## SUPPLEMENTAL REVIEW OF ACCUTANE SAFETY ISSUES

### Background

During a time when it took years to receive a new drug approval, in 1982 the FDA approved Accutane within 9 months. The FDA has reviewed the original application for Accutane and has told committee members and staff that Accutane would never be approved by today's drug regulatory standards. The original new drug application trials showed that of the 523 people given Accutane in test studies only 89 were children and only 6 had a diagnosis of acne. The Accutane labeling is misleading "in stating that efficacy for severe nodular acne was established in clinical trials, given the extremely small sample size." Because Accutane has significant adverse effects associated with its use, it is to be prescribed only to patients with severe recalcitrant cystic acne. It is unknown whether these 6 children had severe recalcitrant cystic acne. **Exhibits #1, 2, and 3.**

Female Accutane users were warned about the possible birth defects associated with Accutane and there has never been any question about the teratogenicity of Accutane. The FDA's safety focus has been on the birth defects and not the psychiatric injuries caused by Accutane. In 1985, the first suicide attributed to Accutane was reported to the FDA. Dr. Huene, FDA Medical Officer, requested a review of the "number of CNS [central nervous system] effects reported in patients on Accutane. These have included severe headaches, seizures, tremors, disorientation, numbness and parethesias, blurred vision, memory loss and behavioral changes other than depression." **Exhibit #4.**

In 1987, Dr. Huene requested assistance with the "difficulty of reviewing the adverse reaction reports associated with Accutane therapy....well over 3,000 adverse reaction reports....(the number is probably approaching 4,000 by now)....we find it impossible to deal with this volume of information coherently...." without an additional full-time reviewer to "....adequately collate, review and make recommendations" regarding all the adverse reaction reports associated with Accutane. **Exhibit #5.**

In 1997, the French health authorities ordered HLR to change its package labeling to warn patients and families, stating that with Roaccutane (European name for Accutane) "In rare occasions, neuropsychological problems have been recorded (behavioural difficulties, depression, convulsion and suicide attempts)." HLR never notified the FDA of this safety labeling change although HLR was required to do so under the Federal Food, Drug and Cosmetic Act. **Exhibit #6.**

In 1998, the FDA conducted an audit of 31 attempted and completed suicides of Accutane users. The report found that in the 12 completed suicides, "For the majority, there was no antecedent history of depression and patients were not noted or known to be depressed prior to their suicide". After this report, FDA's Medical Review Officer for Accutane wrote in a Memo to FDA officials 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 use is associated with severe psychiatric disease in some patients". **Exhibit #7 and 8.**

The FDA required the manufacturer, HLR, to issue another "Dear Doctor" letter in February 1998 warning health care providers that the WARNINGS section of the Accutane package insert would be revised to read in bold letters that "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." This 1998 "Dear Doctor" is in addition to "Dear Doctor" letters health care providers received in 1985, 1986, 1997 and 1998. "Dear Doctor" letters and package inserts go only to health care providers and pharmacists and not to patients or their families. The only possible notice that patients and families receive of labeling changes is through press releases or their health care provider. **Exhibit #9.**

September of 2000, the FDA convened an Advisory Committee to discuss the continual problems of birth defects and psychiatric injuries associated with Accutane therapy. The Advisory Committee recommended and the FDA endorsed a "registration and certification of all patients and practitioners who prescribe Accutane" to eliminate birth defects and "the psychiatric events associated with Accutane". **Exhibit #10.**

On October 5, 2000, a press conference was held in Washington, DC by several Members of Congress and family members of Accutane suicide victims who made recommendations to the FDA and HLR to improve patient safety. These recommendations included conducting independent controlled studies on Accutane's risks of depression, suicidal ideation, suicide and other psychiatric disorders; better information for all patients through Informed Consent Form, MedGuide, labeling on Accutane packages to include all warnings, requiring HLR to disclose all serious Accutane adverse drug reactions and notify the FDA of all international regulatory action; and, requiring HLR to refrain from direct-to-consumer and children advertising. **Exhibit #11.**

The FDA had required HLR in May of 2000 to change the Accutane package labeling to include the warnings highlighted in the February 1998 "Dear Doctor" letter, but as of late December of 2000 Accutane packages were still being sold without the February 1998 warnings as to depression, psychosis, suicide ideation, suicide attempts and suicides. **Exhibit #12, 13 and 14.**

The Informed Consent and the MedGuide were scheduled to be made available to patients in February of 2001. Since the FDA has not mandated that practitioners give or

have their Accutane patients signed the Informed Consent, it is estimated that only 50% of the prescribing physicians use the Informed Consent. The MedGuide is not being used by some pharmacies and others are not aware of its required distribution to Accutane patients. **Exhibit #15.**

The FDA failed to institute the registration and certification of all patients and practitioners who prescribe Accutane. No independent controlled studies on the risks of depression, suicidal ideation, suicide and other psychiatric disorders have been completed. In April of 2001, the FDA began the SMART program as its pregnancy prevention program. In February of 2001, the FDA began working with the National Institute of Mental Health (NIMH) to explore possible areas of basic science and clinical research relating to the effects of Accutane on the central nervous system. **Exhibit #16.**

BIRTH DEFECTS

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. **Exhibit #1, 17 and 18.**

As early as 1988, the FDA sought to restrict Accutane use in women to prevent birth defects. At the 1989 and 1990 Advisory Committee meetings, HLR was able to convince the FDA that the sales of Accutane to young women were being limited. HLR testified that Accutane sales would not increase because there are only about "5,000 new cases per year" and that dermatologists were prescribing Accutane only to those women with "severe nodular acne". As Dr. William Cunningham of HLR testified, "it's my belief that the number of patients who are going to be treated will be decreased." Dr. John Strauss testified for HLR that "somewhere between one-half and one patient per month that the average practicing dermatologist might need to put [a woman] on Accutane." **Exhibit #19.**

As each pregnancy prevention program failed to prevent Accutane birth defects, the FDA would convene another Advisory Committee to receive recommendations. Finally, the September 2000 Advisory Committee recommended and the FDA endorsed a mandatory patient registry and certification of practitioners whose prescribe Accutane. Once again, the FDA succumbed to HLR pressure and the registry and certification was abandoned. Each time the Advisory Committee made recommendations to limit the distribution and use of Accutane, HLR pressured the FDA to protect and increase its sales of Accutane. In fact it is estimated that the defeat of the mandatory registry and certification will benefit HLR by approximately $450 million. **Exhibit #10 and 20.**

Not only has HLR been able to pressure the FDA into preventing its distribution and sales of Accutane, but the FDA extended HLR's patent by six months in granting a Pediatric Exclusivity within six weeks of its application. The granting of the Pediatric Exclusivity when the FDA's actions on Accutane have been questioned by Members of Congress, the media, and with an on-going Congressional inquiry, only demonstrates HLR's power over the FDA. For these reasons it appears that FDA's management has completely lost focus of its mission in protecting the American people. As the following quote from an FDA email shows, not everyone within the FDA thought the granting of the Pediatric Exclusivity was proper, "How in the world could the FDA have the nerve to grant extension of the patent on Accutane based on approval for use in patients 12 to 17!!!! 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." **Exhibit #21.**

Despite the assurances given by HLR at the 1989 and 1990 Advisory Committee Meetings that the sales of Accutane were in a "significant downward trend"; its advertising was focusing "on contraindication and proper usage of pregnancy prevention. It was not focused on usage...and the two ads you've seen are representative of the type of advertising you will see in the future"; "that number of patients who are going to be treated will be decreased"; and, "we've [HLR] been very careful not to promote the drug to non-dermatologists...." HLR sales of Accutane skyrocketed through the 1990's by targeting other health care providers to treat teenagers with mild to moderate acne. Currently, HLR advertising is directed at mothers of young males and specifically at African Americans and Hispanics. **Exhibit #19, 22 and 23.**

With increased sales and the new pregnancy prevention program (S.M.A.R.T.) it is difficult to determine the number of Accutane caused birth defects each year. At our December 11, 2002 hearing, Dr. Janet Woodcock of the FDA stated that under the new S.M.A.R.T. program there would be minimal birth defects. At one point, Dr. Janet Woodcock testified that the number of babies exposed to Accutane *in utero* would be very limited. Dr. Graham, FDA, has told investigators that there have been tens of thousands of Accutane exposed pregnancies and the S.M.A.R.T. would not change this fact. Dr. Graham testified that he did not expect the S.M.A.R.T. program to achieve its objective of preventing Accutane exposed pregnancies.

Dr. Woodcock claimed not to know of any problems with the S.M.A.R.T. program, yet FDA files tell a different story. FDA files contain two emails describing how "a physician is future-dating Accutane prescriptions" for a female to get around the S.M.A.R.T. program yellow sticker requirement to signify the female patient had a negative pregnancy test and another where the medical clinic was "pre-dating" prescriptions so the patient could fill more than one prescription within the 7 day limit of the negative pregnancy test. **Exhibit #24 and 25.**

Another email reports a woman who called the California Teratogen Information Service stating that she had taken Accutane and was now pregnant. "The most alarming part of her exposure is that she purchased Accutane at the Spring Valley Swap Meet (therefore

no prescription was required, no consent forms were signed,...)". This is not surprising when Members of Congress asked the North American President of HLR, Mr. Abercrombie, to discontinue the sale of Accutane in Mexico due to the fact that it is so easily obtainable across our southern border without a prescription and Mexico does not have a regulatory scheme such as the S.M.A.R.T. program, pregnancy testing, informed consent, or MedGuide. Mr. Abercrombie refused to acknowledge the problem or to stop selling Accutane along the border even though another pharmaceutical company agreed to do so with another problem prescription drug. **Exhibit #26.**

Other problems with the S.M.A.R.T. program are health care plans that electronically dispense its prescriptions and will not be able to verify the yellow negative pregnancy sticker, and the fact that S.M.A.R.T. program is viewed as voluntary, not mandatory. Kaiser Permanente of Northern and Southern California, the Veterans Administration and others have voiced their concerns that they are not set up to handle the S.M.A.R.T. program or to verify the negative pregnancy tests. **Exhibit #27.**

The FDA has declared that one birth defect from Thalidomide would require the drug to be pulled from the market. Thalidomide is used to treat leprosy and is seldom prescribed for individuals of child bearing years. The FDA anticipates that anywhere from 150 to 600 Accutane exposed pregnancies occur each year. This estimate does not include Accutane exposed pregnancies that are aborted. **Exhibit #28, 29, 30 and 31.**

HLR does not report abortions caused by Accutane because "abortions.... [are] not included among the 'serious' events because the dead fetus is not considered a patient." However, in the last quarter of 1999, HLR reported serious events due to Accutane, including "93 unwanted pregnancies" and "42 abortions". This equals one exposed Accutane pregnancy per day and one abortion every other day that we know of. Another FDA email dated September 29, 2000 states that the elective abortions in the Accutane quarterly report, "Additional exposed pregnancies, and abortions (induced, missed and spontaneous) are reported under the following:

1. 1420 Reproductive Disorders, Female;
2. 1500 Fetal Disorders;
3. 1600 Neonatal and Infancy Disorders

**Exhibit #32 and 33.**

Not only does Accutane trigger spontaneous abortions, HLR actually recommended that "any woman exposed to Accutane during pregnancy have an elective abortion.... as it is nearly 100% teratogenicity". **Exhibit #34.**

After more than 20 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 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. With the U.S. equivalent to Thalidomide, 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 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." **Exhibit #29.**

## PSYCHIATRIC INJURIES

As our December 11, 2002 hearing showed, the first concern of psychiatric injuries associated with Accutane was reported in 1985. Even though the FDA required HLR to inform physicians through "Dear Doctor" letters in 1985, 1986, 1997 and 1998 of possible psychiatric injuries, little notice was given to patients and their families. **Exhibit #4, 35, 36, 37 and 38.**

In 1997, the French health authorities ordered HLR to change its package labeling to warn patients and families, stating that with Roaccutane (European name for Accutane) "In rare occasions, neuropsychological problems have been recorded (behavioural difficulties, depression, convulsion and suicide attempts." HLR never notified the FDA of this safety labeling change although HLR was required to do so under the Federal Food, Drug and Cosmetic Act. **Exhibit #6.**

In a November 1996 FDA Memorandum on Accutane and Depression, the investigators found that "Of note, previous psychiatric illness was reported in 29% of our cases, and 10% had previous drug psychiatric drug use. Most patients experiencing depression with isotretinoin [Accutane] had no past history of psychiatric disease....The high percentage of patients without past psychiatric illness who developed a serious 'Depression' adverse drug event while receiving therapy with isotretinoin is a cause of concern." As the evidence has shown, in 1998 the FDA conducted an audit of 31 attempted and completed

suicides of Accutane users. The report found that in the 12 completed suicides, "For the majority, there was no antecedent history of depression and patients were not noted or known to be depressed prior to their suicide". After this report, FDA's Medical Review Officer for Accutane wrote in a Memo to FDA officials 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 use is associated with severe psychiatric disease in some patients". **Exhibit #39, 7, and 8.**

Still, HLR denies any causation between Accutane therapy and psychiatric injuries. In a November 27, 1997 telephone conference with HLR concerning depression and suicides, not only did the FDA require HLR to send another "Dear Doctor" but also to solicit help from the medical community to "....further our [FDA's] understanding of adverse events by reporting all cases to Hoffman La-Roche, Inc....or to the FDA MEDWATCH program....." The Memorandum of this Teleconference states, "The Sponsor [HLR] indicated 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." **Exhibit #40.**

The Sponsor, HLR, has indicated on more than one occasion that there is a causal connection between Accutane and psychiatric injuries. In the Memo provided by the FDA Medical Review Officer, HLR admitted that in this "...specific case implicates a causal relationship between Accutane and psychosis...." and ".... [HLR] could not exclude a causal relationship..." between Roaccutan and depression. **Exhibit #41.**

Approximately three months later, the February 1998 "Dear Doctor" letter was sent to the medical community by HLR stating in the WARNINGS section, "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." **Exhibit #38.**

In a later FDA email, the word "rarely" is discussed as being "too small to detect a signal (suicide)" in Accutane patients. But by July 2002, as the number of Accutane suicides mounted, some FDA officials advocated removing the word "rarely" in the Accutane Warnings. "The labeling still says "rarely" in regards to SIB [self inflicted bodily injury]. We use 'rarely' for fatal pancreatitis (a handful at best since 1982). If we added up all the reports we have for events called 'rarely' in labeling (ideation, attempts, completed suicide, aggression, violent behavior), I bet we are easily pushing 1000 reports. Is there a definition of 'rare' for post-marketing events? I think this matters, because if we allow them to use 'rarely' inappropriately, we are feeding into many derms' notion that the numbers are small and thus the issue is of no real concern." **Exhibit #42.**

As with pregnancy prevention programs, HLR was not going to let these warnings and "Dear Doctor" impede its sales of Accutane. Just four months later, HLR received a Warning Letter from the FDA concerning HLR's "...advertising and promotional labeling for Accutane.... [FDA] has reviewed these materials and has determined that they are false or misleading and promote Accutane

for an unapproved use..." The FDA Warning Letter further states, "Roche's promotional materials state or suggest that Accutane is safe and effective in the treatment of what Roche describes as the 'psychosocial trauma' and 'emotional suffering' associated with acne, including 'negative psychosocial effects such as depression and self-image.....This claim is particularly troublesome in light of information recently presented in a Dear Doctor letter, that Accutane may cause depression, psychosis, and rarely, suicidal ideation, suicide attempts and suicide." This warning letter did not stop HLR's strategy to increase its sales of Accutane through its public relations campaign in targeting mothers and young males. Still, the FDA remained silent. **Exhibit #43, 22 and 23.**

Hoffman-LaRoche continued to bombard the public and the medical profession with questionable studies claiming that there was no causal connection between Accutane and psychiatric injuries. Each of these studies, Spontaneous Reports, Clinical Psychiatric Analysis of Suicide Cases, United HealthCare Study, Prescription Sequence Symmetry Analyses, Jick Study, NAMCS, and Dr Jacob Study provided by HLR have been discredited or found "inconclusive" by the FDA in determining whether Accutane caused psychiatric injuries. In January of 2001, the FDA finally wrote one article to discredit the HLR sponsored studies which appeared in the October, 2001 Journal of American Association of Dermatology. The "independence" of the Jick study should have lost all credibility when it was learned that the study was co-authored by Dr. Kremers of HLR. Yet, when the FDA instituted MedGuides for Accutane in 2001, HLR had so influenced the dermatology community as to the safety of Accutane that "....dermatologists are actually distributing copies of the paper [inclusive Jick study] to patients to 'off-set' the [psychiatric] warnings in the new Medication Guides!" **Exhibit #44 and 45.**

Exhibit #33 presented at our December 11, 2002 hearing, showed nine ways to establish causality between Accutane and psychiatric injuries. Eight of these nine ways did establish that, in fact, Accutane did cause psychiatric injury. The third of these nine ways of showing causality is re-challenge/de-challenge cases which "....are of particular interest and highly suggestive of a linkage." The ninth way asks, "has a mechanism of action been established to account for the observed events?" To this factor the FDA answered NO. But a closer review of published studies and literature reaches a different conclusion. In addition to these studies, the FDA outlined 34 different publications which showed Accutane (Isotretinoin) causing psychiatric adverse side effects; literature showing the precedence and biologic plausibility of Accutane (is a synthetic analogue of vitamin A and is a retinoid) to the causation of psychiatric adverse effects; and, the biologically plausible mechanism between Accutane use [retinoids active in the central nervous system] and psychiatric disease. **Exhibit #46 and 47.**

Again, at the December 11, 2002 hearing, I questioned HLR on why they never submitted a 1981 study with its initial application which showed that Accutane had some effect on the central nervous system of mice. HLR's witness, Dr. Smith, stated that "under the regulations at the time, it [study] should have been submitted". I then asked HLR to submit all studies, documents and reports that were included in the development of the 1981 FDA Accutane patent application and in support of the 1971 FDA application which HLR later withdrew. To date, HLR has not provided any further studies or documents to the committee as requested. **December 11, 2002 Committee Hearing Transcript, starting on or about page 225.**

Like the 1981 study that HLR never submitted to the FDA, FDA has come across two more studies that show how Accutane affects the central nervous system of mice and rats. Again, these studies were never submitted to the FDA and the committee never received this information until the day of the hearing. The FDA discovered these studies in its review of a drug application submitted by Basilea, a HLR related company. **Exhibit #48.**

These four studies which never were submitted by HLR to the FDA prior to or while Accutane was being marketed clearly demonstrate that Accutane affects the central nervous system causing psychiatric injuries. It is not for the drug applicant to decide which studies it will or will not submit with its application. There is a continual requirement of the manufacturer to inform the FDA of all studies which may affect the safety or effectiveness of its drug. HLR suppressed these studies which go to the very issue of causality and which may warrant further study to determine whether Accutane affects the central nervous system in humans. HLR's duty and responsibility to inform the FDA of these studies was even more critical as the FDA had been expressing its concern that Accutane may cause psychiatric injuries. HLR even acknowledged that "there does appear to be a problem [with Accutane and psychiatric injuries]" in the November 24, 1997 Memorandum of Telephone Conference. **Exhibit #40.**

A study by Dr. Robert Nelson, formerly of the FDA and now a HLR consultant, submitted a study to FDA to prove that there was no direct causation between Accutane therapy and suicidal behavior. At the end of his presentation, Dr. Nelson had to conclude that "there are a very small number of reported cases that imply causality" between a described psychotic disorder and Accutane administration, at the individual case level. An even more interesting statement attributable to Dr. Nelson is that, "A 1999 citation, that showed diagnosable mood disorders stated that it takes more than acne to show depression." **Exhibit #49 and 50.**

HLR cannot claim that it was not aware of the requirement to inform the FDA of recent scientific and medical studies showing that Accutane, vitamin A, retinoids or retinoic acid affect the central nervous system. As part of its annual report to the FDA, HLR submits a list of medical studies and scientific research on Accutane therapy, vitamin A, retinoids and retinoic acid. Some of these studies and research demonstrate a cause-effect relationship between Accutane therapy and psychiatric injuries. For example, some of these studies and research from as early as1980 raise the concern of vitamin A toxicity from retinoid use affecting the central nervous system. **Exhibit #51, 52 and 53.**

In addition, HLR submitted an article written in 1989 by Diana M. Hanno, RN, stating that, "Depression has been reported [in Accutane therapy], 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 off as age related or stress induced". Ms. Hanno stated that this information that she cited was accurate and based on information received from HLR in her dermatology practice. **Exhibit #54.**

Based on independent medical studies, scientific research, and the FDA's own audit of reported cases of psychiatric injuries with Accutane use, the FDA concluded in 1998 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 use is associated with severe psychiatric disease in some patients". Still, the FDA did not require HLR to conduct further studies

or research on the cause of Accutane therapy and psychiatric injuries. When questioned by the media in 1998 on causality, Dr. Wilkin of the FDA stated that "...the FDA won't take further action, such as compelling Roche to conduct a study. Right now, we don't have a good feeling for what would be a good way to evaluate the hypothesis....But if someone had a way of pursuing possible causality, we'd be interested in knowing what kind of research to conduct." **Exhibit #9 and 55.**

It was only after several Members of Congress and the September 2000 Accutane Advisory Committee recommended that HLR and the FDA conduct independent studies to determine if Accutane caused psychiatric injuries that each began to explore ways to conduct studies or tests. **Exhibit# 10 and 11.**

HLR never took the charge from the Advisory Committee or the Members of Congress seriously as it has never submitted an approved protocol to conduct the requested independent study. **Exhibit #56.**

Beginning in February 2001, the FDA began to work with the National Institute of Mental Health (NIMH) to recommend and develop "safety/tox [toxicology] studies for Accutane". **Exhibit # 16.** On November 19, 2002 the NIMH held a workshop on its preliminary findings on functional effects of retinoids in the adolescent and adult central nervous system. Representatives of the FDA and HLR were present. Some of these preliminary studies show a direct casual effect of retinoids on the central nervous system in the brain of mice and rats which demonstrates that Accutane does have a harmful casual affect on the brain. It was interesting to note in another study that while Accutane actually stimulated brain cell growth in the first week, after the third week "there was a significant decrease in the number of brain cells, decrease in rat body weight, decrease in PET1, and decrease in serotonin transporter genes." These are just some of the findings that preliminarily demonstrate causality between Accutane and psychiatric injury in the brain. **Exhibit #57 and 58.**

Why Accutane clearly affects some patients and not others remains unknown. However, HLR has used the term "high risk patient" in its discussions with the FDA concerning psychiatric injuries. To date, HLR has never defined or clarified its definition of "high risk patient" to the FDA or Accutane users. **Exhibit #59.**

At our December 11, 2002 hearing, our colleague Ted Strickland picked up on the deadly spontaneous action caused by Accutane in young people when he asked, "Is it possible that this medication has an effect, an action that results in spontaneous, impulsive, self-destructive behavior that is different from that which occurs from a clinical depression"?

The "spontaneous action" mentioned by Congressman Strickland and testified to by the Turney and Benz family members at our December 11, 2002 hearing separates Accutane caused psychiatric injuries from clinical depression. Even the dermatologist at the hearing testified that she could not predict when spontaneous events may occur in Accutane patients.

In the case of Matthew Turney, age 16, he was alone for 10 minutes when he came home from school and shot himself. Matthew and his parents were watching for any signs of depression as they were aware that Accutane may cause psychosis, suicidal ideation, suicide attempts, and suicides.

Yet, his parents never saw signs of depression and are asking how do parents protect their children when there are no clues as to when the fatal 10 minutes can occur! **Exhibit #60.**

Michael Benz was a 31 year old fire fighter who never had acne but was prescribed Accutane. A tri-athlete, Michael cried out for help from his physician and was told to come back on Monday. Michael Benz drowned himself by weighting his body down with weight lifting plates. The investigation into his death showed that he had logged onto an Accutane website the weekend he died. As a fire fighter and an EMT, Michael Benz must have had some idea what was happening to him. Still, he could not resist the sudden urge to take his own life. **Exhibit #61.**

A review of the suicide adverse event reports describes young people with no history of psychiatric problems taking their lives. There are reports of young people talking to their parents one minute and then hanging themselves the next minute. There are reports of young people who have fender bender accidents and when law enforcement arrives to discuss the accident with them, they leave to get their driver's license and instead grab a gun and shoot themselves. **Exhibit #62.**

The FDA also picked up on the spontaneous self-inflicted behavior in the adverse events reports when it distinguished Accutane psychiatric injury different from the "garden variety of depression". "I still think aggression and violent behavior ('OIB' as opposed to BIS) might be a characteristic of this 'syndrome' that distinguishes it from the garden variety depression, especially since it happens to females as well as males." This aggressive behavior referred to as OIB or SIB was referenced in a 1999 email where the Accutane Medical Review Officer remarked that "I gave up trying to track all psychiatric reports and just have the self-injurious behavior cases....sorted into my 'SIB' stack, which is sadly growing tall". **Exhibit #63, 64, and 65.** This aggressive behavior seen in Accutane patients manifested itself not only in self-inflicted injuries but also in four murders and reported murderous ideation amongst Accutane patients. **Exhibit #66.** Of course, HLR denied any causation between aggressive behavior and Accutane therapy. Finally, on October 30, 2002 the FDA added "aggressive/violent behavior to the list of events that Accutane may cause". **Exhibit # 67.**

This aggressive/violent warning is now the 12th Warning for Accutane use. As the FDA noted in its August 31, 2000 email, "The population for whom Accutane is prescribed is overwhelmingly young and healthy. Accutane has been associated with many adverse events affecting nearly every organ system, and is a potent teratogen. Some of these adverse events are serious/life threatening and the current labeling include a Black Box Warning, 11 additional Warnings, and 18 Precautions". Even with this growing list of Accutane warnings/precautions, patients and their families are never told of its hidden dangers. **Exhibit #68.**

As the FDA focused on violent behavior, they noticed Accutane adverse events were "most similar" to testosterone and steroid use in athletes. It is well documented that steroid use in athletes does cause aggressive, violent behavior. As with steroid use, the FDA was beginning to focus in on the biological/medical plausibility of Accutane causing psychiatric injury in some patients. **Exhibit #69, 70, 71 and 72.**

Even with this growing list of evidence supporting causality between Accutane and psychiatric injury, the FDA actually extended HLR's Accutane patent based on a pediatric study and approved

the first of fourteen pending generic Accutane applications. Accutane is now available at lower cost to young adolescents who are still physically and mentally developing and are not aware of the physical and psychiatric injuries Accutane causes in some patients. As the Medical Review Officer asked, "How in the world could the FDA have the nerve to grant extension of the patent on Accutane based on approval for use in patients 12 to 17!!!! 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." This is not the first time that FDA officials working on the Accutane file questioned the lack of support from its upper management when it came to managing the risks of Accutane therapy. **Exhibits #17, 18 and 21.**

In regard to psychiatric injuries, HLR's efforts have been to suppress adverse events reports and medical/scientific evidence. HLR withheld its own studies that shed light on Accutane's effect on the central nervous system. Further, HLR failed to submit safety precautions employed by other countries, provided "junk science", and denied any biological causation between Accutane and psychiatric injuries. The only consistent explanation of these psychiatric injuries put forth by HLR is to blame the patients for their psychiatric problems. Throughout the history of Accutane, HLR claims it does not know how Accutane works. Therefore, HLR cannot claim that Accutane does not cause psychiatric injuries. HLR cannot have it both ways. It is obvious HLR is more interested in protecting its profits than in finding the cause of psychiatric injuries in Accutane therapy. **Exhibit #73, 74, 75, and 76.**

HLR has applied for a patent on its new formula of Accutane. A patent based on a new formula would continue HLR's exclusive distribution and sale of Accutane. In studies submitted by HLR 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 HLR may be over dosing our children. The FDA has not yet approved this new formula. **Exhibits #77, 78, and 79.**

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 HLR 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 HLR 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 HLR. **Exhibits 80, 81, and 82.**

If the FDA had been reviewing the adverse event reports, it would have known that the current formula Accutane caused "severe psychiatric injury in the adult human brain". Instead the FDA granted HLR a "waiver" from having to report non-serious Accutane adverse events to the FDA on November 4, 1999. **Exhibit #83.**

A review of the quarterly adverse event reports that were provided to the committee demonstrates the volume and the correlation between Accutane and psychiatric injuries.

In the last quarter of 1999, HLR reported 2381 Accutane adverse events of which 313 were serious. Of these serious events, 89 were psychiatric, 24 self injurious, 5 attempted suicide, 5 completed suicide, and 5 reports of psychosis. **Exhibit #32.**

In a typed note found in the FDA files and believed to be from 2001, it states that the quarterly reports from HLR "is 9 volumes for a mere 3 month period..... Speaking of this QR [quarterly report], a quick glance at the line listing shows "cases" rec'd between Oct 1 and Dec 31 includes 96 serious depression, 8 psychosis, 6 maniac depression, 34 suicidal ideation, 19 suicide attempts, and 9 suicides." **Exhibit #84.**

In a recent yearly summary of Accutane adverse event reports, Kathryn O'Connell, Accutane Medical Review Officer, writes, "From April 1999 to April 2000 of the 245 total initial cases coded by HLR as serious, 116 are psychiatric with the vast majority being labeled for depression. There are 6 suicides, 9 attempted suicides, 21 suicide ideation and 6 psychoses. "Thus, almost 50% of the serious labeled events for this annual period are psychiatric. Of the 910 initial cases excluding 15 day reports, 551 are psychiatric (again, around half of all reports). Therefore, 306 cases must be non-serious and unlabeled". **Exhibit #85.**

After this yearly review, when the Medical Review Officer was asked about the number of adverse event reports to date she stated, "The answer as of April 30, 2000 is 5,665 serious AE; the organ system with largest percentage of serious AE is psychiatric disorders; deaths 147 (I think AERS has about 250???) PS If reporting rate is 1-10%, there have been a LOT of serious AES out there!) **Exhibit #86.**

HLR states in an August 3, 2001 letter to the FDA that, "During the interval of April 2000 – April 2001, there were a total of 298 cases with 379 events in the organ-system class "Psychiatric" that were waived. These cases were waived because they were non-serious and labeled adverse events." **Exhibit #87.** These non-serious reports for this one year have an occurrence of at least one psychiatric event, per day for a year!

The FDA became concerned about the quality and accuracy of these non-serious Accutane psychiatric reports when it stated in the following email, "The new PADE Report, I think, underscores our 'need to know'. The NON-SERIOUS Unlabeled listings have 166 initial reports (not follow-ups) with psychiatric events. This includes 3 with suicide attempts and 13 ideation. How can SIB be a non-serious??? WHO KNOWS what is invisible to us under NON-serious LABELED, especially since everything psychy is labeled (meaning "non-serious" psych events only get exposure now if there is a concurrent event in a different body system that fits that bill as "unlabeled"...and the fox is guarding the "non-serious" henhouse!!!)". The FDA now requires HLR to report all Accutane adverse events. **Exhibit #42.**

As the June 25, 2002 FDA email states, "So...even if you make a VERY conservative guess at number of waived cases, adding this up for just this ONE year exceeds the numbers derms have

available on their radar since the drug was approved in 1982.....As it stands right now, we do not even know how many such reports fall under each Body System. I am very concerned that someone "outside" is going to get their hands on, and publish, the real numbers of psych reports obtained during the legal discovery processes no doubt going on.....FDA is going to look pretty sad if someone else points out there are thousands more than we acknowledge publicly!!" **Exhibit #42.**

Pretty sad is an understatement, when the HLR reported to the FDA that there are more than 4700 psych cases in its database that the FDA never saw! **Exhibit # 88.** What do these 4700 plus cases show, attempted suicides, suicide ideation, psychosis?

The typed note by the FDA's Accutane Medical Review Officer, exhibit #86, is worth noting that "If the reporting rate is 1-10%, there has been a LOT of serious AES out there!" It was testified at our December 11, 2002 hearing that the number of unduplicated suicides is approximately 200. If the actual number of suicides reported to the FDA is 1%, then the actual number of suicides is 20,000. If the actual number of suicides reported to the FDA is 10%, then the actual number of suicides is 2,000. The actual number of Accutane caused suicides probably lies between these two numbers, between 2,000 and 20,000 patients.

The reporting of adverse events to the FDA is voluntary for the general public, patients, their families and the health care profession. The health care profession only reports an adverse event if they believe the drug may have caused the adverse reaction. Many people are not aware of how or if they should file an Accutane adverse event report with the FDA. Since the October 5, 2000 press conference held by Members of Congress, 54 suicides have been reported to Congressman Stupak and only 23 had previously been reported to the FDA. **Exhibit #89 and 90.**

Only HLR is required to submit adverse event reports to the FDA. With the adverse event reports, HLR controls all the information and determines which reports are actually forwarded to the FDA. Unfortunately, the FDA waived the non-serious Accutane adverse event reports. With HLR controlling what reports are labeled serious versus non-serious, the true number of Accutane adverse events and deaths will never be known. This is especially true, when HLR submits death reports to the FDA as "death by adolescence"! **Exhibit #32.**

In 1999, the FDA was so concerned about HLR's reporting and "soft coding" of Accutane psychiatric injuries that they did a "surprise" inspection of HLR's plant and its adverse events database. The inspection resulted in a Warning Letter from the FDA for not timely submitting adverse event reports for several years and failing to disclose over 2,000 more Accutane adverse event reports. **Exhibit #91, 92 and 93.**

Why would HLR suppress the evidence of psychiatric event reports for Accutane, its second leading sales drug? HLR will do anything to limit its liability and keep Accutane sales escalating. In July of 2002, HLR received another Warning Letter from the FDA for "making false or misleading oral statements.....relating to psychiatric disorders in Accutane" at their "promotional exhibit booth at the American Pharmaceutical Association's Annual Meeting and Exposition. HLR's representative down played the risk of psychiatric injuries associated with Accutane therapy when they stated, "We don't feel it's an issue....News has hyped it up....Like any drug used in patients with depression, such as penicillin, it could bring it out....These oral statements made by the Roche representative are

in violation of the Act because they minimize the risk described in the bolded warning for Accutane and misleadingly suggest that the drug may be safer than has been demonstrated by substantial evidence." **Exhibit #94 and 95.**

There can be no doubt that based upon the evidence submitted at the December 11, 2002 hearing and the documents submitted by the FDA and HLR to our committee, HLR can no longer argue that Accutane does not cause psychiatric injuries of depression, psychosis, suicidal ideation, attempted suicides and suicides. Accutane should be immediately removed from the market.

**CORPORATE RESPONSIBILITY**

In a December 5, 2001 meeting, Chairman Greenwood asked the FDA what kind of corporate citizen was HLR. In response, FDA officials mentioned how HLR controls the information dermatologists receive in their professional journals. The FDA was particularly upset with the "educational supplement" consisting of 69 pages found in the November 2001 issue of the Journal of the American Academy Dermatology. The FDA found this "educational" supplement especially offensive and misleading as to Accutane therapy. The FDA voiced its frustration in being unable to respond as the FDA simply cannot keep up nor possess the same financial resources to buy the "advertising" in the professional publications to inform the health care providers as to the dangers associated with Accutane therapy. **Exhibit #96 and 97.**

The FDA did respond to this "educational supplement" with an article that was eventually printed in the Journal of Dermatology approximately a year later. The FDA article had little or no impact on balancing the "educational supplement" and it suspects that "....HLR tentacles run deep...this is the same thing that happened when Diane tried to publish her criticism of Jick study as a letter in Archives...." **Exhibit #98.**

A magazine distributed to dermatologist, Skin & Aging, prompted this response from the FDA, "If anyone was curious about the HLR tea party at the Ritz in March, this article will give you a clue before we have our meeting with sponsor next month. I thought that the biased and misleading talk on this subject that I heard given at the Am Acad Dermat meeting in March could not be beat. This article, however, is even more outrageous (different person...I have no idea who this one is). Does it look like there a well-orchestrated effort in the derm community to undermine the progress we made for patients with the MedGuide and Informed Consent? And what are we doing about it? Not nearly enough, in my view." **Exhibit #99.**

It is interesting to note, as the FDA did, that HLR only submits their articles to publications utilized by dermatologists and not to the scientific community which may question the validity of the science and the favorable support of Accutane. **Exhibit #100.**

HLR will put out information they know is wrong and very little is done to correct it. For example, when Charles Bishop flew his airplane into the bank in Tampa and Accutane was mentioned as a possible cause in Bishop's behavior, HLR cranked up its PR machine. The thought was planted that we would have to wait until the autopsy report to see if Accutane was present in Bishop's body. HLR knows full well that standard autopsies do not test for the presence of Accutane. As the FDA pointed out in an email, "Given the bad news about the poor kid in Florida, it is even MORE urgent

that we get the letter out to JAAD (Journal of the American Academy of Dermatology)....The derms are being poisoned with absolute nonsense and it is downright dangerous in my book...I know we can't compete with the Roche machine for their attention, but we have to try anyway!" In another email the FDA states, "It is a misconception that began with the Tampa place case [Bishop] and here it is again....it would seem NOT in the public health to let this ride, since the risk management strategy for this deadly AE absolutely depends upon people taking the warning seriously. We surely cannot depend on Roche to clear this scientific matter up for understandably clueless consumers." **Exhibit #101 and 102.**

In the FDA documents, there is a two page document titled, "Rough Draft of Items wish to discuss on Wednesday" which states, "5. Public disclosure on monies from Roche/Hoffman-La-Roche to the following parties and the extent to which such monies influenced these parties". The document alleges that the main funding for the American Academy of Dermatology, American Journal of Dermatology, Archives of Dermatology, British Journal of Dermatology and other journals" are mainly funded by HLR and it had to pay 1.6 billion dollars paid by Roche to U.S. suppliers for fraud....plus 800 million to European suppliers.....[and] 500 million FBI fine, etc" **Exhibit #103.**

Throughout the twenty years that Accutane has been on the market, HLR has delayed, stalled and failed to provide information requested by the FDA on numerous occasions. In fact, the FDA is still waiting for HLR's data of a retinal function study conducted back in 1985! On a number of occasions, the FDA requested this information from HLR and were told that the data "....was in prep for a couple of years, then they said eye data was 'lost', then it was found, but no report forthcoming, now it is 'found' and here, etc". This information is critically important as there are vision problems and night blindness associated with Accutane therapy but the critical data has never been provided to the FDA. **Exhibit #104 and 105.** There is an FDA email talking about how they must pressure HLR to provide the necessary language for the MedGuide "....so they do not drag this thing out for another 18 years because we do not have their approval letter." Again, in December of 1999, the FDA writes, "I wonder where the promised psychiatric re-analysis [for Accutane labeling revision draft] is...I'm not holding my breath because blue is not in my color chart!!!" **Exhibit #106 and 107.**

When Members of Congress have raised this issue of HLR not providing the1985 retinal function study to the FDA's Dr. Janet Woodcock, she claims that the FDA can threaten to pull the drug off the market if the manufacturer refuses to comply with its request. When pressed as to if the FDA has ever used this threat to obtain information, Woodcock admitted it has not. When asked if subpoena power would help the FDA to obtain this study, Woodcock advised against giving the FDA this power. Still, Dr. Woodcock had no solution to the dilemma FDA officials find them in. FDA medical review officials are put in a position of insisting on information to properly address the safety concerns of the American public while being ignored by the drug manufacturer with no hope of enforcement of their request to protect the health, safety and welfare of the American people. There is no enforcement mechanism to insure that the information requested from a drug manufacturer is provided to the FDA. **Exhibit #108 Energy and Commerce Committee hearing, March 6, 2002, pages 72-74.** Yet, the opposite is true, when HLR wants documentation from the FDA. As the August 13, 2001 email states, "In my now painfully long experience with Roche, this is their modus...they stall and obstruct and then all of a sudden it is 'ready to go' and they pressure

for 'expedited review' and to say OK...it has backfired before (like May 2000 mess for instance) and it will again, I promise". **Exhibit #109.**

Besides stall, delay and obstruct there is another problem with HLR that deals with credibility and honesty of their officials. As the emails from June 27, 2001 state, "An after thought to yesterday's meeting about Accutane on how to deal with Roche delays.....We could potentially cite Ellison's [President of HLR] 'misspeaking' about what IMS could do to measure prescription compliance as a reason why we want to have all information from them in writing....delays on document submission....The second on assertions by Dr. Ellison: Do we need to develop a list of broken promises/mis-statements and offer up for discussion clarification..." **Exhibit #110.** By June of 2001, it appears that the FDA could no longer trust HLR officials to tell them the truth or to provide them with documentation. The lack of credibility and honesty on behalf of HLR 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 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 our 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." **Exhibit #111.** 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 HLR pressure and the registry and certification was abandoned. Each time the Advisory Committee made recommendations to limit the distribution and use of Accutane, HLR pressured the FDA to protect and increase its sales of Accutane. In fact, the latest defeat of the mandatory registry and certification will benefit HLR 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." **Exhibit #10, 20 and 21.**

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 HLR to market Accutane which has caused death and devastation amongst our young people? Even when a patient registry and physician certification is recommended and endorsed by the FDA, HLR 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!

FDA REFORM

As I stated on page one in my letter to Chairman Greenwood, this Accutane investigation and hearing demonstrates why the Energy and Commerce Committee should overhaul the FDA's drug review and approval process, give the FDA the authority to rein in exaggerated claims by manufacturers, and strengthen FDA's post-marketing surveillance of prescription drugs. The hearing also magnified the FDA's inability to control the flow of prescription drugs at our borders, over the internet, and through the mail. All of these issues have been ignored by the FDA.

Despite the questions surrounding Accutane's birth defects and psychiatric injuries, the FDA automatically granted a patent extension because HLR did a pediatric study. Just because a study is done, should a patent be automatically granted when there are unanswered safety questions and safety data being withheld by the drug manufacturer?

Should the FDA receive subpoena power to safety information from drug manufacturers? It is my understanding that the FDA is the only regulatory agency in the federal government that does not have this authority.

It appears that MedGuides are not being properly given out with the 15 dangerous drugs that have MedGuides issued for them. The FDA does not appear to have any type of follow up to make sure the mandatory MedGuides are given to patients.

To the surprise of everyone, the Accutane Informed Consent Form is not required to be given to patients. The Informed Consent should be mandatory and should contain all labeled warnings and precautions associated with the drug.

As I requested at our December 11, 2002 hearing, we should bring in for a hearing, the CDC and NIMH which have also looked into the controversy surrounding Accutane and see what they have learned.

As pointed out in this Supplemental Review, the life threatening warnings on Accutane patient's prescription package were not consistent throughout the country. How much time should drug manufacturers be granted to replace prescription drug packages when the warnings are changed to prevent serious injuries and death? Should the drug manufacturer have over 2 years to recall their packaging when the latest warnings include serious injury and death? Or should the packages be immediately recalled and the new warnings are printed before the drug is made available to consumers?

Another issue that I did not raise in this Supplemental Review is the fact that consumers receive their information on the potential side effects from either the Pharmacy Information Pamphlet when you pick up your filled prescription or on the drug packaging. In our investigation, the Pharmacy Information Pamphlet, contained different information depending on where the prescription was filled. A prescription filled in Boulder, Colorado contained the latest February 1998 safety warnings about depression,

psychosis, suicide ideation, suicide attempts and suicide but the Accutane prescriptions filled in Northern Michigan and Washington, DC did not contain these warnings.

HLR used false advertising, misleading studies and statements to promote Accutane and increase its sales. As we saw in the Erbitux case, when the FDA knows that a drug company is presenting questionable and misleading statements and studies to promote their product should the FDA remains silent? We should examine what authority the FDA possesses to keep the public informed as to the accuracy of the information being provided by the drug manufacturer?

We should also examine the impact of direct-to-consumer advertising to young people. What medium is the direct-to-consumer taking place? How is it monitored? Which group is being targeted?

These are just some of the issues that the Accutane investigation has raised and is applicable to other hearings that this committee has held.

Respectfully submitted,

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Congressman
Michigan's First District