old is going through a pregnancy test?

Ms. BERSON. Yes, everyone has to have a pregnancy test.

Mr. DEUTSCH. And two means of contraceptives?

Ms. BERSON. If they've already started menstruating, yes.

Mr. DEUTSCH. Okay. 14-year-old, more than likely. So those 10 girls are probably in that situation? Or 15 or 16? I mean it'd be unlikely for a 15 or 16-year-old girl not to have started menstruating. So I mean for those girls what is their primary and secondary form of contraceptive?

Ms. BERSON. Most of the girls that I'm treating I think are using abstinence and I speak to them about and document it. But obviously——

Mr. DEUTSCH. Again, I don't want to interrupt you, but I have a very short amount of time. I have a girl who's a little bit young, a daughter who's a little bit younger than this. But you know I lived in the real world, I was a teenager once. And you know we've dealt with this from legislative issues. That's why in States like Florida it's come up again and the Florida Supreme Court has said you can't require parents to, you know, grant birth control use for children. Most 14, 15, 16, 17-year-old girls don't want their parents to know they're sexually active so they're going to tell their parents they're abstinent. I mean you know we're in the real world. And you know, is it surprising that we're going to have unwanted pregnancies. Now, again if you're using primary and secondary birth control devices and you're sexually active, the chance of being pregnant is very small. All right. But I mean, you know, this whole concept that you're going through these conversations—every, it just so happens all 10 of those girls are abstinent.

Ms. BERSON. No, I would say most of the 10 girls who I'm treating right now with Accutane are also on the birth control pill. The birth control pill is approved for girls age 15 and over and because of the medical-legal aspects associated with this and the potential for pregnancy, I actually place these girls on the birth control pill

for their 5-month course of treatment even if they tell me that they're abstinent.

Mr. DEUTSCH. Right. And again I would have to tell you that you're at Cornell Medical School, and for the rest of the United States of America I really doubt that's happening.

Just one quick follow-up question for Ms. Martinez. Can you describe some of the girls that you get calls from? Who are these girls?

Ms. MARTINEZ. Okay. A lot of them are not teenage girls. A lot of them are older, in their twenties. The majority of the people we get calls from are in their twenties. But I can give you an example of a teenage girl that I spoke with on our risk line who—whose mother went in with her of course to the doctor's office. She was given the Accutane after having had a urine pregnancy test. She was very, very early in her pregnancy so the pregnancy test missed the fact that she was pregnant. She did not tell the doctor that she was pregnant because her mother was there with her, or that she was sexually active because her mother was there with her. She took the Accutane up through about 4 months of that pregnancy and didn't say anything to anyone about the thought that she could be pregnant because she didn't want her parents to know being a teenager with sort of magical thinking and not thinking about the fact that eventually people would know. And so that pregnancy is still in progress. We don't know the outcome yet, but we've—based on ultrasound there are problems that, you know, could potentially be there.

Mr. GREENWOOD. The time of the gentleman has expired. The gentleman from Michigan, Mr. Stupak, for 5 minutes.

Mr. STUPAK. Thank you and thank you to all the witnesses for appearing here today. Dr. Berson, are you a member of the American Academy of Dermatology?

Ms. BERSON. Yes, I am.

Mr. STUPAK. Okay. Are you familiar with a Dr. Pariser, the President of the American Academy of Dermatologists?

Ms. BERSON. Yes.

Mr. STUPAK. Okay. He testified in December 2000 and he indicated, and I'm going to quote from his sworn testimony, and he says—we were talking about how much time physicians spend with their patients and dermatologists in particular. He says I am personally heart saddened by the fact that many of my colleagues seem to be less informed on this than they should be, and I have no defense for that. Now, would you agree or disagree with this?

Ms. BERSON. I would probably agree with that.

Mr. STUPAK. So your practice and the way you do it, would you say you're an exception as opposed to the rule in dermatology practice and work with Accutane?

Ms. BERSON. I would hope that other dermatologists spend a lot of time with their patients also. But I do spend a lot of time with my patients, and I also am very interested in treating acne because I don't discard it as an insignificant condition.

Mr. STUPAK. Sure. And Dr. Pariser, the President of the American Academy of Dermatologists, said in his experience they don't spend enough time with them, correct?

Ms. BERSON. I'd like to feel that I personally spend enough time with the patients.

Mr. STUPAK. Oh, no, I'm not talking about you. That's what he testified before the committee on the safety of Accutane. Did you say that you require a patient before you put them on Accutane to go to a psychiatrist?

Ms. BERSON. No. No, I was asked if the patient had a preexisting history of depression or suicidal ideations would I prescribe Accutane before consulting with a psychiatrist.

Mr. STUPAK. Okay. When you talk about a preexisting history, is that the patient or is it the patient's family? How is that or is it just the patient you're concerned about?

Ms. BERSON. It's usually the patient history. If there were a family history but the patient denied any problems, I wouldn't send them to a psychiatrist. But I would certainly closely monitor them, meaning I tell them if they develop any mood swings or depression or sadness that I not only want them to let their parents know, but that I want them to let me know. And I do make myself available to my patients for phone conversations at the end of hours any day they need to speak to me.

Mr. STUPAK. Okay. In the labeling that we've seen on the Accutane boxes, it indicates that—I'll find it here. This writing's so small it's hard to read. It indicates that if there's a family history of heart attack, liver disease, or depression, then you should let your doctor know. Should that warning be if you have a personal history, or——

Ms. BERSON. Well, we usually perform a blood test before we start anyone on this treatment, and included in the blood test are liver functions and triglyceride levels.

Mr. STUPAK. Sure.

Ms. BERSON. If they were to come back in normal range and I was dealing with an otherwise young, healthy patient, I don't think I would withhold the drug.

Mr. STUPAK. Okay. But here, it says right here, for all patients, and this is before you begin your treatment, if you have a family or personal history of medical conditions such as diabetes, liver disease, heart disease or depression, please inform your doctor. Your emphasis is then on the personal history of that patient and not necessarily the family history?

Ms. BERSON. Well, I always do get a complete family history, social history and personal medical history on any patient, not just on acne patients.

Mr. STUPAK. Is the blood work you said, is that mandatory before you begin your course of treatment on Accutane?

Ms. BERSON. Definitely.

Mr. STUPAK. Okay. So no matter how you answer these questions, before you get Accutane you should have blood work to see what your triglycerides and cholesterol levels and things like that are?

Ms. BERSON. Right. First, because we want to make sure there are no preexisting elevations which would—obviously I wouldn't give the medication if someone had an elevation and also we do it as a baseline to monitor any changes during the course of therapy.

Mr. STUPAK. Now is that your own practice or is that required by the manufacturer as part of their protocol in using this drug?

Ms. BERSON. I think it's common practice and it should be performed by every doctor. I can't speak for others though.

Mr. STUPAK. Sure. You know, the Benczes and the Turneys here testified today. They talked about the spontaneity of the act. How can you detect that? Can you decipher spontaneity for us?

Ms. BERSON. No, I think that's definitely a difficult question to answer, and I haven't experienced that with a patient. But I can't explain it.

Mr. STUPAK. There's really no way to warn about the spontaneity that may occur with this drug, is there?

Ms. BERSON. No.

Mr. STUPAK. Would you be surprised if I said of the 90 names I turned in to the FDA on suicides, three of them were doctors who lost their sons and they never saw the warning signs? Would that surprise you?

Ms. BERSON. No.

Mr. STUPAK. Okay.

Mr. GREENWOOD. The time of the gentleman has expired. The gentleman, Mr. Strickland, is recognized for 5 minutes.

Mr. STRICKLAND. Thank you, Mr. Chairman. I'm just sitting here listening to the various witnesses and I have two thoughts before I ask my question, or questions, I guess that I would like—unanswerable questions at this point that I'd like to share with the committee and with the witnesses.

The first question I would ask myself is, is it possible to set up a system where this drug is administered as carefully and cautiously as thalidomide is administered? And I'm not saying that's desirable. It's just a question. Is it possible to do that?

But the more troubling question is what my friend Representative Stupak just referred to, and that's what seems to be the spontaneous impulsive behaviors that are sometimes associated at least anecdotally with young people who take this drug. And a question as to whether or not it is possible through—as I believe Ms. Wallace said, she talked to her son. She asked probing questions, not just are you feeling well, but, you know, a wide variety of questions to try to probe to see if there was something going amiss with this young person. And I'm wondering if it's possible through research to determine if there is some aspect of this drug that does lead to spontaneous impulsive behaviors that we have not been able to isolate or recognize or predict. I guess the fact that they're impulsive makes them difficult to predict. But that, in my judgment, is at the center of the dilemma that we face today as we talk about this drug. Is it possible to understand beforehand that something may be going wrong in the emotional life or the thinking of the person that's on this drug?

Does anyone want to respond to that? You don't have to. I'm not sure you—I'm not looking for a definitive answer. But, yes, sir. Mr. Turney.

Mr. TURNEY. Even if we had to do it over again, knowing what we know, looking back and seeing little things about Matthew, if we had to do it over again today, and he was on that medication, there was nothing, nothing that anyone could have put on a pack-

age, no kind of warning that would have stopped what happened to him. It was approximately—we come up with about 10 minutes from the time he was seen extremely happy, making plans for the future to the time he committed suicide. I don't know how you could watch for that. I don't know how you could ask any more questions. I don't know—I really just—and this is knowing, knowing what's happened to him. You couldn't prevent it. I just don't see how any registry or anything could stop what happened to him. I just don't.

Mr. STRICKLAND. Thank you. And I have a question for Dr. Green. Yes, Dr. Green.

Dr. Green, I have a memo here that was written on June 20, 2000. It is an FDA memo written by Dr. Jonathan Wilkin. And I won't read all of the memo, but just a small portion of it. In this memo he's speaking about some concerns regarding fetal exposure to Accutane. He says there's no doubt or debate that Accutane is a potent teratogen, teratogen. And then he proceeds to say, pediatric groups and the CDC have concerns about the apparent asymmetry between the restricted distribution of thalidomide to a population less likely to become pregnant, and the open and liberally promoted distribution to a population more likely to become pregnant.

Do you have a response to that, that quote?

Ms. GREEN. Yes. We were also concerned about that asymmetry and in fact at the FDA hearing in September 2000 I also testified that we wanted a mandatory system analogous to that used for thalidomide. I mean, remember that the thalidomide tragedy affecting about 10,000 infants occurred, did not occur in this country because of the astute, as you heard earlier from FDA, the astute analysis of the FDA officials. It could very easily have happened here. You know, before Accutane was marketed in 1982 it was well known that Accutane causes a very similar syndrome of birth defects in multiple experimental animal species to that which is caused in children and in fetuses, human fetuses. So we're very concerned about that asymmetry, yes.

Mr. STRICKLAND. Mr. Chairman, can I ask one quick follow-up question?

Mr. GREENWOOD. Very quickly. We are under a tight time schedule.

Mr. STRICKLAND. Dr. Green, we treat thalidomide with a mandatory registry. We treat Accutane it appears with a voluntary registry. What justifies that difference in your mind?

Ms. GREEN. I can't speak for FDA obviously. But as a pediatrician as well as a representative of the March of Dimes, I cannot justify that difference. The thalidomide program is admittedly complex to administer but, as you've heard, is very successful.

Mr. STRICKLAND. Thank you. Thank you, Mr. Chairman.

Mr. GREENWOOD. The gentleman from Florida is recognized for 5 minutes.

Mr. STEARNS. Yeah. Thank you, Mr. Chairman. This is a question for Dr. Berson. If we have a registry and they mandate certain things that you must do, is it a possibility that this would be onerous to doctors that they might say the heck with it; if I have to prescribe this under these conditions or the possibility of litigation,

with the possibility of government mandates, that they might say the heck with it. You know, I might be under some kind of breaking of the law and so maybe I just won't be hassled with it and go somewhere else. I guess—what is your comment to that?

Ms. BERSON. I assume there would be some physicians who would have that attitude. I would like to think that the patient's benefit is a priority and whatever the situation would be if we felt that a patient clearly needed this drug and would benefit from it, I would like to think that the patient would still be able to be offered it. But I can't speak for other physicians. If I felt the patient still needed Accutane, I would do whatever I could to get it for them, assuming they were the appropriate candidate.

Mr. STEARNS. Has anyone ever told you, like how long after Accutane is stopped are there still possibilities of effect?

Ms. BERSON. Of effect on the acne or——

Mr. STEARNS. No. The residual, I know, you might tell me both on acne and any psychological effects like 30 days, 60 days. I mean, how long is it pretty much out of the system and is not affecting any possibility of psychological problems or is not affecting the prevention of acne?

Ms. BERSON. The drug is actually out of their system after a few days. I do tend to see some of the side effects such as dryness for about a week or 2 after and I'm sure that's just because the skin in the area is still dry. But we recommend for instance, with respect to pregnancy prevention, that pregnancy be avoided for at least 1 month after treatment. But in reality the medication is out of the system in a few days.

Mr. STEARNS. So for all intents and purposes, 30 days is the safe requirement to before—for your estimation.

All right. Thank you, Mr. Chairman.

Mr. GREENWOOD. The Chair thanks the gentleman. The Chair thanks all of our witnesses and let me say again, particularly to the Turneys and the Benczes, I know how difficult it is to come here and bear your souls so publicly, and we appreciate that and this committee will do what we can to make sure that neither your losses nor your journey here to Washington were in vain. Thank you again. And you are excused and are free to go.

We'll then call our final witness, George Abercrombie, who is the President and Chief Executive Officer of Hoffman-La Roche, inc. Welcome, Mr. Abercrombie. And you're accompanied by William Levi Smith, and Dr. Smith is the Director of Medical Science at Hoffman-La Roche, and Dr. Susan P. Ackerman, who is the Global Head Risk Management Director for Medical Outcomes Research, Economics, and Epidemiology Department of Hoffman-La Roche. We welcome all three of you and I'm assuming that you may be relying on your colleagues to respond to some of our questions.

So I'll ask all three of you—first inform you that this is an investigative hearing. It is our practice to take testimony under oath and ask if any of you object to giving your testimony under oath today. You are then informed that pursuant to the rules of this committee and the House of Representatives you are entitled to be represented by counsel. Do any of you choose to be represented by counsel today?

Mr. ABERCROMBIE. We have Lanny Brewer representing counsel for Roche here today.

Mr. GREENWOOD. Very well. All right. Then if you would each all stand and raise your right hand.

[Witnesses sworn.]

Mr. GREENWOOD. Okay. You are under oath and, Mr. Abercrombie, you are recognized for your opening statement.

TESTIMONY OF GEORGE B. ABERCROMBIE, PRESIDENT AND CHIEF EXECUTIVE OFFICER, HOFFMAN-LA ROCHE INC.; ACCOMPANIED BY WILLIAM LEVI SMITH, DIRECTOR, MEDICAL SCIENCE, HOFFMAN-LA ROCHE INC.; AND SUSAN P. ACKERMAN, GLOBAL HEAD RISK MANAGEMENT DIRECTOR, MEDICAL OUTCOMES RESEARCH, ECONOMICS, AND EPIDEMIOLOGY DEPARTMENT, HOFFMAN-LA ROCHE INC.

Mr. ABERCROMBIE. Thank you, Mr. Chairman and members of the subcommittee. I am George Abercrombie, President and Chief Executive Officer of Hoffman-La Roche Incorporated, a research based pharmaceutical company. I am a registered pharmacist and after practicing pharmacy I joined the pharmaceutical industry about 20 years ago. I came to Roche as President and Chief Executive Officer in January 2001, and you have introduced Dr. Ackerman with me here today, who is our Head of Risk Management. Dr. Smith is our Director of Medical Science.

I'd like to begin today by letting everyone know in this room that I am the proud father of two teenage sons who are very, very precious to me and my family. I love my sons very, very much and as a parent, I want to convey to the Stupak family, to the Bencz family, the Turney family who testified earlier today my deepest and sincerest sympathy. I cannot begin to imagine the pain you have endured or how devastating each of your individual tragedies must be. It is in that spirit that while I am sure we may differ on some important points that you have my personal commitment that me and my colleagues here today will do everything we know how to directly and vigorously respond to the subcommittee's questions and issues.

Accutane is an important medication. As you can see from what I hope are photographs we have to show you, or that you will see later, in typical cases of severe recalcitrant nodular acne, nodules or inflammatory lesions can cause permanent scarring if left untreated. If other treatments fail, Accutane is the only therapeutic option available. Over 6 million U.S. patients have benefited from Accutane since it was first approved in 1982. However, like many drugs that offer a significant benefit, Accutane is an extremely powerful medication and presents risks that must be carefully managed.

As the company who developed and markets Accutane, we have and continue to take our responsibilities very seriously. Since the approval of Accutane 20 years ago, we have been committed to managing the known risks associated with Accutane as well as to addressing—based upon sound scientific principles and methods—potential safety concerns derived from adverse event reports. Indeed, we have been leaders in developing and implementing new methods for managing pharmaceutical risks. Our central concern

throughout this medication's history has been physician and patient awareness of the potential for birth defects. The most recent development of the evolution of innovative Accutane pregnancy prevention programs is our system to manage Accutane-related teratogenicity. You've heard about it today. We call it the SMART program. This program incorporates new and enhanced methods of ensuring that pregnant women are not prescribed Accutane and that women do not become pregnant while on the drug. Our goal is to accomplish both.

We have also addressed adverse events that have not been proven to be associated with Accutane but serve as signals for further evaluation. These include psychiatric adverse events reported in the Accutane patient population. Such spontaneous adverse event reports, however, cannot be considered in isolation from the public health facts about serious psychiatric problems in young people. As the Surgeon General recognized in the 2001 National Strategy for Suicide Prevention, in young people 15 to 24 years old suicide is the third leading cause of death, almost 4,000 suicides per year. Additionally, the National Institute of Mental Health estimates that up to 8 percent of teenagers suffer from depression.

Given the widespread nature of psychiatric events among young people, it is unfortunately not surprising to find reports of depression, suicide attempts and suicide in the Accutane population. We have responded to such reports with a vigorous scientific effort completing several epidemiological studies that specifically probed these psychiatric concerns using different methodologies and data sources and one clinical study that included the evaluation of depression in patients. The science has not demonstrated that Accutane causes psychiatric events and, even using very conservative assumptions, the rate of psychiatric events among Accutane patients is no higher than in the same age general population. Most importantly, despite the absence of any scientific evidence of causation, I want you, Mr. Chairman, and every member of this committee to understand that we label this medication as if such causation does exist.

In closing, my company, Roche, is proud to have offered the millions of severe recalcitrant nodular acne patients with an alternative to the prospect of disfiguring scarring acne, and we have done so while acting responsibly in addressing the broad range of complex issues associated with this important medication. I thank you for the opportunity to present our views, and I look forward to your questions.

[The prepared statement of George B. Abercrombie follows:]

PREPARED STATEMENT OF GEORGE B. ABERCROMBIE, PRESIDENT AND CHIEF EXECUTIVE OFFICER, HOFFMANN-LA ROCHE INC.

Mr. Chairman and Members of the Subcommittee, I am George Abercrombie, President and Chief Executive Officer of Hoffmann-La Roche Inc. ("Roche"), a research-based pharmaceutical company. I am a registered pharmacist, and I practiced retail pharmacy prior to spending almost 20 years in the pharmaceutical industry, joining Roche in January, 2001. I am accompanied today by my colleagues Dr. Susan Ackermann, who is the Head of Risk Management in our Department of Drug Safety and Risk Management, and Dr. William Smith, Director of Medical Science.

You have invited us here today to discuss Accutane® (isotretinoin), our pharmaceutical product indicated for the treatment of Severe Recalcitrant Nodular Acne.

In my testimony, I will describe some of the issues we have faced in ensuring the safe and effective use of Accutane, and our scientific and risk management initiatives.

Let me first personally convey our tremendous sympathy for the Stupak family, whose tragedy served as the impetus for the Subcommittee's review of Accutane. Although I can only imagine how devastating such a tragedy must be, as the father of two teenage sons I know how precious they are to me and my family. Congressman Stupak, although we may differ on some important points, I hope you know that we have tried to directly and vigorously address the concerns expressed by you and your colleagues.

We also fully appreciate that this hearing is based upon the broader oversight role of this Subcommittee. It is our hope that this hearing can be a part of the ongoing constructive dialogue on how best to address the complex issues often associated with adverse events and risk management, particularly in the context of a teratogenic drug product. Moreover, although we may differ as to whether Accutane is associated with psychiatric adverse events, we strongly believe that the broader issue of depression and suicide among young people is a major public health concern that calls for further research and education.

ACCUTANE AND SEVERE RECALCITRANT NODULAR ACNE

In considering the issues presented today, it is critical to understand why Accutane is such an important medication. I have appended to my testimony several photographs of typical cases of Severe Recalcitrant Nodular Acne for your review. As you can see, unlike in less severe forms of acne, in Severe Recalcitrant Nodular Acne a number of factors combine to cause nodules or inflammatory lesions. These lesions, typically found on the face, chest and back, can be extremely painful and often result in a lifetime of scars if left untreated.

As in many other medical conditions, the causes of Severe Recalcitrant Nodular Acne are not fully understood.[1] However, Accutane is a uniquely effective treatment for this disfiguring condition. Accutane is typically used after patients have failed topical and systemic antibiotic treatments for this severe form of acne, and have no other therapeutic options. Over 80 percent of patients require only one 4-5 month course of treatment to eliminate the Severe Recalcitrant Nodular Acne and avoid disfiguring scars.

Over six million U.S. patients have benefited from Accutane since it was first approved by the Food and Drug Administration (FDA) in 1982. We believe such prescribing is generally appropriate and intended to alleviate the suffering of patients with Severe Recalcitrant Nodular Acne rather than less severe conditions. In a small number of patients, Accutane is also used in the treatment of a variety of cancers. Ultimately, we must rely on the physician to use appropriate judgment in the practice of medicine, weighing the risks and benefits of the drug in consultation with patients and their families.

We are quite proud of the benefits of Accutane, and we often receive spontaneous letters and e-mails from patients providing personal testimony as to their dramatic experience with the drug. These patients often document how Severe Recalcitrant Nodular Acne fundamentally affected their lives—including complete isolation from social situations and the bleeding and constant pain of acne nodules—and how Accutane transformed their lives greatly for the better. We are thus committed to ensuring that the many patients with Severe Recalcitrant Nodular Acne have access to this important medication.

However, Accutane is a very powerful medication, and the profound benefits of the drug are accompanied by serious risks that must be managed by all who are responsible for its manufacture, prescribing, dispensing and use. Roche takes these responsibilities very seriously. Since the introduction of Accutane in 1982, we have been committed to continuing to manage the known risks associated with Accutane, as well as to addressing, based upon sound scientific principles and methods, potential safety concerns derived from adverse event reports. Indeed, because we take our

[1] We do know that there are at least four basic mechanisms by which isotretinoin treats Severe Recalcitrant Nodular Acne—

First, Accutane reduces sebum production by 60-80 percent, indicating alterations in the maturation of the cell that produces sebum. After treatment, sebum levels return to normal.

Second, Accutane restores the proper balance of cell growth and eliminates cohesion or stickiness in the hair follicle.

Third, Accutane significantly decreases the amount of bacteria on the skin and in the hair follicle. After treatment, the normal bacteria levels are restored.

Fourth, Accutane reduces the immune response in the skin by about 98 percent, and a normal skin immune response returns within two months after therapy.

responsibilities so seriously, we have led the industry in developing and implementing innovative risk management programs.

SAFETY OF ACCUTANE

Although there are a number of well-recognized adverse events associated with Accutane, our central concern throughout this drug's history has been teratogenicity, or the potential for birth defects. Unlike some of the other adverse events in the Accutane patient population, such as the issue of psychiatric adverse events, there is no scientific doubt that isotretinoin is a potent teratogen. Since the approval of the drug in 1982, we have worked with FDA to assure that prescribers and patients are aware that Accutane can cause birth defects, and that every effort must be made to prevent pregnancy for one month prior to starting treatment, while taking Accutane, and for one month after concluding therapy. Indeed, although our patient labeling and risk management measures have evolved significantly over the last 20 years, it is worthwhile noting that Accutane was one of the first drugs to be accompanied by a patient brochure, which communicated the teratogenic risks associated with the drug at the time of introduction.

In the late 1980s, these early efforts evolved into a revolutionary Pregnancy Prevention Program, which was recently enhanced in close coordination with the FDA and is now called the "System to Manage Accutane Related Teratogenicity," or the "S.M.A.R.T." program, which I will describe in detail.

I have appended the physician, pharmacist and patient materials associated with the Accutane Risk Management Program, which I urge you to review, as it represents the most extensive program of its kind for a major prescription pharmaceutical. It is our hope that this enhanced program will ultimately enable us to reach our public health goals of no woman starting Accutane while pregnant and no woman becoming pregnant while on Accutane.

PSYCHIATRIC EVENTS IN THE ACCUTANE PATIENT POPULATION

We have also addressed adverse events that have not been proven to be associated with Accutane, but serve as signals for further study, analysis and, when appropriate, labeling. These include psychiatric adverse events reported in the Accutane patient population.

First, let me relate some critical background facts about psychiatric problems among young people. Simply put, depression and suicide in that population—a group which is highly represented in the population prescribed Accutane—is an enormous public health problem. According to the Surgeon General's 2001 *National Strategy for Suicide Prevention:*

- For young people 15-24 years old, suicide is the third leading cause of death, behind unintentional injury and homicide.
- Every 17 minutes, another life is lost to suicide. Every day, 86 Americans take their own life and over 1500 attempt suicide. There are now twice as many deaths due to suicide than due to HIV/AIDS.
- For every completed suicide, there are five hospitalizations and 22 Emergency Department visits for suicidal behaviors—over 670,000 visits in a year.

Psychiatric adverse events are not like typical adverse events that have a clear physical manifestation. Rather, there are a complex range of behavioral, biochemical, genetic and environmental factors implicated in psychiatric disease. Unfortunately, due to a number of factors, including the unfortunate and unwarranted stigma associated with mental health issues, these problems are often hidden by those who suffer from them. Thus, suicides often occur without any clear indication of a need to intervene. Mental disorders are also difficult for even many medical professionals to diagnose accurately, despite the relatively high background rate in the patient population. In fact, one of the major themes of the *National Strategy for Suicide Prevention* is integrating suicide prevention into existing health services activities, including clinics and medical offices.

Given the widespread nature of psychiatric events, including suicide, it is unfortunately not surprising to find deaths by suicide in the Accutane patient population. Indeed, you will find that a broad range of prescription pharmaceutical products have labeling regarding depression, suicidal ideation, and suicide in patients, including products as diverse as oral contraceptive, anti-infective, anti-viral, anti-seizure and anti-fungal medications. Typically, there is no scientifically proven relationship between the events and the prescription drug product.

In fact, as a matter of science it is often extremely difficult, if not impossible, to discern whether events of this type are related to a medication. This Subcommittee may be presented with theories regarding how a relationship *could* exist between Accutane and psychiatric events. We can only respond to such theories with the sci-

entific methodologies that form the foundation for drug safety, labeling and risk management. In addition to the extensive studies conducted for approval of Accutane, and 20 years of drug safety monitoring, Roche has completed several epidemiological studies specifically probing these psychiatric concerns using different methodologies and data sources, and one clinical study that included the evaluation of depression in patients. The science has not shown that Accutane causes depression, suicide, or other psychiatric events. Indeed, even using conservative assumptions, the rate of psychiatric events in the Accutane patient population does not appear to deviate from the background incidence of such events in a comparative population. Thus, we continue to believe the psychiatric conditions reported in temporal association with Accutane therapy are consistent with the multiple risk factors in the population as a whole, as well as the subpopulation of young adults afflicted with the disfiguring disease of Severe Recalcitrant Nodular Acne.

However, we have by no means abandoned our effort to discern any potential link between Accutane and psychiatric events. Last year, we convened an expert panel, to which we invited both FDA and the National Institutes of Mental Health, to provide input on the design of a prospective clinical study. We then submitted an extensive draft protocol to FDA, engaged in a series of discussions with the Agency, and produced multiple iterations of the protocol. Ultimately, FDA found that the revised protocol could not overcome the daunting methodological problems associated with addressing this issue. For example, although we made extensive efforts to ensure that the study would be blinded—*i.e.*, patients would not know whether they were on Accutane or placebo—FDA remained concerned that patients who were on the drug would recognize its dermatologic effects and avoid disclosing psychological symptoms. We will continue to evaluate other sound methodological approaches to the issue.

FDA also asked the National Institute of Mental Health to screen isotretinoin and its metabolites for biochemical activity, and Roche provided the research material for those studies. It is our understanding that these studies, like others in the past, were inconclusive. However, studies of this type could conceivably help us arrive at new hypotheses to explore.

ACCUTANE LABELING AND RISK MANAGEMENT

As noted, our efforts to ensure safe and effective use of Accutane treatment are not limited to scientific study. We have broken new ground in programs that both manage known risks and address the psychiatric events that occur in the patient population. Nonetheless, although more and more labeling information is now directed to patients, the success of pharmaceutical risk management has historically been, and remains, dependent upon the physician as the learned intermediary. We must continue to rely upon the physician to make an informed judgment as to the need for a given treatment, and to communicate critical information to patients.

Beginning in 1983, Roche began receiving occasional reports of psychiatric adverse events in patients who were taking Accutane or had taken Accutane sometime in the past. We submitted these reports to FDA, and in December of 1984 we approached FDA to request that the professional labeling information for Accutane be revised to include the reports of depression and emotional instability in the Accutane patient population.

In 1985, and again in 1986, we sent letters to the medical community describing the changes to the Accutane professional labeling relating to the small number of reports Roche had received regarding depression in some patients who were taking Accutane. During this time, the patient brochure, and later the patient blister packaging, specifically alerted patients to be aware of potential changes in mood during Accutane treatment, and counseled patients experiencing such symptoms to discontinue taking the product and to check with their physician as soon as possible. These materials also instructed patients to inform their physicians of any personal or family history of depression prior to beginning treatment with Accutane. Over the years, we actively monitored spontaneous psychiatric adverse event reports along with all other adverse event reports in the Accutane patient population. Notably, although the exposure to Accutane increased over time, the reporting of psychiatric events remained steady and well below incidence levels in the overall population.

As a result of ongoing discussions with FDA, in 1997 FDA asked Roche to take a closer look at the adverse psychiatric event reports in patients who were taking Accutane. Roche conducted a cumulative safety review and engaged various outside independent experts to study this issue. We met with FDA in February 1998 to review the spontaneous adverse event reports and consider labeling changes. Although the scientific evidence does not establish a causal link between Accutane and psychiatric events, in light of the seriousness of the issues raised, we nonetheless im-

plemented a highly precautionary labeling change. Roche distributed a Dear Doctor letter to prescribers pointing out the addition of new language on depression and suicide to the package insert. Our representatives called on dermatologists across the country, and the letter was sent to 210,000 physicians in the United States with specialties in dermatology, psychiatry, general practice, internal medicine, family practice, osteopathy and emergency room care.

The 1998 package insert that was the subject of this broad, precautionary communication to prescribers stated as follows:

WARNINGS:

"Psychiatric Disorders: **Accutane may cause depression psychosis, and, rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events (see ADVERSE REACTIONS)."**

Adverse Reaction language on central nervous system effects and depression was also amended as follows:

ADVERSE REACTIONS:

"In the post-marketing period, a number of patients treated with Accutane have reported depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide. Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstitution of therapy (see WARNINGS)."

During this period, Roche commissioned or sponsored a number of epidemiological studies and reviews to further explore any potential causal connection between ingestion of Accutane and psychiatric events. These analyses, using a variety of methodological approaches and data sets, found no association between Accutane and certain psychiatric events.

Ultimately, in consultation with FDA, and in connection with a significant restructuring of Accutane labeling, we issued a revised patient brochure in May 2000 that specifically noted the rare cases of suicide attempts and suicide that have been reported in the Accutane patient population. In 2002, in consultation with FDA, we made a series of labeling changes, including adding similar precautionary labeling information regarding violent and aggressive behaviors. Information regarding this labeling change was also sent to physicians and pharmacists across the country.

We have also implemented precautionary measures relating to psychiatric events as part of our broader Accutane risk management program. The elements of this program include:

- A revised informed consent form is provided to all patients who may be prescribed Accutane. This form ensures that patients have been told and understand essential information. Notwithstanding the absence of proof of causation, the informed consent form clearly states that some patients have reported that they became depressed or developed serious mental problems, including suicidal ideation, while taking Accutane, and that some people have ended their lives. This informed consent document is signed and dated by both the prescriber and the patient. For minors, a parent or guardian must sign the form and consent to treatment. Only a handful of pharmaceutical products have implemented a broad, mandatory requirement of this type.
- An Accutane Medication Guide developed by FDA in consultation with Roche is also dispensed with each prescription. This Medication Guide serves as a reminder of the proper use of the drug, its risks, and some warning signs to be aware of during treatment. In addition to being glued into the product package, since January 25, 2001, pharmacists dispensing Accutane have also provided every patient with this plain language summary of the product labeling. The Medication Guide specifically states as follows:

  Mental problems and suicide. Some patients, while taking Accutane or soon after stopping Accutane, have become depressed or developed other serious mental problems. Signs of these problems include feelings of sadness, irritability, unusual tiredness, trouble concentrating, and loss of appetite. Some patients taking Accutane have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people ended their own lives. There were reports that some of these people did not appear depressed. No one knows if Accutane caused these behaviors or if they would have happened even if the person did not take Accutane."

The revised informed consent and Medication Guide went to over 350,000 physicians, 130,000 pharmacists and 55,000 pharmacies.

- For many young people, physicians treating acne are one of the few health care professionals they see on a regular basis. Thus, consistent with the recommendations of the Surgeon General, we have created a unique brochure intended to educate physicians on recognizing the signs of depression and suicidal ideation, and intervening before a tragedy occurs. We believe this brochure will have benefits well beyond the isotretinoin patient population.
- Finally, through an unrestricted grant, we funded a major National Mental Health Awareness Campaign program focusing on psychiatric concerns, and suicide specifically, in the teenage population. This general public health program was designed to have broad benefits in helping teenagers overcome the unwarranted stigma associated with mental health problems so they seek prompt medical attention.

Overall, the steps we have taken to address the psychiatric events in the Accutane patient population are highly precautionary and unprecedented in scope.

As noted, we have also instituted the S.M.A.R.T. program to further address Accutane teratogenicity concerns. Although many elements of S.M.A.R.T. are intended for patients, the role of the physician and pharmacist remain critical to success under this program. Under the S.M.A.R.T. program—

- Detailed informed consent language for female patients confirms awareness of the risks of pregnancy during treatment with Accutane, the necessity of avoiding pregnancy before beginning therapy, during treatment, and for one month after treatment, and the recommendation that two effective forms of contraception be used simultaneously.
- Prescribers must study the S.M.A.R.T. "Guide to Best Practices" provided by Roche, and then sign and return to Roche a Letter of Understanding, certifying their knowledge of Severe Recalcitrant Nodular Acne and of measures to be taken to minimize fetal exposures to Accutane. We have also developed and presented a Continuing Medical Education (CME) course throughout the country for prescribers that includes specific, practical information about pregnancy prevention.
- Prescribers receive special self-adhesive Accutane Qualification Stickers. All prescriptions for Accutane should have the special yellow sticker attached to the prescriber's regular prescription form. This sticker indicates to the pharmacist that the patient is "qualified" according to the new package insert, which means that the female patient has had negative pregnancy tests, has committed to the use of two safe and effective forms of contraception, has signed her informed consent, and has been offered the opportunity to join the Accutane Survey as well as receive education and counseling about pregnancy prevention. The pregnancy test is repeated every month throughout the Accutane treatment course.
- All female patients must have two negative urine or serum pregnancy tests, provided by Roche at no cost, before the initial Accutane prescription is written, and for each month of therapy they must have a negative pregnancy test result before receiving their next prescription, regardless of whether they are sexually active. Female patients who are, or might become, sexually active must also select and use two forms of effective contraception simultaneously for at least one month prior to initiation of Accutane therapy, during therapy, and for one month following discontinuation of therapy. As noted, women must sign a Patient Information/Consent form about Accutane and birth defects, as well as the general Consent Form addressing other risks and drug information that all Accutane patients—including men—sign.
- Female patients are given the opportunity to enroll in the Accutane Survey. This confidential, voluntary survey has been in place since 1989 and is designed to collect data to help Roche and FDA determine if the pregnancy prevention program is effective. We relied upon this survey information to build the current S.M.A.R.T. program, and patients who agree to participate in the survey make a major contribution to the public health by helping to identify aspects of S.M.A.R.T. that could be improved.
- Pharmacists dispense Accutane only upon presentation of a prescription with the special Accutane Qualification Sticker. Pharmacists dispense a maximum 30-day supply of Accutane, fill prescriptions within seven days from the date of "qualification," and provide a Medication Guide for patients with each Accutane prescription. Requests for refills (*i.e.*, more Accutane without a new prescription) and electronic and phoned-in prescriptions cannot be filled.
- To measure the effectiveness of the S.M.A.R.T. program, Roche is using several independent outcome assessment approaches. These include the Accutane Survey and an independent audit of pharmacies to assess the proper use and

verification of Accutane Qualification Stickers by prescribers and pharmacists. Prescribers, patients, and pharmacists all must participate fully in these critically important measures to ensure that fetal exposure to Accutane does not occur.

- The Accutane package also continues to serve as a risk management tool, including a blister package bearing written and symbolic pregnancy warnings.
- We also provide toll-free telephone counseling in thirteen languages, as well as a free referral to a health care professional who can provide contraceptive and pregnancy counseling. The S.M.A.R.T. program materials also include informational videos and story boards. We have structured our risk management implementation efforts to ensure that we have the most current information—specific to Roche—on progress toward our goals. We believe it is equally important for generic isotretinoin programs to produce data permitting identification of subtle but important differences between risk management programs.

We share the Subcommittee's concerns regarding unlawful Internet prescribing and dispensing. Such practices, while representing what we believe is an extremely small number of isotretinoin prescriptions, could endanger patients by confounding risk management efforts. Thus, isotretinoin labeling specifically precludes electronic transmittal of prescriptions, and over the last several years we have notified FDA of a number of websites purporting to offer Accutane. We recently submitted to the Agency information on Accutane from a more comprehensive Internet survey, and we strongly support vigorous enforcement action against such sites by FDA, the states and foreign health authorities. To this end, Roche will continue to monitor Internet prescribing of Accutane and will alert FDA of activity.

Finally, I would like to note that Roche has not engaged in direct-to-consumer advertising that specifically mentions or promotes the Accutane brand. We have engaged in non-branded educational efforts that focused on dispelling acne myths. Few public resources are available for acne education, and we believe such messages play an important role in helping parents and patients understand the causes of acne and the existence of effective dermatological treatments.

CONCLUSION

The issues I have addressed are complex, and I would like to close by emphasizing some important points for the Subcommittee—

- First, we are extremely proud of the dramatic positive benefits provided to patients over this medication's 20-year history.
- Second, as is the case with any prescription medication, every stakeholder in pharmaceutical treatment plays an important role in ensuring safety and efficacy. We need the active involvement of physicians, pharmacists, patients and their families to ensure the safe and effective use of isotretinoin.
- Third, we have acted in a responsible manner by adopting precautionary measures to communicate psychiatric information to prescribers and patients, and we have engaged in a very significant scientific effort to address this extremely difficult issue.
- Finally, we have also acted responsibly in addressing the risks known to be associated with isotretinoin, including its teratogenicity. Although we constantly seek improvement, our risk management program is highly innovative and a model for other drug products.

I fully recognize the depth of this Subcommittee's interest in Accutane, and hope that today's hearing clarifies many of the issues that have been raised. I know that our common goal is to ensure that Accutane is used safely and effectively.

Thank you for the opportunity to present our views on this issue, and I look forward to your questions.

Mr. GREENWOOD. Thank you, Mr. Abercrombie. And as the photos that you've displayed there indicate and as the testimony has demonstrated all day, this is indeed a powerful substance, powerfully capable of powerfully good results and tragically awful results.

Let me ask you a question about how your company markets this product in Mexico. I am told that you can obtain Accutane over the counter in Mexico without a prescription. Is that true?

Mr. ABERCROMBIE. Mr. Chairman, that is not my understanding. My understanding is that in Mexico, Accutane requires a prescrip-

tion from either an internist or a dermatologist and cannot be purchased by simply walking into a pharmacy.

Mr. GREENWOOD. Mexican pharmacies are not required to have a university educated pharmacist on staff. There are no licensing requirements for pharmacists in Mexico, nor are there continuing education requirements.

And let me ask you the question this way. It's pretty evident that action is available on the Internet. I was on the Internet last night looking at sites around the world where it appeared that Accutane was available. It is—there's a good body of evidence that indicates that Accutane is being brought across the border from Mexico. What is your company doing to try to prevent access to this powerful drug, particularly to potentially pregnant young females?

Mr. ABERCROMBIE. Congressman, we ensure that we sell Accutane in the U.S., and whatever country my company operates in, strictly to only licensed distributors to ensure that it is distributed——

Mr. GREENWOOD. There is no licensing of pharmacists in Mexico, so what is the standard that your company applies in Mexico?

Mr. ABERCROMBIE. Sir, I am—I am not responsible for Mexico. I'm not intimately familiar with the registration requirements of pharmacists there. I do know that we abide by the spirit in the law of all Mexican distribution policies, and as I said, it is my understanding that a prescription is required for distribution or prescribing of this product.

Mr. GREENWOOD. Why don't you just tell us generally what corporate security measures you use to prevent diversion of the product into illicit channels where it could easily fall into the hands of young females and males who have not been advised as to its potential risks.

Mr. ABERCROMBIE. Again, sir, we make sure that any wholesalers, distributors, pharmacists, who we sell Accutane to are fully licensed in accordance with both Federal and State laws and regulations.

Mr. GREENWOOD. How do you know it becomes—how does a Web site—how does a supplier in Australia who will ship Accutane into this country without a prescription, where do these people get their Accutane?

Mr. ABERCROMBIE. Congressman, I do not know. You asked earlier. I can tell you that whenever we are made aware of any distribution that is illegal, unlawful, we immediately, as we did recently with the FDA, turn that over to the appropriate authorities.

Mr. GREENWOOD. Well, let me ask you this, though. That's well and good, but does your company itself—I would think if I had a—for no other reasons than legal liability, if I could go on the Internet, as you could today, and see the number of Web sites that market Accutane without anything near the kind of precautions that are necessary, that I would want to do more than simply refer this to the FDA; that I would want a company the size of Hoffmann-LaRoche to be—to appoint its own resources, financial and personnel, to scramble, to figure out how to prevent this thing from happening. Is the company engaged in that kind of intensive effort, given the potential consequences?

Mr. ABERCROMBIE. Let me be clear, sir. In no way do we endorse Internet prescribing of Accutane. It's strictly prohibited in the FDA-approved labeling. We constantly monitor, given our expertise, availability of our product. Whenever we learn about it being available inappropriately, we immediately contact the appropriate authorities. We do not endorse, support in any way——

Mr. GREENWOOD. Of course you don't endorse the illegal distribution of your product. But I'm asking you—there's a long way between not endorsing it and vigorously going after these forms of distribution. For instance, have you talked to Federal Express or any of the other carriers that bring this product—these products into this country—to say, look, there's a—we've discovered that there's a facility in Thailand or there's a facility in Australia or there's a facility in Canada that is shipping our product illegally into this country, and we want you to be aware of that and we want you to work with us to stop picking up these shipments?

Mr. ABERCROMBIE. Again, sir, we are not an enforcement agency, but I can assure you that when we are made aware through our security department of instances of the type that you mention, whether it's through Federal Express or any other means of distribution, our security personnel work with hand in hand and provide all the information we have available to the appropriate authorities.

Mr. GREENWOOD. Well, I understand that. We had a hearing last year on counterfeit drugs, and we had testimony from a variety of pharmaceutical companies who talked to us about how—their persistent efforts to prevent the importation of counterfeit drugs, improperly labeled drugs into this country, and I would like you—I'm not expecting you to necessarily know all of this from memory right now, but I would like you to submit to this committee a response to these questions that I'm asking you about what efforts that your corporation has engaged in, both on the Internet side of things and the importation across the border from Mexico. If you would put that in writing to us.

[The information referred to appears at the end of the hearing.]

Mr. GREENWOOD. Let me ask you a question. You've been here throughout the hearing for the last nearly 6 hours and you've heard a lot of discussion about a voluntary registry. You're well aware that the FDA has—is considering a backup plan if the voluntary registry doesn't meet the metrics that—as set forward. And you've heard the discussion about whether or not that such a registry would simply squeeze the balloon and have—enlarge the access through the black markets. And it's my view that if you're going to prevent the tragedies—let's just talk about the birth defects—that you're going to have to—really the multifaceted approach that attacks the problem from a variety of sides.

What is your view with regard to a mandatory registry, and why do you think that would or would not improve things?

Mr. ABERCROMBIE. Sir, given the information we have available today, given our company's vast experience in being at the leading edge of developing pharmaceutical risk management programs—put the first program in place in the late eighties—we believe that all of the measures we have put in place with the SMART program as a voluntary program is the right thing to do at this time. And

as Dr. Woodcock said today, we developed that program fully in concert with the FDA, and we have established metrics by which we will judge the effectiveness of this program. It was just launched officially in April, and we will be looking to see if we are improving our goal—toward our goal of zero pregnancies while taking Accutane. At this point, sir——

Mr. GREENWOOD. I understand your statement that you believe that the voluntary registry is a superior approach to the mandatory registry. I'd like you to give us the whys and wherefores. What is it specifically that causes you to think that it is superior to a mandatory registry?

Mr. ABERCROMBIE. I will comment generally, sir, and then I'll ask my colleague Dr. Ackerman to elaborate.

The primary concern is the concern about patient confidentiality, and we believe that if we ask patients to register personal medical information in a registry linking their care to specific physicians, that it heightens the risk that they will not seek legitimate care, and, as you suggest, seek black market availability of this product.

Mr. GREENWOOD. And we've heard that expressed by Dr. Woodcock today, and as I asked her, I would ask you: Upon what research does that conclusion—is that conclusion drawn? Is there data to support that? Is that a hunch? Is that based on similar experiences?

Mr. ABERCROMBIE. Sir, to the best of my knowledge, that's our best judgment working in concert with the FDA.

Dr. Ackerman.

Ms. ACKERMAN. It is actually in our best judgment. As you mentioned, any system has to cover all bases. The SMART program is very unique, because it adds the pharmacists to the mix. Now we have the woman working in concert with her dermatologist or prescriber in addition to her pharmacist. So in total we have a comprehensive system where all aspects of her care is taken care of. It's very important to note that in a mandatory system or a mandatory registry, you cannot control a woman's behavior every single day——

Mr. GREENWOOD. Well, what has the experience been in Europe in that regard where they do have a mandatory registry?

Ms. ACKERMAN. It's not the same type of mandatory registry which was described by steps, where a woman registers and provides her confidential information to the physician and the registry. In our case, we believe that the yellow sticker, which means that the woman had—the physician has attested to the fact that the woman has had a negative pregnancy test. She's using two safe and effective forms of contraception. She's signed her informed consent, meaning that she understands the teratogenic or birth defect risks, and she has been offered the opportunity to join the Accutane survey. That yellow sticker attests every month that she has complied with the system. Her physician has complied with the system——

Mr. GREENWOOD. My time is expired, but let me just ask you: Is there any evidence that there's been a black market that's arisen in the European experience?

Mr. ABERCROMBIE. Sir, I'm not aware of the European experience. I am responsible for North America.

Mr. GREENWOOD. Okay. Well, then I'm going to ask you, then, similarly if you would submit to this committee a written response as to what your—those who are responsible for the European market have observed with regard to the impacts of the registry, such as it is there, and whether or not it has resulted in adverse impacts and black market.

[The information referred to appears at the end of the hearing.]

Mr. GREENWOOD. My time has expired. The gentleman from Florida is recognized for 10 minutes.

Mr. DEUTSCH. Mr. Abercrombie, your company actually supplied the committee with a rough survey conducted by Roche of literally dozens of Internet sites reportedly selling Accutane, and the staff put together some additional sites yesterday from Mexico. Do you believe this is a problem?

Mr. ABERCROMBIE. Yes, sir. The inappropriate prescribing or distribution of any medication is a problem.

Mr. DEUTSCH. Now, I'm assuming that the sites are up because people are buying from them, and, again, this committee has spent a great deal of time in terms of purchases, you know, through the Internet, through our—basically through mail facilities around the country. If this is going on, I mean, how good a field does the SMART program have? Does it really—it's not working at all with anyone who's purchasing Accutane through an Internet site.

Mr. ABERCROMBIE. Sir, again, we do not condone, support, believe in, or think it is good medicine to buy or distribute Accutane over Internet sites. We only sell our product through regulated distribution channels, and when we're made aware that those sites exist, we inform the appropriate authorities.

Mr. DEUTSCH. Now, do you have—I mean, these are sites that your staff, again, has provided us with a number of the sites. Where would they be getting the drugs?

Mr. ABERCROMBIE. Sir, I have no idea how or where they're getting the drugs. I'm not familiar with those companies or Internet sites or how they conduct business.

Mr. DEUTSCH. Now, I mean, you mention obviously you have an enforcement internal division. Again, you're not an enforcement agency. I don't expect you to be, but you have a security apparatus inside the company. How aggressive are you in looking at where these companies are getting your product?

Mr. ABERCROMBIE. Again, sir, whenever our internal security folks, or by whatever means, whenever we're made aware of the inappropriate distribution of any of our products, we gather as much information as we possibly can but immediately involve the appropriate regulatory and enforcement authorities, and we cooperate fully.

Mr. DEUTSCH. Focusing, you know, in terms of the SMART program—and, again, I appreciate your desire, all—or our desire to get to that zero percent. What else—I mean, I'm looking at the practical side, 16, 17, 18-year-old girls, you know, both in terms of pregnancy tests and basically acknowledging or saying that they're using two forms of contraceptive. How can we really expect it to work? I mean, how can we even expect a zero result? And, again, you know, what the best evidence seems to be—and I'd be curious if you are going to refute it—that there are several thousand preg-

nancies that are occurring for uses of Accutane this year—last year, next year. I mean, what would your estimates be? Would you challenge those estimates?

Mr. ABERCROMBIE. Dr. Ackerman has those figures, sir.

Ms. ACKERMAN. To date and the numbers that were quoted previously, there are approximately 2,300 pregnancies from the 3 million exposures to women since the launch of the product.

Mr. DEUTSCH. Twenty-three hundred pregnancies, or that's deliveries?

Ms. ACKERMAN. Pregnancies.

Mr. DEUTSCH. What about Dr. Graham's number of 10,000, between—prior to 1990? You would refute that?

Ms. ACKERMAN. I think as Dr. Woodcock appropriately indicated, Dr. Graham's figures were estimations, and he used those estimations based on failure rates of single methods of contraception. In addition, he estimated those rates from a 1990 figure which he indicated that was previous to the pregnancy prevention program that was launched in 1989.

Our rates are data that we collected in two different ways, both through spontaneous adverse event reports to Hoffmann-LaRoche through either physicians or females or parents, perhaps, and through the Accutane survey which has been in effect since 1989.

Mr. DEUTSCH. So this year—I mean, again, all of us acknowledge a goal of zero—or this past year, which we're coming to a conclusion—I mean, what would your estimate be of the number of pregnancies with Accutane exposure this year?

Ms. ACKERMAN. Since we have full data for 2001, the number of pregnancies reported to Hoffmann-LaRoche through both of those methods, through spontaneous reports and through the Accutane survey, were 79. And, again, I think it's important to point out that since the launch of the pregnancy prevention program in 1989, through the launch of the SMART program in 2002, we have seen a dramatic decrease in the overall pregnancy rate. We went from approximately 4 in a thousand to 2.2 in a thousand. We have some preliminary indications from the SMART program indicating that we fully expect to have an even lower pregnancy rate, again to our goals of no woman should become pregnant while on Accutane and no woman should start Accutane while pregnant.

Mr. DEUTSCH. So the last year you have complete result—or complete data would be 2001, 78 pregnancies?

Ms. ACKERMAN. Seventy-nine. And because of the gestation period, it may not be——

Mr. DEUTSCH. Got it. So 78 and 79. Have you looked at each of those pregnancies? Why was there failure in those 79 cases?

Ms. ACKERMAN. Actually, we do look at those data quite closely, either through the spontaneous reports, more importantly through the results of the Accutane survey. The results in the Accutane survey provide us several markers of which we use that data to inform the SMART program. So we had data from 1989 moving forward——

Mr. DEUTSCH. If you can just give me some anecdotal—of 78 cases, there's not that many. What happened?

Ms. ACKERMAN. For example, women don't get necessarily pregnancy tests prior to starting Accutane. They didn't get two preg-

nancy tests, which is now on our label. They weren't practicing safe and effective forms of contraception. Again, as some of the other witnesses testified, that each woman is very unique. What we've tried to do is create a comprehensive program with a variety of different methods to ensure she doesn't get pregnant while on Accutane nor does she start Accutane while pregnant.

Mr. DEUTSCH. Okay. Why would the system have failed, then? I mean, has the physician failed the system? I mean, who failed the system in those cases?

Ms. ACKERMAN. In the 79 cases, again, each woman is very unique. A woman has to practice safe and effective forms of contraception for 1 month prior to therapy, during their therapy, and for 1 month after. What we can provide is a system of education of the physician, the pharmacist, the patient, videos, 1-800 numbers——

Mr. DEUTSCH. Let me jump—because, again, our time runs by very quickly. One of the statements that Dr. Woodcock mentioned—and, you know, all of us have looked at the package of the pregnant woman with a cross through her. You know, obviously when I see that, I can interpret it. But what she was saying is some women have interpreted that as a contraceptive. I mean—and then I've read through the directions; that really the directions are anyone who can't understand this shouldn't be taking the drug. I mean, do you have any evidence that that is in fact going on?

Mr. ABERCROMBIE. Congressman, I'll ask Dr. Ackerman to comment specifically, but I think Dr. Woodcock said that specific visual is not, by any means, all that we rely on to ensure that women are made well aware of the risks of Accutane. We have an informed consent form, and as a physician testified, we educate and encourage physicians to have a very open discussion about the risks of taking——

Mr. DEUTSCH. Let me just—as I see my time is running out, just a couple questions. I mean, what would your estimate be of the off-label use of Accutane?

Mr. ABERCROMBIE. Sir, we believe generally the vast majority of use is on-label. We believe physicians in America prescribe this product on-label.

Mr. DEUTSCH. So, again, the FDA—or Dr. Graham's estimate of 90 percent, I mean, you think that's just way out of the ballpark?

Mr. ABERCROMBIE. We do not agree with that estimate, no, sir.

Mr. DEUTSCH. I mean, 50 percent—I mean, the doctor from Cornell said that basically she's doing it 2 percent off-label. If you have FDA saying 90 percent off-label, then obviously there's a difference. In her practice—then at least one person at FDA is saying that that's his impression.

Mr. ABERCROMBIE. We believe that the vast majority of physicians in this country do not prescribe this product off-label. We have been obsessed since the launch of the product with promoting and educating physicians that it should be used only for severe, recalcitrant, nodular acne.

Mr. DEUTSCH. Let me ask two final questions. One is what about nondermatologists prescribing it? What's your opinion about that?

Mr. ABERCROMBIE. There are likely some nondermatologists prescribing. Any physician is licensed to prescribe Accutane. It's up to

the individual physician to determine if he or she is adequately informed and educated to use this product.

Mr. DEUTSCH. And my last question relates to the advertisements regarding acne. Now, I mean, we have copies of them. I mean, can you—I want to offer you the opportunity. What's the best—I mean, what is your corporate reason for doing that advertising?

Mr. ABERCROMBIE. Well, first of all, sir, at the moment we have no advertising for Accutane, and we have never——

Mr. DEUTSCH. I understand you're not——

Mr. ABERCROMBIE. We have never advertised Accutane, the drug, to patients. We have only sponsored disease awareness ads, and we have only advertised the product to physicians. And I believe that we have done so responsibly. The advertising we sponsored in the nineties directed to patients were to make patients with this severe debilitating condition aware that alternative treatments are available.

Mr. DEUTSCH. You know, again, when you say that, I hate to say this to you, but you're really questioning everything else you say, because the ads—and we have them somewhere up here—you know, this is not a severe case of acne. I mean, it's just—what you just said is not a truthful statement. I'm sorry. It's just not a truthful statement. This is not a severe case. It's not the pictures that you put up on the wall.

Mr. ABERCROMBIE. Sir, with all due respect, all of our ads undergo rigorous physician expert review to ensure that they depict strictly the indication approved by the Food and Drug Administration.

Mr. DEUTSCH. You're beyond the straight-face test. I'm sorry.

Mr. STEARNS [presiding]. The gentleman's time has expired. I'll start with my questions.

One question I should have asked the FDA, why they haven't they mandated that you do a study to determine why it causes depression in teenagers and why it affects young women or women that are pregnant? Have you done, since the—you're starting to get all this information. Have you done a definitized study? And can you tell me today why it affects teenagers and causes depression?

Mr. ABERCROMBIE. Well, sir, first of all, there is no evidence, no scientific evidence demonstrating causality. We have sponsored——

Mr. STEARNS. You're saying Accutane does not cause depression?

Mr. ABERCROMBIE. Sir, I'm saying that there are no scientific data demonstrating causality. We have sponsored a number of studies——

Mr. STEARNS. Let me stop you there. But your literature says, in effect, that women get pregnant, that there could be birth defects. Isn't that true?

Mr. ABERCROMBIE. Absolutely. We know——

Mr. STEARNS. Okay. So that's true. You are saying that you realize that the Accutane does cause birth defects in women who are pregnant. That's true. Right?

Mr. ABERCROMBIE. From its launch, Accutane has been known to——

Mr. STEARNS. But you're saying today, in your mind, there's no proof that it causes depression?

Mr. ABERCROMBIE. Sir, what I'm saying is that there are no——

Mr. STEARNS. Just yes or no. Just yes or no, does it cause depression or not, in your mind?

Mr. ABERCROMBIE. Sir, there are no scientific data demonstrating causality with depression.

Mr. STEARNS. Or suicide?

Mr. ABERCROMBIE. Or suicide.

Mr. STEARNS. Okay. In Tab 2 of the notebook you have, there's a document from Dr. Edward Lammer of the Center for Disease Control, and then there's one from—in which it reads, on July 25, 1983, Godfrey Oakley of BBB—which I think is the Birth Defects Branch—he basically says that your company was considering the drug to be about 100 percent effective—would 100 percent affect a woman with genetic defects, and that the implication was that Roche's recommendation was that any woman exposed to Accutane during pregnancy should get an abortion.

You know, the question is, is the Center for Disease Control—when they say that, is that correct that you would say today that if a young woman or a woman has Accutane in her blood or takes it, that she should get—and she gets pregnant, that she should have an abortion?

Mr. ABERCROMBIE. Absolutely not, Congressman. To my knowledge we have never, nor do we today, say that. Our obsession is to prevent pregnancies in the beginning. If they should occur, the decision as to what to do is very——

Mr. STEARNS. Dr. Burns, who's in this tab I think, who worked at Roche, that's what he had said.

Mr. ABERCROMBIE. Again, sir, I'm not familiar with Dr. Burns or this memo. It is my knowledge and understanding that we have not, nor do we today, ever tell a woman what to do if she becomes pregnant while taking Accutane. That——

Mr. STEARNS. So you're saying if a woman is pregnant, you would not advise the doctor that the woman go ahead with the delivery of the infant or not?

Mr. ABERCROMBIE. Sir, it is not our domain or responsibility or—it is not our job to tell patients and physicians what to do in very sensitive matters——

Mr. STEARNS. I understand. But just earlier you did indicate there could be birth defects and that your company recognizes that——

Mr. ABERCROMBIE. Of course. We know——

Mr. STEARNS. [continuing] and if that's true, then you probably don't know, and probably no one knows that if a woman is pregnant, whether it's going to be a 100 percent birth defect or 50 percent, because we have cases where children were born normal.

Mr. ABERCROMBIE. Sir, our obligation and one that we take seriously, is to make sure that patients and physicians are fully aware of the risks of birth defects and the possible consequences if a woman becomes pregnant, and then it's up to that patient and her physician to determine the best course of action.

Mr. STEARNS. The research in your company to determine why these birth directs occur, do you have this definitized? Have you done the research to determine why—Dr. Smith, can you tell us

today why there's probable cause for birth defects with Accutane? Can you tell us definitively why? E.

Mr. SMITH. Congressman, the studies have—that were performed prior to registration of this product in animal species—indicated that isotretinoin is a teratogen in these animal species, and we labeled it as that. And it was not until it was on the market that we saw demonstration of——

Mr. STEARNS. So your research initially before 1985 did not show it?

Mr. SMITH. No. Our research, prior to us filing for registration of the compound, showed in animal models that there were teratogenic effects.

Mr. STEARNS. Now, were there women during the clinical trials that had abortions, that got pregnant and had abortions?

Ms. ACKERMAN. There was no woman during the clinical trial that got pregnant, during the original NDA clinical trials.

Mr. STEARNS. Okay. Let me move to another subject, and that's dealing with—I understand a new generic drug is available, perhaps last week, I'm told, which might complicate the situation, because Amnesteem is a new generic drug, and it must have its own risk management and must—what will happen if a patient, perhaps, uses Accutane and then switches to the generic drug? How is that going to be tallied and made corroborative to what we're trying to understand?

Mr. ABERCROMBIE. Well, Congressman, we have been very open with the FDA that we have concerns about the process by which the sponsor companies and the FDA will evaluate the effectiveness of each company's risk management program in a multisource generic environment. The FDA has told us that they are confident they will be able to do this. We have posed a series of questions to the Agency reflecting our concerns, and to be honest, sir, we take our program very seriously and we're doing everything to demonstrate the efficacy of the SMART program, but it is unclear to us how the Agency will manage this in a multisource environment.

Mr. STEARNS. Is the generic drug similar to yours, almost identical?

Mr. ABERCROMBIE. Sir, it should be virtually identical in terms of bioequivalents.

Mr. STEARNS. Staff is pointing out that we have an FDA memo which is on Tab 12, which is contrary to what you just said, Mr. Abercrombie—or Dr. Ackerman.

"Accutane cannot safely be administered to women of childbearing age or potential, regardless of the setting in which it is used. This is clearly demonstrated by the occurrence of first trimester pregnancy exposures in 5 percent of women participating in the IND studies, despite intensive counseling, signed informed consent, and contraception. The use of Accutane cannot be rendered safe for women even by such a control setting."

So that's a little bit contrary to what you folks are saying, and this is from May 7, 1990. And that's Tab 12. I think what we're saying is there's pretty strong evidence that the government feels that genetic problems are created by Accutane in pregnant women, and it's conclusive and it's strong evidence.

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Mr. ABERCROMBIE. And, sir, we concur. There's definitive evidence that Accutane is a known teratogen, and from the beginning of its availability we have acted in concert with the FDA, acted responsibly to ensure that patients and physicians are made aware of the benefits and the risks of Accutane, including teratogenicity.

Mr. STEARNS. Let me just ask—my time is almost over—but is your company actually trying to study, on your own, ways to make the drug so it wouldn't cause birth defects?

Mr. ABERCROMBIE. Sir, we accept that isotretinoin is a teratogen, and I am not familiar with efforts to remove that from the drug. We think the drug is. We know it is. Our obsession has been and will continue to be to ensure that the drug is used safely and prescribed according to the FDA labeling and that pregnant women do not take this drug and are not prescribed this drug. That, sir, has been and will continue to be our obsession.

Mr. STUPAK. Thank you, Mr. Chairman.

Mr. Abercrombie, you've heard testimony all day about drugs being diverted from Mexico up here to the United States. We talked about Oxycontin, Accutane, or Roaccutane as it may be called in Mexico. And are you willing to promise this committee that you'll do—that you'll stop any shipments of Accutane or Roaccutane to Mexico?

Mr. ABERCROMBIE. Sir, I am willing to promise this committee that we will continue to act responsibly to——

Mr. STUPAK. Excuse me, sir. My question is, will you stop the shipments of Accutane and Roaccutane to Mexico? We had this issue. Another company, Purdue Pharma, actually did that with Oxycontin when it was brought to their attention. As a responsible corporate citizen they said, We will promise you we will not ship any Oxycontin to Mexico.

I'm asking for the same commitment; call it Accutane or Roaccutane, whether it comes out of Nutley, New Jersey or whether is comes out of Basel, Switzerland, will you promise this committee to protect our southern border—we don't have those diversions that we talked about all day—that you will stop Roche, Hoffmann-LaRoche, HLT Technologies, you will stop the shipment of Accutane and Roaccutane to Mexico like other companies have?

Mr. ABERCROMBIE. Congressman, I commit to you and the committee that we will take all available scientific evidence in every——

Mr. STUPAK. So that's a no?

Mr. ABERCROMBIE. No, sir. I'm telling you that we will continue to do——

Mr. STUPAK. Yes or no; will you stop the shipments? Mr. Abercrombie, I don't want to argue with you. I just want a yes or no answer to my question. Will you——

Mr. ABERCROMBIE. Sir, with all due respect, the answer is that we will continue in every market in which we answer—or market this drug—we will evaluate the benefits and the risks of the drug——

Mr. STUPAK. Right here, Mr. Abercrombie, here's a study from the CDC, 1999, out of California. Let me quote. "received and filled the isotretinoin prescription in Mexico." In Mexico, and they bring it back to the United States.

Mr. ABERCROMBIE. Congressman, Mexicans take this drug also. Mexicans have severe recalcitrant nodular acne. Sir, what we will do is everything within our power to make sure——

Mr. STUPAK. Are you going to use the SMART program in Mexico?

Mr. ABERCROMBIE. Sir, I'm not familiar with what the regulatory authorities——

Mr. STUPAK. I thought you said you were head of North American—for Accutane for Roche, that you're the head of North American operations. You don't know what the regulatory scheme is in Mexico?

Mr. ABERCROMBIE. Sir, I'm not responsible for Mexico.

Mr. STUPAK. What does North America include, then?

Mr. ABERCROMBIE. The United States and Canada.

Mr. STUPAK. Just the U.S. and Canada. Okay, let's move on.

Mr. ABERCROMBIE. Every affiliate—my company abides by the spirit and the law of the regulatory authorities, and that affiliate——

Mr. STUPAK. Purdue Pharma, we asked them to stop with the Oxycontin. They did it. They didn't give us this regulatory spirit and all this other good stuff you're giving us. They said, yes, we'll do it. They did it. We're asking the same commitment from Roche to be a responsible corporate party here.

Mr. ABERCROMBIE. And, sir, I do believe we are a responsible corporate party.

Mr. STUPAK. Let's move on. We're not going to go anywhere with this.

Mr. Abercrombie, when you have exchanges, a telephone conference with the FDA, do you exchange and share minutes of your telephone conference; FDA sends their review of that telephone conference; Roche sends their review of that telephone conference?

Mr. ABERCROMBIE. I'm not aware of the standard process for sharing minutes with the FDA. I can tell you that we are totally open and transparent with the FDA, providing information they need.

Mr. STUPAK. So when the FDA writes on November 27, 1994, "Memorandum of telephone conference," the sponsor, meaning you Roche, "indicate that they have completed a comprehensive review of the reported case depression and suicide associated with Accutane therapy. The sponsor concurred that there does appear to be a problem."

That would be a true statement, then, on their minutes?

Mr. ABERCROMBIE. Sir, I'm not familiar with——

Mr. STUPAK. Then you can't dispute that?

Mr. ABERCROMBIE. Again, sir, I'm not familiar with those minutes of the FDA.

Mr. STUPAK. Well, does there appear to be a problem with Accutane—depression, suicide ideation, psychosis and suicide?

Mr. ABERCROMBIE. Sir, there are no scientific——

Mr. STUPAK. I didn't ask you that. I asked you does there appear to be a problem? As these minutes say—as admitted by the sponsor—does there appear to be a problem, an association—I didn't ask for studies—an association to an Accutane use, depression, suicide ideation, psychosis and some suicide?

Mr. ABERCROMBIE. Again, sir, we base our conclusions on sound scientific principles and studies and data, and given all that we have done——

Mr. STUPAK. Mr. Abercrombie, let me move on.

The FDA has had discussions with Roche on the spontaneity of these suicides, have they not?

Mr. ABERCROMBIE. I assume they have.

Mr. STUPAK. When they have these discussions, you're not ever involved in these discussions about the safety and efficiency of Accutane here in the United States?

Mr. ABERCROMBIE. Sir, I am generally involved in my position, but I do not in my position routinely interact with the FDA. We have a regulatory department that works with the FDA.

Mr. STUPAK. Are you aware of the new labeling that's coming out on Accutane? This is the newest box that your company brought around here recently, and they're now going to provide labeling for violent and aggressive behavior associated with Accutane therapy in some patients. Are you familiar with that on your new labeling on Accutane?

Mr. ABERCROMBIE. I am familiar with this recent labeling change; yes, sir.

Mr. STUPAK. Okay. Thank you. Is it true that on March 5, 1998, FDA sent Roche a warning letter, stating that statements and suggestions in Roche promotional materials that Accutane therapy will minimize or improve a patient's psychosocial status, including depression, are false or misleading and promote an unapproved use? Is that correct?

Mr. ABERCROMBIE. I do recall that we received a letter from the FDA on that topic; yes, sir.

Mr. STUPAK. In fact, the FDA went on in that same letter—it was a warning letter dated March 5: This claim is particularly troublesome in light of information recently presented in a Dear Doctor letter, less than a week or so before, that Accutane may cause depression, psychosis and, rarely, suicide ideation, suicide attempts and suicide. Isn't that what is stated?

Mr. ABERCROMBIE. Sir, I don't have the letter in front of me. I presume that is correct.

Mr. STUPAK. Let me go to Exhibit 11. It's probably in that big book right there. It's an article written by Diana Hanel. She's a registered nurse who is the head nurse in the dermatology department of Gundersen Clinic in Lacrosse, Wisconsin. On page 29, or on the second page of that article, left-hand column, second paragraph says, and I quote, "Central nervous system symptoms need to be reported to the dermatologist at once. Unusual changes in your patient you should be aware of are insomnia, fatigue, headaches, double vision and decreased night vision. Depression has been reported, and this tends to be seen more in the adolescent patient. Parents or adults need to understand the possibility of Accutane-induced depression and not brush it off as age-related or stress-induced."

According to the FDA, that document was submitted by Roche.

Mr. ABERCROMBIE. Sir, I'm not aware of the document you reference. What I know, sir, is——

Mr. STUPAK. It's right there.

Mr. ABERCROMBIE. Yes, sir. I don't know the origin of this document. What I know, sir, is that even though there is no scientific evidence demonstrating causality, as I said in my opening testimony, we take this issue very seriously and warn as if there is.

Mr. STUPAK. Mr. Abercrombie, the DDMAC, as part of the FDA, requested that Roche submit the public information that Roche was providing to the public, the article—the article right in front of you, where it says patients or adults need to understand the possibility of Accutane-induced depression and not brush it off as age-related or stress-induced. That was submitted to Roche, to the FDA. The article is one of the documents that Roche submitted. You submitted that document. The information is based upon information from Roche. Isn't that correct?

Mr. ABERCROMBIE. Sir, again, I am not personally—I have not seen this document. I'm not familiar with its origin. What I know, sir, is that we have conducted epidemiological studies——

Mr. STUPAK. Okay. Let's move on. I don't want to get in all the studies. We'd be here forever.

Mr. Abercrombie, February 1998, it says here in the MedWatch, and I read it in my opening statement, "The FDA today is advising consumers and health care providers of new safety information regarding the prescription antiacne drug Accutane and isolated reports of depression, psychosis, and, rarely, suicide thoughts and actions. The FDA and the drug manufacturers are strengthening this label warning, even though it's difficult to identify the exact cause of the problem."

That was February 1998. You didn't put it on the label warning, this package, this package, until February 2000. Why on earth does it take almost 3 years, 2½ years, to change the label packaging when you're talking about things as depression, suicide ideation, psychosis and in some cases suicide? Why does it take 2½ years?

Mr. ABERCROMBIE. Sir, during that period of time, we—as we always have, we work with the FDA to use the best medical judgment available——

Mr. STUPAK. Sir, excuse me, but that was February 1998. June 1998, 4 months later, you revised the labeling on this package. This is my son's Accutane. You knew 4 months before. You promised the American people you were going to inform them. You revised your packaging, and you never changed it.

Mr. ABERCROMBIE. Again, sir——

Mr. STUPAK. Two years later before you finally did it. Why?

Mr. ABERCROMBIE. Again, sir, we work with the FDA to make a determination on what information is most appropriate for the physician to know explicitly——

Mr. STUPAK. What about us? What about the patients, their families? Are we just collateral damage in this big game you're playing?

Mr. ABERCROMBIE. Not at all, sir. At any given point in time, at this time even today, we work with the FDA to make a judgment about what is appropriate for physicians to be told and what patients should be told.

Mr. STUPAK. You know, Mr. Abercrombie, we had testimony from the head of Pharma. That's your drug lobbyists guys. They came

in. We were talking about PADUFA and how we expedite these things to the market and how we get these things here right away.

I asked him the same question that you're stalling on right here. I said, if you have a package that you have to get out, something as serious as depression, psychosis, suicide, suicide ideation, and you've got to change this package and you're going to revise it, how long should it take? Just a matter of weeks, Congressman. That's a very serious side effect. That should happen——

Mr. ABERCROMBIE. Absolutely.

Mr. STUPAK. So why does it take you 2½ years?

Mr. ABERCROMBIE. I understand your reference now. The time delay between 1998 and 2000 was not a delay in getting a package out. At the time we made the physician labeling change in 1998, we did not change the patient inserted brochure.

Mr. STUPAK. You changed this. You changed this, the one thing, the one thing that the patient and their families get. You changed it 4 months later and you still couldn't put that warning on there.

Mr. ABERCROMBIE. Again, sir, we work with the FDA, and whenever a change is warranted in a package, we move swiftly, once those changes have been agreed upon, working with the FDA, and the timing of what is in a patient package circular and what is in a prescriber's package circular may differ, sir. And these are always——

Mr. STUPAK. These aren't patient package circulars. This is the real thing, and this is the package they get. I'm not talking about Dear Dr. Larrys. I'm not talking about the little inserts you may put in there. I'm talking about the package.

Mr. ABERCROMBIE. Yes, sir. But what is given to the patient with the package has and may differ from what is offered to the physician. And as I said, sir, we work with the FDA——

Mr. STUPAK. Let's go to an earlier e-mail that was sent out of—Cynthia DaNella. Do you know Cynthia DaNella—from Nutley, New Jersey it looks like?

Mr. ABERCROMBIE. Yes, sir. I do. She is our head of regulatory affairs.

Mr. STUPAK. October 30, 2001. Please try to celebrate the following.

You're celebrating now because you defeated the registry that was supposed to be in place, that the advisory committee recommended that on October 6, 2000, you received a letter from the FDA saying we're going to implement this registry; we're going to require certification of the doctors who prescribe it, and you indicated that it was time to celebrate because it was defeated. And one of the things, according to your documents, that are found in our files, one of the things you celebrated was the fact there was no registry because—here's your documents right here. Your successes, because it's no psychiatric registry. You view this more as a registry for psychiatric as opposed to teratogenic effects of Accutane, do you not?

Mr. ABERCROMBIE. Sir, today I was just made aware of this e-mail, and I can tell you while I'm not aware—I was not aware that it was sent—I can tell you that my company worked hard for months with the FDA to develop what we believe is a state-of-the-art pregnancy prevention program.

Mr. STUPAK. You're celebrating the fact there is no registry and no psychiatric registry. This is the successes right out of your handbooks that you use.

Mr. ABERCROMBIE. Sir, I'm not aware of that document. I'm referring to Dr. DaNella's e-mail where I say we worked very hard to make sure we have the best possible program out, sir, and this own e-mail also celebrates success in getting physician education into the label.

Mr. STUPAK. Dr. Smith, you indicated in response to the chairman's question—you were talking about the research; we were talking about the animal studies and the teratogenic effect that Accutane had. And if I understood you correctly, you said that it would show in animals but would not necessarily show in humans. Is that correct?

Mr. SMITH. No, sir; that's not correct. My statement was that the studies that we did prior to registration were in animal models, and we did not see a teratogenic effect until after the product was introduced into the market.

Mr. STUPAK. So you saw it in the animal models but you didn't see the effect, until it was made available to the general public, that it would occur in humans. Right?

Mr. SMITH. Correct.

Mr. STUPAK. You saw the teratogenic effect in animals, but you said, we don't believe it will happen in humans?

Mr. ABERCROMBIE. Not at all, sir. It was warned in the labeling from the beginning. Accutane had the strictest warning available, a category X warning——

Mr. STUPAK. Dr. Smith, explain that statement about how you have your animal studies but you didn't see—thought you'd see it in the humans. Explain that to us.

Mr. SMITH. Yes, Congressman. We never do studies to determine teratogenic effects in humans. We do animal studies. That's indicated there. And so since that's a potential, we had the most severe label to indicate that there is a danger in humans that they would have that effect, and unfortunately we subsequently have seen that effect in humans.

Mr. STUPAK. In 1981 before you were approved for Accutane, you also did a study on mice and what effect isotretinoin or your Accutane may have on the central nervous system. And in mice in particular, there were some effects on the gross behavior. And that was by a Doctor Holmes, I believe it was. Correct?

Mr. SMITH. Congressman, I believe you're referring to work that was performed in their England offices. That particular test is called the Irwin Profile. It's in mice. Mice were dosed with it. And then there's a subjective measure, and there's a series of other tests that look for drug interaction.

Mr. STUPAK. Sure, but the one about the central nervous system, you looked at mice, and in that study they found there was increased irritability, loss of grip, increased touch response and hyperactivity of these mice. And they said, however, we won't believe that that will happen in human beings. But they did see that increase with the use of isotretinoin, did they not?

Mr. SMITH. That is what is reported in that study, but one has to keep in mind the type of study that it is.

Mr. STUPAK. Sure. You can downplay it if you want. But let me ask you this: Why wasn't this study, then, submitted with your original application to get Accutane approved?

Mr. SMITH. That is a very good question, Congressman. I do not know why it was not submitted at that time.

Mr. STUPAK. In fact, Dr. Smith, it should have been required, should it not? It should have been submitted?

Mr. SMITH. Under the regulations at the time, it should have been submitted.

Mr. STUPAK. And through the committee's investigation, we found out about this, and you finally submitted it in January 2002, some 20 years later. Correct?

Mr. SMITH. I do not know the exact date that it was submitted.

Mr. STUPAK. Mr. Smith or Mr. Abercrombie, whoever can make this commitment, will you provide to this committee all of the documents, all of the reports, all of the studies that went into the initial application for isotretinoin, or Accutane, with your application? Whether you've just simply forgot about them 20 years ago or not, will you submit all of them to us? We're not asking for a lot of data. You do a summary report. We want the summary reports. Will you do that for us?

Mr. ABERCROMBIE. Yes, sir, we will.

Mr. STUPAK. You will do that.

[The information referred to appears at the end of the hearing.]

Mr. STUPAK. All right. Did you try to market Accutane back in 1971? Were there some discussions on whether or not you would market Accutane in 1971?

Mr. ABERCROMBIE. Congressman, I'm unaware of any discussions about Accutane in 1971.

Mr. STUPAK. If Roche did that, would you then—you want me to wrap it up there, Mr. Chairman?

Mr. STEARNS. I'd suggest to the gentleman how about—the question I would ask the gentleman, how much more time does he need?

Mr. STUPAK. Well, I would like all day, but I'm sure the chairman will not give that to me, so let me just wrap it up with this. 1997, French authorities changed their labeling. They made you put on the box that Accutane was causing attempted suicide. You're required by law to notify the FDA. Roche never did that because that was pertinent new safety information. Is that correct, you never notified the FDA?

Mr. ABERCROMBIE. No, sir, I do not believe that is correct. At the same time the French authorities were changing the label in France, the FDA in the U.S. had available to them, through us, the same exact data; and at that very same time, we were in discussions with the FDA about a similar labeling change in the U.S.

Mr. STUPAK. But you were supposed to notify them of it, and you never notified them, correct, in 1997? Even if the FDA was looking at it, you never notified them, correct?

Mr. SMITH. Congressman, there's no regulatory requirement for us to have submitted that data. We now have——

Mr. STUPAK. Well, I think under section 314 of the Federal Food, Drug and Cosmetic Act, any pertinent new information, no matter where it occurs, you have to notify them.

Mr. ABERCROMBIE. And Congressman Stupak, as I said, at that same time, FDA had the same data that led the French authorities to change their label. So they were available——

Mr. STUPAK. According to the FDA and the discussions they had with this committee, they do not know why the French changed the authority. They've asked for the information. They've asked for the raw data. It's never been provided.

Let me show you another letter. This is from an FDA e-mail: We've received confirmation from the Medical Control Agency, MCA, in the UK, England, that neither Roche nor the French regulatory authorities notified the MCA about changes to the product information for Roaccutane in France.

There's a letter here from MCA saying, we were not notified by Roche of a change in Roaccutane about the suicides. So the MCA is wrong; the French is wrong?

Mr. ABERCROMBIE. No, sir. What I'm saying is I'm not aware of when the exact labeling change that occurred in France was told to the FDA. What I do know is——

Mr. STUPAK. The point is that you never told——

Mr. ABERCROMBIE. No, sir. The data that the French authorities used to make a decision about the labeling was fully available to the FDA. The data was fully available to the FDA at the time of the French authorities' labeling change, and we were in fact in discussions with the FDA about a similar labeling change in the U.S. at that exact time.

Mr. STUPAK. Mr. Chairman, thank you.

Mr. STEARNS. I thank the gentleman. The gentleman from Ohio is recognized for 10 minutes.

Mr. STRICKLAND. Thank you, Mr. Chairman. And if Mr. Stupak would like, I at the end of my questioning would be happy to yield whatever time I have left to him.

I'm sitting here a little puzzled at the use of this term "depression" when it comes to suicides that are perhaps related to this drug. I know of no clinical concept of depression that has an instantaneous onset, and what we've heard described are people who are emotionally, psychologically healthy, with none of the clinical signs of depression, spontaneously doing something to themselves. And so I'm wondering if we're dealing with something here other than depression and that we ought to recognize that. Is it possible that this medication has an effect, an action, that is the result—that results in spontaneous, impulsive self-destructive behavior that is different from that which occurs from a clinical depression?

Without a doubt, teenage suicide in this country is a huge problem, and correlation is not necessarily causation. But are we looking at something here, at a phenomenon that is different than self-destructive behavior coming from depression? As I've listened to this testimony today, this is the one thing that has kind of gnawed at me, because as these young people have been described to us, they have not been depressed, using any clinical standard that we normally would use to diagnosis depression, and yet they have engaged in behaviors that seem to be unexplainable—inexplicable. And the question that I have in my mind: Is that spontaneous impulsive behavior the result of some action coming from this drug? And I think that requires a deeper look and further research.

And the pictures that were put on the screen are compelling. I'm sympathetic, as I think many of us are, with young people who may be experiencing those problems and who may be in need of this medication, but obviously there is greater need for more information.

I'm going to move away from that, though, for just a few moments. In 1996, Dr. Shepherd, who was with the College of Pharmacy at the University of Texas, completed a study which he entitled "The Examination of the Type of Pharmaceutical Products Being Declared by U.S. Residents Upon Returning to the U.S. From Mexico at the Laredo, Texas Border Crossing." And this is what he found in his study——

Mr. STEARNS. Just a moment. Did you want to put something in the record?

Mr. STRICKLAND. If I could include this in the record, it is a letter from Mr. Dingell of this committee, dated September 29, 2000.

Mr. STEARNS. Okay. Unanimous consent, we'll just put it in the record.

Mr. STRICKLAND. What that study found was that there was an average of 2.48 drug products listed on each claim form, those coming into the country. The top 15 drug products listed by people declaring a product was as follows: First, Valium and second, Rohypnol. And then going on later in this letter which was sent to the FDA, on average, 11,000 Valium tablets were being declared a day at this border crossing, and this extrapolates to approximately 4 million Valium tablets per year. Rohypnol, over 4,000 tablets were found to be declared each day, and this extrapolates to 1.5 million tablets a year coming into the U.S.

These two examples point to that a large number of pharmaceutical products are being allowed into the U.S., and when we realize that many of these products have tremendous abuse potential and some are not even approved by the FDA for use in the U.S., the seriousness of the issue becomes even more pronounced. And I would like—Mr. Abercrombie, your company is or was the maker of Rohypnol. Isn't that correct?

Mr. ABERCROMBIE. It is Roche who sold Rohypnol in Mexico. It has never been approved or marketed in the U.S.

Mr. STRICKLAND. Isn't it the case that Rohypnol was considered by the FDA to be a prohibited substance because it had no medical value, and for that reason it was not allowed into the U.S.?

Mr. ABERCROMBIE. Sir, I was not with the company at that time. It is my general understanding that the company did not seek FDA approval of Rohypnol for inducing sleep, for helping people to sleep, because we had a product in the U.S. called Dalmane. So to my knowledge, although I'm not familiar with this—it was before my time—we never sought approval with the FDA for Rohypnol.

Mr. STRICKLAND. Isn't it the case that Rohypnol is often referred to as the date rape drug, because it was one of the drugs that have been slipped into the drinks of unsuspecting women and then they would be abused?

Mr. ABERCROMBIE. Sir, it's my general understanding that there was a time when it was characterized just as you say. But later evidence suggested that there were other compounds that were

used much, much more frequently than Rohypnol for the reasons—for the purposes you cite.

Mr. STRICKLAND. Does Roche continue to make and distribute Rohypnol?

Mr. ABERCROMBIE. I do not know the answer to that. Again, we do not sell Rohypnol in North America. I am not aware if we continue to make or distribute it in Mexico.

Mr. STRICKLAND. That is a surprising answer. I——

Mr. ABERCROMBIE. Again, sir, I am responsible for our North American operations, not South America, below the U.S. border.

Mr. STRICKLAND. Well, sir, it's my understanding that Roche continued to make and distribute Rohypnol in Mexico even though it was considered a prohibited substance in the U.S.

Mr. ABERCROMBIE. Again, sir, in any country in the world, we market and distribute many, many different products, and they can differ dramatically from the products that we market here in the U.S. So it would not surprise me if what you say is true. But, again, we never sought FDA approval of Rohypnol here in the U.S.

Mr. STRICKLAND. You know, I fully understand that it is not your responsibility or the responsibility of your company to protect our borders. And I fully understand that we have got a problem that is related not only to Rohypnol, but to lots of drugs crossing our borders, substances which are perhaps legal in other countries but illegal here. I think—my purpose in asking these questions, quite frankly, was to try to get some sense of the values embraced by your company. And, you know, without wanting to be judgmental, I think that these kind of questions are relevant, and that although you are not responsible for Mexico, it would be very helpful for us as a committee to know more about the distribution of this drug and why it continues to be made available when at least our FDA has such a negative opinion of it.

Mr. ABERCROMBIE. I can assure you, sir, that as a company and as an industry, we are vehemently opposed to drug reimportation or importation of any kind. I have personally attempted to educate Members of Congress about the dangers of bringing drugs across the border from either Canada or Mexico, and that only drugs approved by and monitored by the FDA are appropriate for U.S. consumption. So I assure you, sir, my company and I wholeheartedly support and endorse the values you talk about. We are vehemently opposed to drug reimportation.

Mr. STRICKLAND. The fact is—I mean, I understand that, and I—you know, we may disagree about that particular issue, but the fact is that if a drug is deemed by the FDA to have no medical value—I mean, I assume that we cannot make decisions for every country on the face of the Earth, but, quite frankly, to me it raises questions about the values embraced by your company if you would continue to make and distribute drugs such as this available, especially in a country where the restrictions, the regulations are so much less than they are in this country. That causes me to——

Mr. ABERCROMBIE. Again, sir, we do not endorse the unauthorized or inappropriate use of any of our medications. In any country I am certain we work with regulatory authorities to ensure their drugs are labeled appropriately. And, you know, that is clearly a value this company endorses.

Mr. STRICKLAND. Mr. Chairman, I would like to yield to Mr. Stupak for whatever remaining time.

Mr. STEARNS [presiding]. The gentleman yields to Mr. Stupak. You are out of time. I think what we will do is by unanimous consent let Mr. Stupak have an additional 5 minutes. Would that work?

Mr. STRICKLAND. That would be fine. Thank you, Mr. Chairman.

Mr. STUPAK. Thank you. And thank you, Mr. Chairman.

Mr. Abercrombie, are you familiar with the three-volume report? This is only one of three. It's called The Dead, The Death, and the Dizzy; Accutane Manufactured by Hoffmann-LaRoche, an American illustration of marketing gone mad. Are you familiar with that?

Mr. ABERCROMBIE. No, sir, I am not.

Mr. STUPAK. Have you ever seen the report before?

Mr. ABERCROMBIE. No, sir, I have not.

Mr. STUPAK. Have you ever looked to see if it's in your files in Nutley, New Jersey?

Mr. ABERCROMBIE. As I said, sir, I am not aware of that report.

Mr. STUPAK. Okay. You know, in adverse event reports in the U.S., they go first to Palo Alto, California; do they not?

Mr. ABERCROMBIE. I'm not sure where they go first.

Dr. Ackerman?

Dr. ACKERMAN. No, they don't.

Mr. STUPAK. So they don't go—according to the FDA and the documents we've seen, they don't go to Palo Alto, California, first for a review, collected there, and then from there they go to England, and then from there they go to Basel, where then they are reviewed by a 16-member team, scientific team?

Ms. ACKERMAN. No, sir.

Mr. STUPAK. That's not true?

Ms. ACKERMAN. No, sir. That's a mischaracterization.

Mr. STUPAK. Pardon?

Ms. ACKERMAN. No, sir. That's a mischaracterization of how our adverse event reports come in. If they are reported in the United States, they will come into Nutley, New Jersey.

Mr. STUPAK. Okay. Do you have a facility in Palo Alto, California?

Ms. ACKERMAN. We have a research facility in Palo Alto, California.

Mr. STUPAK. Do they get a copy of the adverse event reports?

Ms. ACKERMAN. Not to my knowledge.

Mr. ABERCROMBIE. I don't know, sir.

Mr. STUPAK. Okay. In 1998, Roche received a warning letter from the FDA for late filing of thousands of reports; did it not?

Mr. ABERCROMBIE. Yes, we did.

Mr. STUPAK. Okay. And in 1997, you were investigated up in Nutley, New Jersey.

Mr. ABERCROMBIE. Congressman, I'm not sure it was thousands. I do not know the number. But we did receive a——

Mr. STUPAK. Two thousand from Australia; twelve hundred from France. I can go down the line if you want me to, but it was quite a few.

Mr. ABERCROMBIE. Again, I'm not familiar with what the number was.

Mr. STUPAK. Okay. So then you can't dispute my numbers either, then, if you are not familiar.

Well, let me take you this way. We have seen this one before. This is one-quarter of adverse event reports. The adverse event reports come in mostly from Roche, right? You provide most of the adverse event reports we see in the FDA files. You are the reporter.

Ms. ACKERMAN. We—individuals report in to Hoffmann-LaRoche.

Mr. STUPAK. Sure.

Ms. ACKERMAN. Be it physicians or patients. We then——

Mr. STUPAK. And if they are serious, you've got to do it within 15 days; if they are nonserious, you do it, what, once every 6 months is it?

Ms. ACKERMAN. Depending on the seriousness.

Mr. STUPAK. Sure.

Ms. ACKERMAN. Depending on the "labeledness."

Mr. STUPAK. Sure.

Ms. ACKERMAN. For Accutane, we have quarterly reports for pregnancy.

Mr. STUPAK. Right. Like suicide, that's not considered seriously anymore, because you put it on a label here, so we don't consider it serious anymore. So you don't have to do that until, what, once every 6 months?

Ms. ACKERMAN. We have a quarterly reporting system——

Mr. STUPAK. Quarterly.

Ms. ACKERMAN. [continuing] for all psychiatric events.

Mr. STUPAK. Okay. Well, here is a replication of your Accutane quarterly report, last quarter 1999; 2,381 adverse events, 313 were serious. Of the 313 that were serious, 89 were psychiatric, 24 self-injurious behavior, 5 attempted suicides, 5 completed suicides, 5 reports of psychosis, 93 of pregnancy unwanted. This is exactly how it was in there; we took it word for word. Forty-two abortions. Note that the abortions, however, were not included among the serious events, presumably because the dead fetus is not considered a patient.

Does Roche consider a dead fetus a patient?

Mr. ABERCROMBIE. Sir, I am——

Mr. STUPAK. Yes or no.

Mr. ABERCROMBIE. I don't know we consider a dead fetus. I do not know.

Mr. STUPAK. Okay. A child that did not come to full term, either a spontaneous, induced, or stillborn; is that a patient?

Mr. ABERCROMBIE. Sir, I'm not familiar with the terminology the company used.

Mr. STUPAK. Are you required—are you required in your adverse event reports to report abortions?

Ms. ACKERMAN. In our quarterly reports for pregnancies, we do report abortions.

Mr. STUPAK. Okay. Now, here is the real—what I want to ask you. This is your report. One death is included under the serious labeled listing. The comment says that the coroner's conclusion was: Unexplained death from adolescence.

Can you tell me what unexplained death from adolescence is?

Mr. ABERCROMBIE. Sir, if that was from the coroner's report, I presume we do not know what he meant other than the words on that report.

Mr. STUPAK. Have you ever known anyone to die of adolescence?

Mr. ABERCROMBIE. Sir, I'm not a coroner. I'm not an expert.

Mr. STUPAK. You are submitting these reports, so the FDA has used the word, so it could be a signal. Don't you think you should at least follow these reports up to see what's going on?

Ms. ACKERMAN. We do follow adverse events.

Mr. STUPAK. Did you follow up on this one about death by adolescence? I mean, my own curiosity would really pique me. I think I would want to call that reporter up.

Ms. ACKERMAN. I can't speak to that specific report.

Mr. STUPAK. Okay. Well, how many of these—let's take suicides. We know 167 that FDA has in their market. That represents about—I mean, in their reports. That's about 1 percent of the known. Do you follow up these suicides with these confounding factors?

Ms. ACKERMAN. First off, we don't believe it's 1 percent.

Mr. STUPAK. Well, I know you don't agree, but FDA testified it's 1 percent. I will give you tons of documents that show it's 1 percent, but we will disagree on the 1 percent. It could be as much as 10 percent, whatever. But even 10 percent at 200 suicides, now that's still, what, 2,000? But anyway, instead of arguing that point, have you ever followed these up?

Ms. ACKERMAN. We follow normal reports procedures that any pharmaceutical company follows for following adverse event reports.

Mr. STUPAK. So you get a suicide in. Do you go contact these people and say, jeez, sorry to hear about your son? Tell me a little bit about him. We want to see if there is some other factor here that might have happened. We know one thing, he was taken Accutane. Do you do that?

Mr. ABERCROMBIE. Sir, I—as Dr. Ackerman said, I'm sure we follow up on adverse event reports consistent with——

Mr. STUPAK. I'm asking, do you do that? Do you contact anyone? Do you contact schoolmates? Do you contact their priest, their pastor, the local police department, anyone, to see? See, you tell us there are no scientific reports here, no scientific evidence. We know about challenge and dechallenge with Accutane. It would seem to me, if we really wanted to know about this—and since your report says it's more than just teenage depression—that you would want to find out what these confounding factors are.

Mr. ABERCROMBIE. And, Congressman, I assure you, we want all available data, information.

Mr. STUPAK. I know you want to assure me, but I just want to know if you want to follow up with it. Do you follow up with these people? Do you really go out and study and see what's going on?

Mr. ABERCROMBIE. Again, sir, we follow up on adverse events reports.

Mr. STUPAK. How do you follow up then? Let me ask you that; if you follow up, how do you follow up then?

Ms. ACKERMAN. When a reporter calls into the company, regardless of the adverse event, we follow up with the reporter and gather

information about the patient, the patient's characteristics, the product they were on, according to the Med Watch. We can go down——

Mr. STUPAK. You just follow Med Watch. You don't go any outside that Med Watch, do you?

Ms. ACKERMAN. Well, we collect the information.

Mr. STUPAK. Outside the Med Watch. All you do is collect the information from the reporter. You go down the form and you check the marks and the boxes. That's all you do, right?

Ms. ACKERMAN. The Med Watch form has a lot of information.

Mr. STUPAK. Yeah, I know. It's one page. I'm very familiar with them. And you check some boxes, and there is a little line like that—to put some things in there if you want to do a narrative. But after that, after you fill out that Med Watch report, do you follow up? Do you do anything further with it? Do you contact the people?

Mr. ABERCROMBIE. We take every adverse event report seriously, Congressman.

Mr. STUPAK. I don't doubt you do.

Mr. ABERCROMBIE. We investigate——

Mr. STUPAK. All I want to know——

Mr. ABERCROMBIE. [continuing] every adverse event report——

Mr. STUPAK. After——

Mr. ABERCROMBIE. [continuing] to ensure that we have done our due diligence.

Mr. STUPAK. After the adverse event, do you follow it up other than doing the Med Guide? Yes or no. That's all I want to know.

Mr. ABERCROMBIE. Again, sir, I can tell you that we——

Mr. STUPAK. All right.

Mr. Abercrombie.—take every adverse event report very seriously and provide the information to the FDA.

Mr. STUPAK. Let me go to one more thing. It's called your annual report. It was just submitted to the FDA on 6/27/02. And Roche describes distribution of Accutane packages—I think it's on about page 7, should be in your book there. And it says that Accutane comes in a box with 10 individual packets, 10-pack—10, it says. And on there is a national drug code, a national stock number, dosage form, and packaging insert; isn't that right?

Mr. ABERCROMBIE. Sounds correct.

Mr. STUPAK. Okay. And then in there it goes on to say where they went, in the United States or Canada or wherever they might have gone; is that correct?

Mr. ABERCROMBIE. Sir, I'm not familiar with that report.

Mr. STUPAK. Okay. Well, let me ask you this. If you know the national drug code, the national stock number, the dosage form, package inserts, you even know if they're blister pack, non-blister-packed, you know all that stuff. You know where every box of 10-pack go in this country, don't you?

Mr. ABERCROMBIE. We keep track of the distribution of our products, yes, to wholesalers and to pharmacies.

Mr. STUPAK. Sure. You know everything. So what enforcement do you have to make sure they are not going to Mexico or on the Internet? What enforcement do you have?

Mr. ABERCROMBIE. Again, sir, we only sell or distribute Accutane or any of our products——

Mr. STUPAK. I know. You've said that any times.

Mr. ABERCROMBIE. [continuing] to licensed distributors and wholesalers.

Mr. STUPAK. What enforcement? You have all these numbers. You can track it. It's right in your annual report. Pages 7, 8, and 9. Look at it. It's right there. You can tell where every one of these things went. You have got all these numbers and codes on it. What do you do for enforcement? You wrote this to committee and the FDA and said you have 40 Websites out there that are selling Accutane that's going to lead to birth defects. They don't get the proper warnings from the dermatologists on suicide, all the rest of this stuff. You know where every packet goes. How come you can't go on the Internet and buy one of these packs and say, aha, according to our codes and numbers, this went to Smith Pharmacy up in northern Michigan; it shouldn't have, this is on the Internet. Let's stop and see where it went.

Mr. ABERCROMBIE. Whenever we discover drug conversion——

Mr. STUPAK. Have you ever done that?

Mr. ABERCROMBIE. [continuing] or inappropriate distribution, we are the first to go to the appropriate parties.

Mr. STUPAK. But have you done that? But have you done that? With those numbers, have you gone on those Websites, purchased it, and tracked it and done it to crack down on this so-called black or gray market, whatever you want to call it?

Mr. ABERCROMBIE. Again, Congressman, we—whenever we are made aware of the inappropriate distribution of our products, we gather all the information we can, and we make the appropriate authorities aware of that.

Mr. STUPAK. I'm looking at a Pharmacist Magazine. Are you familiar with the Pharmacist Magazine?

Mr. ABERCROMBIE. I'm sorry, sir?

Mr. STUPAK. The Pharmacist Magazine. Are you familiar with the Pharmacist Magazine?

Mr. ABERCROMBIE. I'm vaguely familiar with it, yes.

Mr. STUPAK. Okay. Credible article? Credible magazine?

Mr. ABERCROMBIE. I don't know. I'm not familiar enough to comment on its credibility.

Mr. STUPAK. Okay. Well, if they write that Mexican pharmacies—and I'm quoting now—are not required to have a university-educated pharmacist on staff unless the pharmacy stocks psychotropic medications—and Accutane is not a psychotropic medication. In this case, the university-educated pharmacist need not be present at all times. In fact, this pharmacist may be employed by an unlimited number of pharmacies. In addition, there are no licensing requirements in Mexico for pharmacists, nor are there any continuing education requirements.

Now, how can we justify continuing to sell Accutane or Roaccutane in Mexico based upon what you heard? They don't have the SMART program. They don't even have pharmacists distributing this.

Mr. ABERCROMBIE. Again, sir, we distribute Accutane in Mexico according to the rules and regulations of the local authorities. A

prescription is required, a prescription for—from a licensed internist or dermatologist.

Mr. STUPAK. Are there different birth defects for Mexican kids as opposed to U.S. Children?

Mr. ABERCROMBIE. No, sir. I did not say that. It's the same——

Mr. STUPAK. No. Thank you.

Mr. ABERCROMBIE. [continuing] serious medication in Mexico as it is in America.

Mr. STUPAK. Thank you, Mr. Chairman.

Mr. STEARNS. I thank the gentleman from Michigan. And let me say that we are very glad to give the extra time to the gentleman, and we also are glad we had the hearing.

And let me just say to Roche and to you individuals, I've been in a lot of hearings, and I think it's to you to be commended for coming. Lots of times people don't want to come because it's controversial. You came up here, you answered the questions, you stepped up to the plate, and I think we all have respect for you for doing that.

So, this is a democracy, and we have a job, and you have a job. From time to time products appear on the market that are practically indispensable to some consumers, yet they all contain some element of risk. I think the questions we have to ask ourselves, one, what do we consider adequate risk mitigation by the manufacturer? You have done a good job of talking about that in your literature. How far do we want the U.S. Government, the Federal Government, to intrude in the patient/physician relationship? And, three, armed with full disclosure of known risks, what is the role of free will and personal choice and personal responsibility in consuming this product?

These are very difficult questions. We appreciate again you and the other panels and witnesses for coming. And this——

Mr. DEUTSCH. Mr. Chairman.

Mr. STEARNS. Yes.

Mr. DEUTSCH. If I can also just conclude, thank you again. I thank not just this panel, which, you know, this is my eighth year on this committee. This has been as complete an informational hearing, I think, as I've seen in 8 years. And I appreciate your forthcoming and your seriousness in which you have taken preparation for being here and the testimony that you gave as well as the other panels. And I think, you know, this committee has a long tradition of—really, we pride ourselves. We think we are the best committee in Congress, and this subcommittee is the best subcommittee in the Congress and has a long history of that success. And this is really us doing what we do best.

And, again, I think all of us are aware of the effort that Mr. Stupak has done to bring this to our attention, and I don't think it's the end of the road in terms of this, and we look forward to working with you in the future on it. Thank you.

Mr. STEARNS. And I was also going to conclude by saying I want to thank the gentleman from Michigan for his perseverance in having this hearing, and we appreciate all the work he's done on this.

Mr. STUPAK. Mr. Chairman, before you adjourn, may I?

Again, thank you, and thank—we should really thank our staffs. We have spent hundreds of hours going through documents, and

our staffs have really done a great job in helping to prepare everyone for this hearing.

As this hearing has shown, we have many public policy concerns here with the FDA and how they control drugs. We brought up thalidomide, which is tightly controlled in this country. We have a similar teragenic called Accutane, which is not. We have seen, Mr. Chairman—we have spent a lot of time dealing with the devastating effects of OxyContin because the FDA is either unwilling or unable to control its use here in this country. The same with Accutane.

Mr. Chairman, we have talked about Rohypnol. We just mentioned about the Mexican border, drugs coming into this country from the Mexican border, and no lack of enforcement in that area.

This committee, we have spent a lot of time trying to deal with the explosion of sales of dangerous drugs over the Internet, and the FDA claims to be powerless to do anything about it. So, not only do we have the Accutane hearing, but from that we have 4 or 5 other public health concerns which incorporates Accutane in each and every one of those five.

So I think it's imperative for the U.S. Congress to act to protect the American public, and the bottom line does remain the safety of our children, and people, consumers who use these drugs. And I would ask that we continue these hearings. We mentioned early on that NIH has done some work in this area. We need their information. The Center for Disease Control during our investigation we found has done some extensive work. There is a lot more work to be done here on Accutane. I hope this is not the first but just the beginning of a series of issues that we should address from—like drugs like Accutane and how they are being used in this country.

Mr. STEARNS. I thank the gentleman, and I also want to thank the full committee chairman Mr. Tauzin, who made the final decision to have this hearing, and he is to be commended also.

With that, the subcommittee is adjourned.

[Whereupon, at 2:52 p.m., the subcommittee was adjourned.]

[Additional material submitted for the record follows:]