Statement
Congressman Bart Stupak
FDA Advisory Committee Hearing on iPLEDGE
August 1, 2007

I regret that I cannot appear in person to address the latest isotretinoin Pregnancy Prevention Program, iPLEDGE. As Chairman of the Energy and Commerce Committee's Oversight and Investigations Subcommittee, I am presently conducting a follow up hearing on New Orleans health care system after Hurricane Katrina. Thank you for allowing me the opportunity to submit these remarks for the record.

The history of Accutane (isotretinoin) is a continuing example of inadequate and ineffective risk management by the FDA. The severe birth, brain, heart, developmental defects and spontaneous abortions caused by Accutane have been known since its approval in 1982. After years of hearings by Advisory Committees and many failed risk management plans, the FDA's latest pregnancy prevention program to end birth defects, is called iPLEDGE.

More than one year has passed since iPLEDGE has been fully implemented. iPLEDGE's goal was to track and prevent pregnancy exposures to Accutane. The FDA's standard for evaluating previous pregnancy prevention programs and creating iPLEDGE was preventing all pregnancy exposures. The FDA reiterated their goal of "zero" pregnancy exposures two days ago when it publicly released the iPLEDGE national registry data.

In preparation for this Advisory Committee hearing, I contacted the FDA several times to review the year end report on iPLEDGE. I personally spoke with FDA Commissioner Andrew von Eschenbach on July 17, 2007 before my Oversight and Investigation hearing on food safety. While the Commissioner assured me that my most recent correspondence requesting iPLEDGE pregnancy and adverse events data would be provided, I have yet to receive any responsive answers. I doubt if this Advisory Committee will receive a complete review of the pregnancy exposures or adverse events caused by Accutane.

Unfortunately, my family tragedy has led me to review the history of Accutane. My investigation demonstrates the insidious nature of how the manufacture, Roche, and the FDA continue to mislead Advisory Committees and the American people. I have presented my findings to former HHS Secretary Tommy Thompson, FDA Commissioner Lester Crawford and Andrew von Eschenbach. My investigation can be found on my website www.house.gov/stupak under Accutane, entry #22.

Even though Accutane is nearly 100% teratogenicity, FDA has resisted efforts to restrict the use of Accutane in women of child bearing age. Yet, FDA claims it will pull the drug, Thalidomide, which is not widely used by women of child bearing age if there is one pregnancy exposure.

In 2000, the Advisory Committee recommended a mandatory registry of Accutane patients, prescribers, and pharmacists. FDA failed to require the mandatory registry but instead instituted the voluntary System to Manage Accutane Related Teratogencity (SMART) program. The SMART program failed to reduce pregnancy exposures, resulting in approximately 120 Accutane pregnancy exposures per year.

In January 2004, the FDA reconvened another Advisory Committee which again called for a mandatory registry. At this committee meeting, Roche and the Accutane generic manufactures presented a detailed risk management plan very similar to the final iPLEDGE program. In November 2004, the FDA announced the broad objectives of iPLEDGE, yet it did not finalize the iPLEDGE program and implementation deadlines until August 12, 2005.

Now, iPLEDGE's year end data reveals 122 women who were enrolled became pregnant in the past 12 months (10 women per month) while taking Accutane. This figure demonstrates that 122 pregnancies reported in the first year of iPLEDGE is the same as the number reported in the rejected SMART pregnancy prevention program. iPLEDGE tightened the restrictions on the patients, physicians and pharmacists that can provide Accutane. Still, the reported pregnancy exposures remain (122) even though fewer

women are using Accutane and its generics. While fewer women have access to Accutane, the exposure number (122) results in a greater percentage of pregnancy exposures under the iPLEDGE program than the SMART program. Thus, the iPLEDGE program has not achieved its goal of less Accutane pregnancy exposures and fails to meet the "zero" tolerance level sought by the FDA and the Advisory Committees.

Under iPLEDGE more than 305,000 patients registered to use the drug, including 137,415 women of childbearing age. The program states that 91,894 women received at least one prescription of Accutane. Of the 122 pregnancies, 78 were taking the drug when they became pregnant. Another 10 were already pregnant when they started Accutane, including two who had a prescriber falsify pregnancy test results. Another eight became pregnant in the month after stopping the drug. The iPLEDGE program couldn't provide details on the remaining pregnancies.

Most of the pregnancies appear due to women forgetting to stick with their birth control plan. Some 72 percent of the women had reported they were using birth control pills and a male condom, and 18 percent said they had been relying on abstinence. Two prescribers were kicked out of the registry for not following rules.

Of the 137,415 women who registered under iPLEDGE, two-thirds or 91,894 received Accutane. What happened to the 45,521 women who were denied Accutane? Do you honestly believe they just gave up trying to receive Accutane?

How many of the 137,415 had miscarriages or spontaneous abortions that were not reported?
How many of the 137,415 became pregnant and never reported the pregnancies?
How many of the 122 pregnancies were carried to full term?
How many of these 122 women with Accutane exposed pregnancies had an abortion?

While the FDA does not include abortions or miscarriages in their adverse event reports because "abortions…[are] not included among the 'serious' events because the dead fetus

is not considered a patient." These questions are very relevant to the success of the iPLEDGE program and should be answered by this Advisory Committee.

The iPLEDGE program has failed as has the SMART program and all other pregnancy prevention programs with Accutane and its generics. Therefore, Accutane and its generics should be pulled from the market to protect the American people.

Dr. David J. Graham of the FDA and "a number of medical groups including the Center for Disease Control (CDC)" called for the immediate removal of Accutane from the market in 1990 due to the horrendous birth defects caused by Accutane. Now, a generic version of Accutane, "Amnesteem" has been approved, and 13 additional companies have inquired about approval for an Accutane generic. These generics will make Accutane more readily available at lower prices. The birth defects caused by Accutane will only multiply as more and more Accutane is made available to sexually active young women of child-bearing years.

After more than 25 years of failing to develop a program to prevent Accutane exposed pregnancies, it is time to withdraw Accutane from the market to prevent hundreds, if not thousands, of birth defects and abortions per year in the United States. It is interesting to note that Dr. Ed Lammer, the leading researcher on Accutane exposed babies with birth defects, has stated that Europe only has a few Accutane exposed pregnancies. Even though Europe is comprised of different countries with different regulatory agencies, it has been successful in controlling the Accutane exposed pregnancies. European countries have implemented a process of "registration and certification of all patients and practitioners who prescribe Accutane." Europe suffered through the Thalidomide birth defects and the United States learned from the Thalidomide tragedy. The FDA will not allow one birth defect from Thalidomide or it will be pulled from the market. Yet with Accutane, the FDA knowingly accepts hundreds of Accutane exposed pregnancies per year (not counting abortions) resulting in serious birth defects.

It is difficult to understand how the FDA can knowingly allow hundreds of birth defects to occur per year and remain silent. The FDA's attempt to say nothing about Accutane birth defects is summed up in this email, "As for the 'needle', I think you and a lot of other non-dermatologists are in for a major shock IF the truth is ever exposed. I know that I am going to say is anecdote, but I personally know several derms whose patients have become pregnant on Accutane and NOT A SINGLE one reported it (except to their lawyer). And I don't even know that many derms, as I am not into the local derm scene!!

[.....] Roche and the AAD [American Academy of Dermatologists] are so adamantly opposed to collecting the real number of exposed fetuses for a reason and I personally do not believe them when they say it is concern for patients' privacy (we do NOT have to compromise that in any way to collect the data). I think it is a concern about the public outcry/outrage that will ensue if the truth comes out."

The FDA still refuses to confront two other issues relating to Accutane and its generics, off-label use and proper dosage.

Off-label usage is still not properly addressed by the FDA or iPLEDGE program. There is a high rate of off-label use of Accutane by individuals who do not have recalcitrant cystic acne, which is the only condition the drug is FDA approved to treat. Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, testified that, "A proportion of people treated with this drug in the last decade had mild acne and should've been treated with other drugs."

FDA says that it does not regulate the practice of medicine and therefore has no power to limit the prescription of this drug to the most severe acne. However, as with thalidomide, the FDA can limit the medical use of a product they regulate. The off-label use of Accutane is so prevalent, that some experts estimate that the improper use was close to 90% among women. Knowing the serious risks associated with this drug, why does the FDA continue to allow physicians to prescribe Accutane to patients who don't have recalcitrant cystic acne?

Roche applied for a patent on its new formula of Accutane. A patent based on a new formula would continue Roche's exclusive distribution and sale of Accutane. In studies submitted by Roche in support of the new formula [NF Accutane] application, the smaller dosage seems to clear up the skin with one half the dose of the current formula Accutane. The FDA has suggested that the current dosage of Accutane is too high and that Roche may be over dosing our children. The FDA did not approve this new formula.

The FDA also found that in the new formula Accutane studies there were 11 times more psychiatric reports than the current formula. If the new formula is one-half the dose with 11 times more psychiatric injuries, what does that say for the current higher dose formula? While the FDA points out this dichotomy, it fails to require Roche to provide further studies as to what is the proper dosage of Accutane to prevent psychiatric injuries. If you take into account the claims of Accutane patients who are being over dosed, the current formula has many more psychiatric injuries than are being reported to the FDA. The FDA stated in a letter to Roche that "Patients who received Accutane 1.0 mg/kg/day with food in the therapeutic study likely had approximately 240% higher exposure to isotretinoin than the subjects who received the new formula. The results suggest that the currently recommended dosing range for Accutane is too high". The recommended dosage for Accutane is too high! The FDA noted in its paper titled, Overview of Psychiatric Adverse Event Association with Isotretinoin, that "....there are a number of Accutane cases that also suggest a dose effect". The FDA has not aggressively pursued the dosage issue with Roche.

I stated that Roche cannot be trusted and will mislead this Advisory Committee as to birth defects and adverse events related to Accutane. As my investigation has shown by June of 2001, it appears that the FDA could no longer trust Roche officials to tell them the truth or to provide them with documentation. The lack of credibility and honesty on behalf of Roche in dealing with the FDA must have hit the boiling point when the Accutane Medical Review Officer wrote the following, "...I want to urge everyone on the ATF to resist any urge to buy-into the 'DDD' third metric proposed by HLR (Roche) yesterday. First, 'D' stands for Dishonest to prescribers: if we need to

know what is in their charts, then we need a mandatory patient follow-up system. I still cannot believe I heard them tell us how we would have to be careful what we revealed about the third metric so that the prescribers would not know what the audit was really about....Second 'D' stand for Dysfunctional: I am not epidemiologist, but it sure seems to me that doctors with pregnant patients on Accutane are HIGHLY unlikely to look at a survey that includes questions about Accutane risk management....Third 'D' stands for Disasterous: I can just see it now...when word got out as to what was going on – and it would get out – purposely leaked – documents (such as meeting minutes and approval letters) would appear showing that FDA demanded a third metric and FDA approved the 'DDD'. If anyone doubts this scenario, take a look at the letter they recently sent 'clarifying' their position on psychiatric issues. So...we need to put an end to this nonsense and either come up with a third metric or admit there isn't one and decide if were are still willing to go with a voluntary program." As we know, the FDA dropped the mandatory patient registry and certification of practitioners whose prescribe Accutane to prevent birth defects and psychiatric injuries. Once again, the FDA succumbed to Roche's pressure and the registry and certification was abandoned. Each time the Advisory Committee made recommendations to limit the distribution and use of Accutane, Roche pressured the FDA to protect and increase its sales of Accutane. In fact, the latest defeat of the mandatory registry and certification will benefit Roche by approximately $450 million. After all the devastation this drug has caused teens!!!! What special powers or charm does Roche have with the FDA? Many are starting to ask that question."

It is time for this committee on behalf of the American people to "start asking that question" what is the special power or charm that has allowed Roche to market Accutane which has caused death and devastation among our young people? Even when a patient registry and physician certification is recommended and endorsed by the FDA, Roche still escapes the plethora of information on birth defects and psychiatric injuries that a registry would produce on Accutane's biological and psychiatric effects on patients. It is time for this drug to be withdrawn from the market until this and all questions surrounding Accutane can be unequivocally answered. The American people and our children are not collateral damage in the scheme of corporate profits!

The documents and quotes referenced throughout my testimony can be found in the May 8, 2003 investigation posted on my website at www.house.gov/stupak under Accutane, entry #22.

Respectfully submitted,

Bart Stupak
Member of Congress